Official Journal of the
European Academy of Allergology
and Clinical Immunology

EUROPEAN JOURNAL OF ALLERGY
AND CLINICAL IMMUNOLOGY

Allergy

Volume 55 · Number 2 · February 2000

MUNKSGAARD · COPENHAGEN http://journals.munksgaard.dk/allergy

EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

Allergy

Official Journal of the European Academy of Allergology and Clinical Immunology

Aims and Scope

The aim of the journal is to promote and maintain contact between basic and clinically applied allergology and immunology, and articles which contribute to this purpose are especially welcomed. *Allergy* is an international journal with contributors and readers in all countries. Articles are accepted purely on the basis of quality.

The journal will publish Original Research within its field, give competent Reviews of selected subjects of interest to the allergologist and immunologist, and describe and comment upon aspects of interest in Contemporary Methodology.

Practical clinical implications of recent original research are evaluated by Editorial Comments. The journal includes Selected Abstracts from other periodicals in related disciplines. Letters to the Editor or Short Communications will enable authors to secure rapid publication of results of importance. New sections and activities will be regularly introduced.

Subscription

Allergy is published in 1 volume of 12 issues appearing monthly.
Subscription price 2000: DKK 3,630 * including postage
Supplements are included in subscription.

Subscription orders may be placed with Head Office

MUNKSGAARD
International Publishers Ltd.
35 Nørre Søgade
P O Box 2148
DK-1016 Copenhagen K
Tel: +45 77 33 33 33
Fax: +45 77 33 33 77

Or

Regional office in USA
MUNKSGAARD
International Publishers Ltd.
Commerce Place
350 Main Street
Malden, MA 02148-5018
USA
Tel: (781) 388-8273
Fax: (781) 388-8274

Important – for subscriptions delivered to addresses within the European Union. If you have a VAT registration number, you must provide this. Otherwise, please add your local VAT on journals to the above price in DKK: Austria 10%, Belgium 6%, Denmark 25%, Finland 0%, France 2.1%, Germany 7%, Greece 4%, Ireland 12.5%, Italy 4%, Luxembourg 3%, the Netherlands 6%, Portugal 5%, Spain 4%, Sweden 25%, UK 0%. Canadians: Please add 7% GST.

Allergy (ISSN 0105-4538) is published monthly by Munksgaard International Publishers Ltd, 35, Nørre Søgade, P O Box 2148, DK-1016 Copenhagen K, Denmark. USA subscriptions price is USD 526.00 including airspeed delivery. Periodicals postage paid at Champlain, NY and additional mailing offices. USA Postmaster for North American subscribers: Send address changes to IMS of NY, P O Box 1518, Champlain, NY-12919. Airspeed and mailing in the USA by INSA. Printed by the Charlesworth Group, Huddersfield.

Allergy 2000: 55: 116–134
Printed in UK. All rights reserved

ALLERGY
ISSN 0105-4538

Position paper

Consensus statement* on the treatment of allergic rhinitis

P. van Cauwenberge (Belgium)
C. Bachert (Belgium)
G. Passalacqua (Italy)
J. Bousquet (France)
G. W. Canonica (Italy)
S. R. Durham (UK)
W. J. Fokkens (Netherlands)
P. H. Howarth (UK)
V. Lund (UK)
H.-J. Malling (Denmark)
N. Mygind (Denmark)
D. Passali (Italy)
G. K. Scadding (UK)
D.-Y. Wang (Singapore)

Department of Otorhinolaryngology, Ghent University Hospital, De Pintelaan 185, B-9000 Ghent, Belgium

Prof. P. van Cauwenberge
Department of Otorhinolaryngology
Ghent University Hospital
De Pintelaan 185
B-9000 Ghent
Belgium

Accepted for publication 12 October 1999

1. Introduction

Allergic rhinitis (AR) is a high-prevalence disease in many developed countries, affecting about 10–20% of the general population (1–5). Several studies based on questionnaire and objective testing or medical examination indicate an increasing prevalence of AR in European countries over the last decades (6, 7).

AR is characterized by nasal itching, sneezing, watery rhinorrhoca, and nasal obstruction. Additional symptoms such as headache, impaired smell, and conjunctival symptoms can be associated. According to the time of exposure, AR can be subdivided into perennial, seasonal, and occupational disease. Perennial AR (PAR) is most frequently caused by dust mites and animal dander. Seasonal AR (SAR) is related to a wide variety of pollen allergens including grasses, *Parietaria*, *Ambrosia*, *Artemisia*, birch, olive, hazelnut, and cypress. The morbidity of SAR obviously depends on the geographic region, the pollen season of the plants, and the local climate.

Several other conditions can cause similar symptoms and are referred to as nonallergic (noninfectious) rhinitis: NARES (nonallergic rhinitis with eosinophilia syndrome); aspirin sensitivity; endocrine, occupational, postinfectious, and side-effects of systemic drugs; abuse of topical decongestants (rhinitis medicamentosa); and idiopathic rhinitis. Furthermore, diseases such as nasal polyposis, chronic sinusitis, cystic fibrosis, Wegener's disease, benign or malignant tumours, etc. have to be excluded carefully. Therefore, current guidelines (4) emphasize the importance of an accurate diagnosis of patients presenting with rhinitis symptoms. In fact, several causes may commonly coexist in the same

*European Academy of Allergology and Clinical Immunology.

patient, requiring separate consideration. The diagnosis of allergic rhinitis is frequently straightforward, but may also be very complex and difficult. The mainstay is an accurate history including an allergy history, based on familial and personal history, recent clinical aspects, and prior treatment. The possible presence of lower respiratory tract disease, skin symptoms, or pollen-related food allergies should always be investigated, since they are commonly associated with rhinitis. This is followed by a clinical examination of the nose. A major advance has been the introduction of rigid and flexible nasal endoscopes and, if sinusitis is considered, the availability of CT scanning.

When an allergic pathogenesis of the disease is suspected, the skin prick test (SPT) with standardized allergens should be performed. The measurement of allergen-specific IgE in serum (as single allergens or groups) is a useful diagnostic approach in selected cases (skin test with difficult interpretation or not feasible, children, allergen not available for SPT, etc.). As sensitization to an allergen does not necessarily mean that the individual patient suffers from clinical disease, the clinical relevance of skin or specific IgE results should be demonstrated before introducing therapies such as immunotherapy or environmental control. Whereas the clinical relevance in SAR usually can be demonstrated by carefully analysing patient history, nasal allergen challenge tests may be useful in PAR. Allergen-specific diagnosis (as well as therapy) should be based on purified standardized allergen extracts.

AR appears to impose variable restrictions on the physical, psychologic, and social aspects of patients' lives, and may have an impact on their careers. AR is underestimated as a cause of suffering and impaired quality of life (8–10). If symptoms of AR are not well controlled, they may contribute to learning problems and sleep disturbances (11, 12).

For AR, direct yearly costs are estimated at 1.0–1.5 billion Euro, while indirect costs are estimated at 1.5–2.0 billion Euro in Europe (13). Finally, the possible association between AR and other conditions including asthma, sinusitis, otitis media, nasal polyposis, lower respiratory tract infection, and even dental malocclusion should be considered in evaluating the socio-economic impact of the disease (14).

Table 1. Characteristics of allergic rhinitis

Characteristic	Seasonal	Perennial
Obstruction	Variable	Always, predominant
Secretion	Watery, common	Seromucous, postnasal drip, variable
Sneezing	Always	Variable
Smell disturbance	Variable	Common
Eye symptoms	Common	Rare
Asthma	Variable	Common
Chronic sinusitis	Occasional	Frequent

In recent years, new information on the pathophysiologic mechanisms underlying allergic inflammation has accumulated. Based on these recent data, the therapeutic strategies have been partly modified or improved, and new drugs or new routes of administration, dosages, and schedules have been studied and validated. Intended for the specialist as well as the general practitioner, this paper presents the state of the art of AR treatment, and provides a well-documented review of the drugs available and their place in the management of the disease.

2. Mechanisms of AR

AR results from IgE-mediated allergy, associated with cellular inflammation of the nasal mucosa of variable intensity. The mechanisms of AR have been largely clarified within the last 15 years from studies in naturally occurring disease and by the use of nasal challenge models in which cell infiltration and cell activation have been assessed (15–18). These studies highlight the presence of eosinophilic airway inflammation and identify the enhanced expression of endothelial and epithelial adhesion molecules (19, 20), as well as chemokines and cytokines (21, 22). The release of mediators from infiltrating leukocytes as well as resident tissue cells, such as mast cells, is implicated in both the symptoms and the development of nasal nonspecific hyperreactivity.

Histamine appears to be a major mediator released by mast cells in seasonal and perennial allergen exposure (23), but other mediators such as leukotrienes, prostaglandins, and kinins may also contribute to the symptomatology through their interaction with neural and vascular receptors (24, 25). In addition to these events, there is also neural involvement in the disease, with neuropeptide release from cholinergic and peptidergic nerves. Some different aspects of the two forms of AR are summarized in Table 1.

The enhanced expression of TH2-like cytokines, such as interleukin (IL)-4 and IL-5, within the nasal mucosa, generated by T cells, as well as mast cells, is a hallmark of AR and is relevant to the selective recruitment and survival of eosinophils (26, 27). The local generation of cytokines such as IL-5 and GM-CSF by eosinophils themselves, along with the generation of cytokines and chemokines by the epithelium, leads to the persistence of the eosinophil within the tissue. The epithelium is increasingly recognized as an active cell population, providing cytokines and chemokines relevant to the local tissue cell recruitment (28), with an accumulation of mast cells, basophils, eosinophils, and T cells evident at this location in AR. Once induced, this inflammatory process within the nasal mucosa persists for several weeks after allergen exposure (29). In cases of PAR

where there is continuous low-dose allergen exposure, there is persistent nasal mucosal inflammation (30).

The concept that the mechanisms of disease generation provide a framework for rational therapy in this disorder is based on the complex inflammatory reaction rather than on the symptoms alone.

3. Allergen avoidance

The triggering event of AR is the contact of the responsible allergen with the nasal mucosa. This event, mainly through the degranulation of mast cells, leads to the clinical early-phase response and initiates the subsequent allergic inflammatory process. The severity of the disease and its natural course correlate well with the allergen concentration in the environment (31–33). Thus, the first therapeutic approach to the control of symptoms is prevention, by identification and avoidance of the causal allergen(s) (4, 34). The removal of the allergen has been proven to result in improvement in the severity of the allergic disease (35) and reduction of the need for drugs. The beneficial effect of environmental control may take weeks or months to be fully perceived. In most cases, complete avoidance of the allergen is not feasible due to practical and/or economic reasons. Nevertheless, allergen-avoidance measures should be considered before or in association with pharmacologic treatment, where appropriate.

As far as house-dust mites are concerned, there are some general and specific measures to be adopted for reducing the mite population and the allergen exposure. These measures ideally include:

1) removal of carpets and soft toys from the bedroom
2) use of allergen-impermeable (water-vapour permeable) covers for mattresses, duvets, and pillows
3) careful vacuum-cleaning of beds every week with a paper filter cleaner and damp-cleaning of furniture in the bedroom
4) washing bedclothes at 60°C.

Some acaricides (benzyl benzoate, tannic acid, etc.) appear to be effective in reducing the mite population if used regularly (36–38), but their clinical outcome remains unproven, and the use of allergen-impermeable covers for mattresses seems to be more effective (39–41).

A recent meta-analysis in asthma did not reveal clear evidence of the benefits of measures to avoid house-dust mites (42). However, optimal reduction of mite levels was frequently not achieved, thus not allowing a reduction of symptoms, and similar studies in rhinitis are not available.

The only effective measure for avoiding animal-dander allergens is to remove the pet (cat, dog) from the house and to vacuum-clean carefully all carpets, mattresses, and upholstered furniture. However, even with these measures, it may not be possible to eradicate cat allergens. Although frequent washing of cats reduces allergen recovery in the lavage (43), clinical studies have not shown clear benefit from this procedure when carried out once a week (44). If removal of the cat is not acceptable to the patient, the pet should at least be excluded from the bedroom or kept outdoors. Avoidance of pollen is often impossible due to its ubiquitous nature.

4. Oral antihistamines

General aspects

Histamine is a major mediator involved in the development of AR symptoms: the increase of histamine concentration in nasal secretions of atopic patients after nasal allergen challenge and during natural allergen exposure has been clearly demonstrated (45, 46). The role of histamine in the nasal allergic reaction is also confirmed by the reproduction of nasal symptoms after provocation with histamine. These symptoms – with the exception of obstruction – can be reduced by administering H_1-antagonists. Three histamine receptors are presently recognized, but the nasal effects of histamine are predominantly H_1-mediated. H_1-receptor antagonists reduce the clinical expression of nasal itching, sneezing, and rhinorrhoea, but they are less effective in controlling nasal obstruction (47, 48).

Efficacy

The use of the first-generation antihistamines (chlorpheniramine, diphenhydramine, promethazine, and tripolidine) is considerably limited by their sedative and anticholinergic effects; in addition, their short half-lives discourage the use of these antihistamines for AR treatment. The newer antihistamines (acrivastine, astemizole, azelastine, cetirizine, ebastine, fexofenadine, loratadine, mizolastine, and terfenadine) are effective in reducing nasal symptoms such as itching, sneezing, and watery rhinorrhoea but have less effect on nasal blockage (49, 50) (for review, see refs. 4, 51–57) (Table 2). Antihistamines taken orally have the additional advantage of reducing nonnasal symptoms such as conjunctivitis and urticaria (58). Some experimental

Table 2. Characteristics of pharmacologic treatments

Characteristic	Oral antihist.	Nasal antihist.	Nasal steroids	Nasal decong.	Ipratropium bromide	Nasal cromone
Rhinorrhoea	++	++	+++	o	++	+
Sneezing	++	++	+++	o	o	+
Itching	++	++	+++	o	o	+
Blockage	+	+	+++	++++	o	+
Eye symptoms	++	o	++	o	o	o
Onset of action	1 h	15 min	12 h	5–15 min	15–30 min	Variable
Duration	12–24 h	6–12 h	12–48 h	3–6 h	4–12 h	2–6 h

+ Marginal effect; ++++ substantial effect (under natural exposure conditions).

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.