Allergy 1998: 53 (Suppl. 41): 7–31
Printed in UK – all rights reserved

ALLERGY
ISSN 0105-4538

Executive summary

Allergic rhinitis is now recognized as a major cause of morbidity that significantly impairs function and quality of life. Moreover, it is now widely held that the pathophysiologic mechanisms causing nasal allergy contribute, or predispose many individuals, to the development of other airway diseases, including asthma. Allergic rhinitis may well be a factor in 24% of children with otitis media with effusion (OME), and perhaps 28% of cases of chronic sinusitis. As many as 78% of persons with asthma aged 15 to 30 years have elevated serum IgE antibodies to five common aeroallergens. In many instances, nasal allergy signals the presence of more severe disease.

Considerable evidence now suggests that early and appropriate intervention can improve the quality of life and productivity of patients with allergic rhinitis, enhance the academic performance of children, and reduce the prevalence of airway complications. The goal of treatment has shifted from mere symptom alleviation to blocking the pathophysiologic mechanisms that cause chronic allergic inflammation and leave patients vulnerable to airway infections. The earlier in a patient's life that this can be accomplished, the better the anticipated consequences.

A panel of experts was convened in Amsterdam, The Netherlands, on 2 September 1996, to explore these issues and their impact on allergy prevention and treatment in primary care. Their undertaking was supported by an unrestricted educational grant from Schering-Plough Pharmaceuticals.

New insights into allergic rhinitis

1. The pathophysiology of allergic airway disorders

Allergic inflammation appears to be the first and primary occurrence in the chain of events leading to asthma and other airway disorders. Chemical mediators released during hypersensitivity reactions give rise to the symptoms of allergic rhinitis, and induce the cell infiltration and activation that results in chronic inflammation. A key event in this process is the upregulation of specific intercellular adhesion molecules, including members of the immunoglobulin superfamily intercellular adhesion molecule-1 (ICAM-1), that permits inflammatory cells to migrate into nasal, sinus, and lung tissue. In certain conditions, inflammatory mediators stimulate the expression of ICAM-1, which is also a receptor for the subtype of human rhinoviruses that accounts for 90% of human rhinovirus infections. It is currently under investigation that allergen exposure and viral infection in the first 3 years of life may alter pulmonary and immune function irreversibly in genetically predisposed children.* Moreover, these same mechanisms may contribute to other respiratory problems associated with eosinophilic inflammation, lymphoid hyperplasia, mucosal edema, and viral infection.

Therapies that downregulate ICAM-1 are being investigated as a means of preventing or minimizing allergic inflammation. Treatments presently known to downregulate ICAM-1 include antihistamines (loratadine, terfenadine, cetirizine, and azelastine).

2. Psychosocial sequelae of allergic rhinitis

Allergic rhinitis is associated with impairments in how patients function physically, emotionally, socially, and at work or school. Adults may complain of role and activity limitations, frustration, sleep disturbance, irritability, embarrassment over symptoms, cognitive impairment, decreased alertness, and performance deficits. In children, chronic nasal allergies are associated with learning deficits.

Unfortunately, sedating antihistamines can exacerbate these effects by hampering performance and cognition even when subjects have no sense of being impaired. At least one of the newer nonsedating agents, by contrast, can partially reverse allergic rhinitis' effect on cognition and performance.

Diagnosis of patients with rhinitis

3. Recommendations for improved recognition

Nasal allergy may usually be differentiated from other forms of rhinitis by an allergy diagnosis. This includes personal history of symptoms, the timing of their expression, triggers, and physical examination. Skin prick tests and eventually *in vitro* diagnosis of specific IgE are important. Imaging studies are usually indicated only if the diagnosis is in doubt, if related airway disorders complicate the presentation (e.g., nasal polyps), or when occupational rhinitis is suspected. The

*The **Preventia I** multinational study is currently underway to investigate this.

temporal association of nasal or ocular symptoms with the workplace strongly suggests occupational rhinitis.

4. Management of patients with rhinitis

Treatment of chronic rhinitis and nasal allergies should be individualized, with therapeutic measures aimed at the underlying etiology, likely pathophysiology, and dominant symptoms. Medication is best taken prophylactically for seasonal symptoms – before the anticipated onset of symptoms in seasonal rhinitis or for episodic exposures to specific allergens – and regularly, rather than as needed. Such usage of antihistamines and intranasal steroids has been found to alleviate exacerbations in patients with both nasal allergy and seasonally induced asthma.

5. Recommendations regarding avoidance

Avoidance of inciting factors (e.g., allergens, irritants) can reduce the expression of nasal symptoms and minimize the need for medications. The avoidance measures that are easiest to implement are the ones most likely to be used and therefore to be successful.

6. Recommendations regarding oral medications

- *Antihistamines.* Although traditional agents have some benefits (e.g., low cost), they can no longer be recommended due to their potential for causing CNS impairment. Nonsedating antihistamines are the preferred option.
- *Oral decongestants.* Although topical steroids are the first-line treatments for nasal blockage, α-adrenergic agonists such as pseudoephedrine, phenylpropanolamine, or phenylephrine also ameliorate nasal congestion. This symptom is a major factor in perennial rhinitis. Careful dosing of agonists is required to avoid aggravating hypertension. Moreover, these agents generally should be avoided in patients with cardiovascular disease, thyrotoxicosis, glaucoma, or diabetes.
- *Oral corticosteroids.* A brief course is indicated only to relieve severe nasal blockage so that topical therapy can proceed. In such cases, patients should be referred to an allergist.

7. Recommendations regarding topical nasal sprays

- *Intranasal corticosteroids* are highly effective in reducing inflammation, rhinorrhea, itch, and nasal blockage. They are the first choice for treating nasal blockage and largely reduce, but may not eliminate, the need for other medications to treat ocular symptoms. They may be used safely in children, though youngsters often have difficulty with sprays. In addition to treating nasal allergies, these medications can be used to treat nonallergic rhinitis with eosinophilia syndrome (NARES) and to shrink small nasal polyps or prevent their recurrence after surgery. The onset of action of topical corticosteroids is slow compared to antihistamines.
- *Topical nasal decongestants* may be used to open nasal passages in preparation for the use of other agents, such as intranasal steroids. To prevent rebound congestion, they should be used for 2 to 3 days and no more than 7 to 10 days.
- *Mast-cell stabilizers* include intranasal cromolyn and nedocromil sodium. Cromolyn may be used for the prophylaxis of allergic symptoms, and is considered especially safe for elderly patients, children, and pregnant women. The need for frequent administration can raise compliance issues. Nedocromil sodium, unlike cromolyn, can both prevent an allergic reaction and control a reaction in progress.
- *Topical antihistamines* allay allergen-induced itching, sneezing, rhinorrhea, and ocular symptoms but are less useful for nasal blockage.
- *Intranasal anticholinergics* such as ipratropium bromide are effective in controlling the excessive watery rhinorrhea associated with neurogenic stimuli (e.g., cold air, spicy foods) or the common cold. However, they have no effect on nasal blockage, sneezing or itching, or ocular symptoms.

8. Recommendations regarding specific immunotherapy (SIT)

Patients with rhinitis or asthma caused by allergens for which the clinical efficacy and safety of SIT have been documented by placebo-controlled, double-blind studies, and those requiring daily pharmacotherapy for longer periods (e.g., preventive treatment during a pollen season or perennially) are candidates for SIT.

SIT is most effective if a single allergen is identified, rather than multiple allergens. Injections should be prescribed by specialists and given by physicians only if a specific allergen has been identified. SIT should never be initiated in pregnant women, though the continuation of maintenance therapy is safe. Considerable care must be taken if allergic rhinitis coexists with moderate or severe asthma. Local immunotherapy offers improved safety and equivalent effectiveness.

9. Recommendations regarding poor responders

When patients respond poorly to standard medical care, clinicians should a) ascertain whether compliance has been poor, b) adjust drug doses, c) consider combination therapy, d) reconsider the diagnosis, e) reassess the patient for a nasal structural defect or a complication of allergic rhinitis, or f) refer the patient to a specialist.

10. Recommendations regarding specialist referrals

Referral can be helpful under the following circumstances:

- in most cases when significant airway comorbidity is present (asthma, chronic sinusitis, nasal polyps, or otitis media with effusion)
- when the diagnosis is in question or special diagnostic testing is required
- when occupational rhinitis is suspected, to distinguish between clear-cut allergic reactions and toxic or nonallergic reactions
- when poor symptom control necessitates a consultation for environmental control measures, pharmacotherapy, or specific immunotherapy
- when medication side-effects are intolerable
- when rhinitis is only part of a complex series of mucosal allergies.

Patient education and compliance

Educating patients about their disease and its management, eliciting their concerns and preferences regarding therapy, and discussing potential medication side-effects can build cooperation in treatment of chronic nasal symptoms. Learning points may be reinforced by providing simple written instructions, and by asking patients to confirm what they know. Trust can be established by attending to quality-of-life issues and asking patients what they expect from treatment. Keeping treatment simple is likely to improve the chances of therapeutic compliance.

Introduction

Allergic rhinitis is a seasonal or perennial disorder characterized by mild to severe upper respiratory symptoms such as nasal congestion, rhinorrhea, sneezing, and itching. These symptoms arise from an underlying inflammatory process initiated by a reaction between the allergen and immunoglobulin E (IgE), neurogenic stimuli, and other complex cellular processes.

A panel of experts was convened in Amsterdam, The Netherlands, on 2 September 1996, to explore these issues and their impact on allergy prevention and treatment in primary care. Their undertaking was supported by an unrestricted educational grant from Schering-Plough Pharmaceuticals. Conclusions and recommendations from that meeting are summarized subsequently and presented in expanded form later in this monograph.

Allergens are primarily responsible for provoking chronic inflammatory processes; viral infections underlie acute exacerbations of asthma, chronic sinusitis, and otitis media with effusion.

There is a growing awareness of how allergic rhinitis – and some of the medications used to treat it – can affect patients' quality of life, work or school performance, and emotional well-being. Besides physical symptoms, patients may exhibit fatigue, psychomotor sluggishness, irritability, and mood and cognitive disturbances (1–5). Learning is impaired in children (6), while some adults may report reduced productivity and concentration (7).

This combination of physical, emotional, and functional problems may diminish quality of life in both adults (7) and adolescents (8). Moderate to severe perennial allergic rhinitis has been found to affect quality of life significantly compared to healthy subjects in eight of the nine dimensions of the Medical Outcomes Study Short-Form Health Survey 36 (SF-36) (9).

Clinical implications

The prevalence of allergic respiratory disorders is high and is a burden on the health-care system:

- One study of patients in a London general practice found that nearly one in seven adults had allergic rhinitis (10).
- By the age of 6 years, 42% of 747 children followed from birth in the Tucson Children's Respiratory Study had physician-diagnosed allergic rhinitis (11). Those who developed rhinitis before the age of 1 were more likely to have asthma by age 6 (11).
- As many as 78% of persons with asthma aged 15 to 30 years have been shown to exhibit high levels of IgE antibodies to five common aeroallergens (12).
- Of 200 patients with chronic sinusitis, 27.5% also had allergy in one study (13). About 24–50% of children with OME had allergic rhinitis (14) or nasal allergy (15). For comparison, about one-third of the general population has chronic sinusitis or OME.
- In general, the prognosis for patients with asthma or allergic rhinitis is mixed: Only 10% of patients are cured, about 50% improve, 30% show no change, and 10% deteriorate over time (16).

Medicine has begun to revise its traditional therapeutic approach to allergic rhinitis. It is now acknowledged that impeding the natural course of airway allergies by interfering with the pathophysiologic mechanisms that cause mediator release and chronic inflammation may help prevent related airway disorders. This would reduce overall morbidity and improve patients' quality of life. It also should help make patients less vulnerable to the consequences of viral infection, as well as to environmental factors such as pollution. Recent advances in allergy treatments – most notably the introduction of nonsedating selective histamine H_1-antagonists and intranasal corticosteroid sprays – hold the promise of achieving these goals. Of particular interest are the studies showing that treatment of allergic rhinitis reduces the incidence and severity of asthma (17–19).

The purpose of this monograph is to introduce new ways of thinking about and managing allergic rhinitis in the hope that physicians will look for related airway disorders and individualize therapeutic programs, considering the special needs of populations such as pregnant women, children, and the elderly.

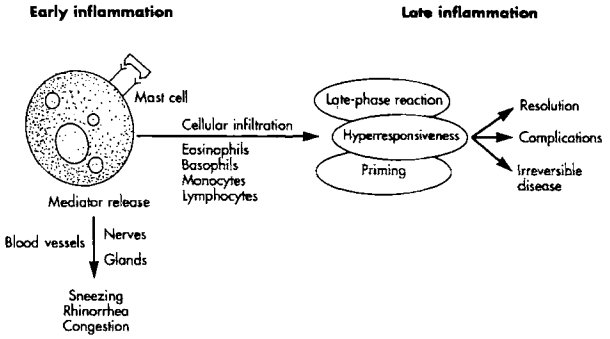

Fig. 1. The onset of allergic rhinitis. Allergic rhinitis generally is the product of both an early-phase and a late-phase inflammatory response. Early inflammation involves mast-cell degranulation and the release of mediators, whereas late inflammation is due to cellular infiltration of the nasal mucosa, involving especially eosinophils and basophils, and subsequent release of additional mediators. When inflammation fails to resolve, the nasal mucosa may become hyperresponsive to irritants or additional allergen exposure (priming). This sets the stage for the development of chronic rhinitis or allergic airway complications. (Adapted with permission from Watson et al. [18].)

The pathophysiology of allergic rhinitis

Persons with allergic rhinitis have IgE antibodies bound to high-affinity receptors on mast cells and basophils, and to low-affinity receptors on other cells, such as eosinophils, monocytes, and platelets. Allergic inflammation is initiated when allergens deposited in the airway bind to IgE molecules, causing cellular degranulation and releasing a number of inflammation mediators (20). This process entails both an early- and a late-phase response (Fig. 1).

Early-phase response

The interaction of antigen with specific IgE antibodies leads to the degranulation of mast cells and basophils and the prompt release of preformed and newly generated mediators, such as histamine, neutral proteases, leukotriene C_4, prostaglandin D_2, cytokines, and kinins (21). The interaction of these chemical messengers with blood vessels, mucous glands, and nerves produces the symptoms of allergic rhinitis, such as sneezing, rhinorrhea, and itching.

Histamine is one of the most important mediators of the early-phase allergic response in the nasal mucosa. Its release stimulates sensory nerves, causing pruritus of the nose, palate, and conjunctiva (21). The resultant excitation of parasympathetic reflexes contributes to vasodilation and mucus hypersecretion. Kinins (bradykinin) generated by mast-cell tryptase and plasma kallikreins stimulate afferent neurons, to cause watery rhinorrhea by inducing vasodilation, edema, and plasma exudation. Chemotactic mediators, such as IL-5 and a range of chemokinins, including IL-8, RANTES, and eotaxin, recruit eosinophils and other inflammatory cells into the nasal mucosa.

Late-phase response

This reaction, manifested by some patients, entails a process of cell infiltration and activation occurring over 4–24 h.

Late-phase allergic reactions begin when autocoid mediators and cytokines released from mast cells during the early-phase response upregulate the expression of leukocyte endothelial adhesion molecules in the postcapillary venules of the nose. Especially sensitive to histamine, postcapillary venules are also the site of blood cell extravasation. Once adherent to the endothelium, these cells pass between adjacent cells to the perivascular space. Various chemoattractants, essentially IL-5 and the chemokines, draw primed leukocytes (eosinophils, basophils, neutrophils, and mononuclear cells) into the submucosal tissue. Once there, by interacting with additional stimuli by matrix proteins, they release their own mediators. This perpetuates the inflammatory response and augments aspects of the immediate hypersensitivity reaction, such as mucosal congestion and mucus secretion. Although pruritus

and sneezing occur, the major symptoms in late-phase reactions are hypersecretion and congestion.

The priming effect

The chronic inflammation caused by repeated allergen exposure lowers the threshold for other provocative stimuli reactions (22). As a result, allergic individuals react more strongly to a) low levels of the primary allergen, b) other allergens to which they are only mildly sensitive, or c) non-specific "triggers", such as cold air, cigarette smoke, spicy foods, and strong chemical odors.

Role of adhesion molecules

A key event in chronic respiratory allergy is the upregulation of specific adhesion molecules that permit inflammatory cells (e.g., eosinophils) to migrate into nasal, sinus, and lung tissue. The first step is the experience of such molecules on endothelial cells and on activated circulating inflammatory cells. The accumulation of eosinophils in these tissues is injurious, and contributes to the pathogenesis of allergic rhinitis, sinusitis, and asthma (23–26). In certain conditions, histamine is known to stimulate the expression of adhesion molecules on nasal epithelial cells of normal subjects (27).

An important adhesion molecule required for effective cell recruitment in allergic disease is intercellular adhesion molecule 1 (ICAM-1) (28). Upregulation of ICAM-1 expression has been shown a) on endothelial cells during bronchial vascular inflammation induced in a primate model of allergic sensitization and exposure (29); b) on bronchial epithelial and on vascular endothelial cells in symptom-free asthmatics (30); c) on epithelial cells of the nose and conjunctiva in patients with perennial and seasonal (31) allergic rhinitis (Fig. 2); and d) on the nasal and conjunctival epithelium of patients with asymptomatic perennial rhinitis when exposed to allergen, though not in cohabiting relatives or healthy volunteers (32).

Besides its role in allergic inflammation, ICAM-1 serves as a receptor for the major subtype of human rhinoviruses; this subtype accounts for 90% of all human rhinoviruses (33, 34). Rhinoviruses are a major cause of the common cold. Evidence of minimal, persistent inflammation in asymptomatic allergic patients suggests that by inducing ICAM-1, subclinical allergen exposure may increase the susceptibility of allergic patients to rhinovirus infection, and thereby explain the greater frequency of colds in asthmatic children (30).

In short, it now appears that both ICAM-1 and viral infection play a role in the pathophysiology of asthma (Fig. 3).

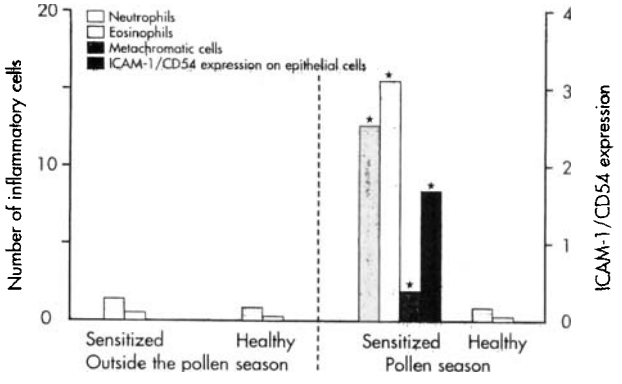

Fig. 2. Induction of intercellular adhesion molecule 1 (ICAM-1) in seasonal allergic rhinitis. ICAM-1 expression was upregulated in the nasal epithelial cells of 10 allergic patients following allergen-specific challenge during natural seasonal exposure, but not out of pollen season. No upregulation occurred in 10 healthy volunteers during either study period. Correlation of ICAM-1 expression with cytologic involvement showed infiltration by eosinophils ($P<0.001$), neutrophils ($P<0.001$, and metachromatic cells ($P<0.001$). (Adapted with permission from Wegner et al. [29].)

The virus/allergy nexus

The epidemiologic link between viral respiratory infection and asthma is strong. Researchers have shown that such viral infections are associated with:

- 86% of wheezing episodes that last longer than 48 h in nonhospitalized children (35)
- 80% to 85% of asthma exacerbations in 9 to 12-year-old children (36).

Among the viruses associated with childhood asthma exacerbations are rhinoviruses, respiratory syncytial virus (RSV), adenovirus, and coronaviruses (36). Rhinovirus infection has been implicated in 50% of acute asthmatic episodes in schoolchildren, followed by coronaviruses in 13% of cases (36). Levels of eosinophil, a major basic protein in children with asthma, have been shown to be

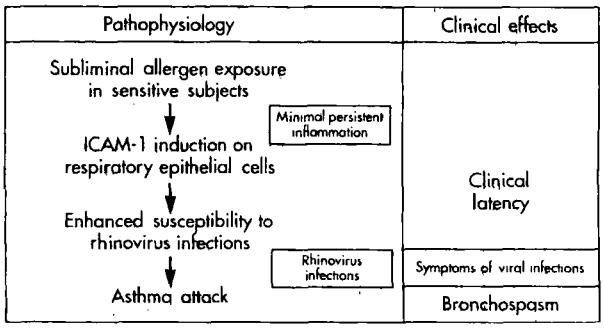

Fig. 3. Possible pathway of rhinovirus-induced asthma. With permission from Canonica et al. Allergy 1994;49:136-41.

higher during exacerbations associated with rhinovirus infection than during asymptomatic periods (37).

Adults with allergic rhinitis exhibit bronchial hyperresponsiveness to histamine and antigen following rhinovirus infection. Rhinovirus infection also predisposes the allergic patient to allergen-provoked late asthmatic reactions (38). In asthmatics, but not in nonasthmatics, eosinophilia in the bronchial mucosa is still evident at 6–10 weeks after rhinovirus infection, probably due to ongoing secretions initiated by the virus in the allergen-primed mucosa (39).

Classification of rhinitis

Rhinitis can be divided into three categories:

- allergic – i.e., acute or chronic conditions characterized by seasonal or perennial symptoms, or both
- infectious – i.e., nasal disorders caused by viral, bacterial, or fungal agents
- nonallergic/noninfectious – i.e., a heterogeneous group of disorders comprising eosinophilic conditions, such as aspirin idiosyncracy; or non-eosinophilic conditions, such as gustatory rhinitis, rhinitis of pregnancy, and vasomotor rhinitis.

Table 1 catalogues the characteristic features of the various forms of chronic rhinitis (10, 40–48). Despite the considerable overlap, it is usually possible to diagnose the disorder by skin prick test and the patient's symptoms, history (including relevant behavioral practices, such as smoking), and physical examination.

Differential diagnosis

The elements of a diagnosis include elicitation of a detailed patient history and physical examination of the nose, eyes, ears, and lungs. Among the many factors that must be explored are patterns of symptom expression, environmental triggers, medication use, family history, and exposure to workplace allergens or irritants. It is important to determine the severity of symptoms and to uncover possible complications such as asthma, sinusitis, otitis media, or nasal polyps. Questions related to psychosocial or quality-of-life problems – such as fatigue or cognitive impairment – also should not be overlooked.

The differential diagnosis of rhinitis primarily depends on use of an allergy skin prick test. Pharmacologic agents that may affect results should be withdrawn for a sufficient time before testing (Table 2). Because of its long duration of action (approximately 7–9 days), the antihistamine astemizole can suppress skin test reactivity for 8–12 weeks after its discontinuation (40). By contrast, this effect lasts only 2–4 days with most other antihistamines.

Symptom patterns

Most patients who present with rhinitis exhibit clusters of symptoms that define them as either "sneezers and runners" or "blockers". Those with seasonal allergic rhinitis are usually sneezers and runners.

Nonspecific symptoms

Some patients with rhinitis have only a single symptom or many nonnasal complaints, such as headache, sore throat, postnasal drip, a "full" or a "stuffy" head, recurrent head colds, chronic "sinusitis", chronic cough, plugged ears, hyposmia, loss of the sense of taste, fatigue, or poor concentration. Often, patients use the term "sinuses" or "sinusitis" to describe symptoms caused by nasal pathology.

Family and personal history

A thorough patient history yields information needed to classify nasal symptoms, determine their cause, and make appropriate therapeutic decisions.

Family studies indicate that environment generally influences the expression of allergic disease (11), but genetics determines the severity and specificity of the symptoms (49). Genetics also is an important component of atopy as a general predisposition, involving multiple as yet unidentified genes. Children not only inherit a tendency to atopy from their parents, but are likely to develop the same allergic disorders (50, 51). Consequently, the following information should be sought:

- the age at which symptoms began
- symptom type, occurrence, and frequency (episodic, seasonal, or perennial)
- symptom duration and severity
- aggravating factors
- allergen exposure in home or work environment
- current medications
- illicit drugs.

The physical examination

Although the physical examination of patients with chronic rhinitis centers on the nose, eyes, and throat, clinicians also should evaluate the ears, sinuses, and lungs to identify any related airway disorders, which often are present. General signs of an atopic predisposition, such as eczema, also are helpful.

Table 1. Classification of rhinitis

Syndrome	Symptoms	Other factors and considerations
Allergic rhinitis		
Seasonal (10)	Sneezing, itching (eyes, ears, nose, palate), nasal congestion, rhinorrhea	Allergens: pollen, mold spores, dust mites, cat dander History: atopy, eczema, family history of seasonal pollinosis Symptom expression: often diurnal; worse on clear, breezy days; better during or after rainfall Occurrence: from early growing season to first frost, or year-round in areas with extended growing seasons
Perennial (10)	Same as seasonal but nasal blockage and catarrh more common; complaint of "permanent cold"	Allergens: dust mites, animal dander, mold spores, cockroaches History: past or current eczema, wheezing, family with nasal problems other than seasonal rhinitis Occurrence: episodic or continuous, depending on exposure; possible seasonal exacerbation during summer and autumn (45) Complications: sinusitis or otitis media from nasal blockage
Infectious rhinitis		
Viral	Runny nose, sneezing, nasal obstruction with subsequent thick, yellowish discharge	Signs: red, irritated nose Duration: about 1 week; longer if secondary bacterial infection occurs
Bacterial rhinosinusitis	Mucopurulent discharge, facial pain and pressure, disturbed olfaction, headache, postnasal drainage, maxillary toothache, cough, occasional fever	Diagnostic clues: frequent or chronic colds; poor response to nasal decongestants; facial pain worsens on bending forward
Otitis media	Purulent drainage, earache, cough (42)	
Nonallergic/noninfectious rhinitis		
Eosinophilic syndromes		
NARES*	Intense, sporadic episodes of paroxysmal sneezing, rhinorrhea, eye and throat itching, tearing (41, 44)	Associated findings: perennial rhinitis (14% of cases) (41) Triggers: nonspecific, including emotions
Nasal polyposis	*Local*: progressively fixed nasal obstruction, rhinorrhea, anosmia, nasal voice; snorting or sniffing in patients without rhinorrhea *Lower respiratory*: throat clearing, chest tightness, husky voice, hacking cough	Diagnostic clue: significant or long-standing nasal congestion Association findings: rhinosinusitis, asthma, cystic fibrosis, aspirin intolerance, allergic vasculitis, allergic fungal sinusitis†
Noneosinophilic syndromes		
Idiopathic rhinitis‡	Profuse rhinorrhea, nasal obstruction	Provoking factors: nonspecific triggers, cold air, exercise, barometric changes, stress, pollutants Occurrence: episodic or perennial, depending on exposure
Rhinitis medicamentosa	Inflammation, nasal obstruction only symptoms	Causes: topically applied drugs (including cocaine or nonprescription nasal decongestants) (47) or systemic drugs taken for nonnasal illnesses¶
Occupational rhinitis	Episodic sneezing, rhinorrhea, nasal obstruction, conjunctivitis	Occurrence: only at work in most cases Common causes: irritants (e.g., exhaust, paint fumes, tobacco smoke, sulfur dioxide), corrosives (e.g., ammonia, chlorine, acrylamide), or allergens (wood dust, latex, animal dander) Associated findings: occupational conjunctivitis, asthma in some cases
Rhinitis of pregnancy (46)	Mostly nasal congestion	Prevalence: about 18% of pregnant women Occurrence: first trimester to parturition Associated findings: allergy, purulent sinusitis, rhinitis medicamentosa
Hypothyroidism (48)	Chronic nasal blockage, postnasal drip, recurrent common colds, laryngeal dryness, perceived laryngeal obstruction, vocal changes	Diagnostic clues: symptoms coexist with only mild or absent signs of nasal, pharyngeal, or laryngeal abnormalities Occurrence: in advanced hypothyroidism and in 45–60% of cases of incipient hypothyroidism
Miscellaneous		
Granulomatous	Nasal obstruction, viscous secretions, crusting	Conditions: rhinoscleroma, Wegener's granulomatosis, polymorphic reticulosis, sarcoidosis, tuberculosis

Table 1 Continued

Atrophic rhinitis	Congestion, hyposmia with copious, foul-smelling nasal crusts	Findings: progressive atrophy of nasal mucosa, turbinates Complications: headache, chronic sinusitis
Gustatory rhinitis (43)	Rhinorrhea, perspiration, facial flushing	Triggers: hot, spicy foods Occurrence: only during ingestion of implicated items
Structural problems	Mostly unilateral symptoms	Causes: septal deviation, tumors, nasal polyps, hypertrophied adenoids

* NARES: Nonallergic rhinitis with eosinophilia syndrome.

† Also called vasomotor rhinitis

‡ Triad of aspirin sensitivity, asthma, and rhinosinusitis should be ruled out in patients with nasal polyps, as unidentified aspirin intolerance in such cases can lead to hospitalization or death.

¶ Implicated systemic agents include guanethidine, phentolamine, methyldopa, α-adrenergic antagonists, chlorpromazine, aspirin, nonsteroidal anti-inflammatory drugs, reserpine, ACE inhibitors, and oral contraceptives (40).

Clinical diagnosis

A clinical diagnosis of allergic rhinitis can be made under the following conditions:

- The patient exhibits symptoms and signs of nasal allergy.
- Symptoms are not consistently unilateral.
- Fever, prominent sore throat, myalgia, or symptoms compatible with other clinical conditions are absent.
- The patient's personal history is negative for other possible causes of chronic rhinitis (e.g., abuse of nasal decongestant sprays, hypothyroidism, pregnancy).

Laboratory testing

Imaging studies are usually indicated only in specific circumstances - most commonly, when the diagnosis is in doubt, when symptoms persis despite appropriate therapy, or when related airway disorders complicate the diagnosis. Persistent symptoms or airway complications may be factors in perennial allergic rhinitis.

Although impaired olfaction is frequently overlooked in cases of nasal allergy, it is relatively easy to assess by olfactory threshold tests. Patients who require more sophisticated testing - such as assessment of mucociliary function or nasal airway patency - should be referred to a specialist.

Treatment of seasonal and chronic rhinitis

Treatment options consist of allergen avoidance, pharmacologic therapy, or allergen-specific immunotherapy.

Allergen control measures

Efforts aimed at environmental control may involve relatively simple activities based on general principles – e.g., limiting outdoor activities during the height of the pollen season, shielding young children from passive tobacco smoke and gas heating or wood-burning stoves. They also may entail fairly complex undertakings aimed at specific allergens; e.g., cat dander. As people spend increasing amounts of time indoors, environmental control is focused largely on containing exposure to house dust, animal dander, mold, and cockroaches. As a rule, measures to avoid allergens are effective when they are likely to be used – e.g., simple to follow and inexpensive to implement. Patients should be informed that even partial compliance can help control symptoms and lessen the need for medication. They should be encouraged to persevere, as it may take weeks or months of avoidance before an improvement in symptoms is noticeable. (See Appendix for a patient information sheet about allergen-control measures.)

Principles of pharmacotherapy

The selection of an appropriate and effective medication for the treatment of chronic rhinitis entails consideration of several factors:

- *Underlying etiology.* Especially in patients for whom immunotherapy is being considered, this requires careful diagnosis of the allergen (s), primarily through skin prick testing.
- Likely *pathophysiology.* Symptoms due to inflammatory processes (as in nasal allergy) require different medications than those caused by noninflammatory neurogenic mechanisms (as in gustatory, idiopathic, or atrophic rhinitis).
- *Dominant symptoms.* Medications should address the patient's most prominent complaints. Combination therapy may be warranted for patients with a mix of moderately severe to severe symptoms.
- *Safety.* It is important to determine whether medication side-effects may impede a patient's performance at work or school, diminish quality of life, or enhance risk of sustaining personal

Table 2 Withdrawal of pharmacologic agents that affect skin test reactions (38)

Medication	Withdrawal period before testing
Antihistamines	
Sedating	2–4 days
Nonsedating	
Loratadine	7 days
Terfenadine	7 days
Astemizole	8–12 weeks
Ketotifen	7 days
Phenothiazines	2 days
Topical corticosteroids applied on test site	2–3 months

(Adapted with permission from International Rhinitis Management Working Group [40].)

injury or significant morbidity. The potential for drug interactions also must be considered when patients are taking multiple medications.

- *Patient age and other special considerations.* The needs of special populations – pediatric patients, the elderly, pregnant women, and competitive athletes must be evaluated.
- *Coexistence of related airway disorders.* In patients with coexisting airway disease, the treatment of nasal allergy is important to prevent exacerbation of sinusitis or asthma.
- *Patient preferences and compliance history.* In some countries, patients prefer oral medications to sprays (52). Additionally, individuals differ greatly in their capacity to adhere to therapeutic regimens. Consequently, an attempt should be made to determine each patient's understanding of and willingness to comply with a specific treatment program. Factors that may adversely affect compliance include poor symptom relief, the nature or severity of the side-effects, and the inconvenience or complexity of the therapeutic regimen (53, 54).

Prophylactic therapy

As a rule, it is best for patients to start therapy *before* the anticipated onset of symptoms, to suppress those immunologic and mediator mechanisms that cause inflammatory reactions and to minimize the priming effect. Prophylactic therapy is usually possible in seasonal allergic rhinitis, when the onset of symptoms is relatively easy to predict, or for episodic exposures to specific allergens (e.g., before visiting the home of someone with pets). As a rule, patients with seasonal or perennial rhinitis should take their medication regularly, rather than as needed, because consistent use best controls mucosal inflammation. In turn, this helps lessen the risk of related airway complications in susceptible individuals. Regular antihistamine use over weeks or months has been found to reduce asthma symptoms significantly in allergic rhinitis patients with seasonal and chronic rhinitis (55–57).

Therapeutic choices

In its 1994 consensus statement, the International Rhinitis Management Working Group advocated a stepwise approach to therapy that took into account specific diagnoses and patient characteristics (40). This approach is summarized in Table 3.

Stepwise management certainly represents a reasonable starting point for therapeutic decisions in cases of chronic rhinitis. Nonetheless, the complexity and interrelationship of these disorders suggest that, while taking account of the guidelines, a case-by-case approach provides added value.

What follows is a review of the benefits and limitations of various medications used to treat chronic rhinitis. Among the agents considered are topical and oral antihistamines, topical and oral corticosteroids, topical and oral decongestants, cromolyn sodium, nedocromil, sodium intranasal anticholinergic agents, and saline sprays. The discussion concludes with a review of combination drug therapy and the indications for immunotherapy.

Oral medications

Antihistamines

There are at least three classes of histamine receptors, designated H_1, H_2, and H_3. Histamine can exert local or widespread effects on smooth muscles and glands. Bronchoconstriction and contraction of the intestine are mediated by H_1-receptors, while gastric secretion results from H_2-receptor activation (58). H_3-receptors appear to exist predominantly in the central nervous system (CNS) and at presynaptic nerve endings (58).

Histamine causes capillary dilation; H_1-receptor stimulation leads to a rapid, brief dilator response, while H_2-receptors mediate a response that is slower to develop and more sustained (58). It also plays a role in extravascular smooth-muscle contraction and (more rarely) relaxation, with H_1-receptor activation responsible for contraction and H_2-receptor stimulation usually resulting in relaxation (58).

The class of agents known as H_1-receptor antagonists comprises drugs that act rapidly to antagonize the histamine activity of H_1-receptors, thereby relieving the main symptoms of allergic rhinitis (sneezing, watery rhinorrhea, and itching of the nose, eyes, and palate). In addition, some of the newer agents have been shown to possess antiallergy

Table 3. Stepwise management of chronic rhinitis: guidelines of the International Rhinitis Management Working Group (40)

Condition	Special features	Treatment(s)
Seasonal allergy		
Adults and children	Mild or occasional symptoms	Allergen avoidance *plus* – Rapid-onset nonsedating antihistamines *or* – Topical antihistamine or cromolyn to eyes, nose, or both
	Moderate disease – Prominent nasal symptoms	Allergen avoidance *plus* – Topical nasal steroid started early in season *plus* – Topical antihistamine or cromolyn to eyes
	– Prominent ocular symptoms	Allergen avoidance *plus* – Nonsedating antihistamines *or* – Cromolyn to eyes
Perennial allergy		
Adults	Chronic disease	Allergen avoidance *plus* – Topical nasal steroids
	Intermittent disease	Allergen avoidance *plus* – Nonsedating antihistamines *with or without* – Occasional use of oral decongestants
Children		Allergen and irritant avoidance *plus* – Topical cromolyn sodium *or* – Nonsedating antihistamines daily *or* – Topical nasal steroids if above medications fail or exposure is long-term
Perennial nonallergic allergy		
Adults and children	Little watery discharge	Irritant avoidance and cessation of smoking *plus* – Topical nasal steroids (may be needed long-term if effective) – Topical antihistamine or cromolyn to eyes, nose, or both If response ceases after 1 month – Short-term systemic steroids *with or without* • Oral decongestants • Referral to specialist
	Copious watery discharge	– Topical anticholinergic agent (ipratropium bromide)

properties that may contribute to diagnosis and treatment. These properties include the ability to:

- inhibit histamine release from human basophils (59, 60)
- block histamine, and partly block prostaglandin D_2 release, in the nasal secretions of highly allergic subjects (61)
- directly inhibit eosinophil activation (62, 63)
- reduce vascular permeability (64)
- block histamine activation of airway epithelial cells by suppressing the expression of surface markers, such as ICAM-1, and the major histocompatibility complex class II antigen HLA-DR, involved in antigen presentation (27).

The ability both to inhibit histamine release and downregulate ICAM-1 makes certain antihistamines (e.g., terfenadine [65, 66], loratadine [27], cetirizine [65], azelastine [65], oxatomide [65], and levocabastine [65] particularly suitable for treating allergic inflammation, because ICAM-1 is a marker of allergen-induced inflammation as well as a receptor for human rhinoviruses (33, 65).

Sedating vs *nonsedating antihistamines.* "Sedating" agents are distinguished from "nonsedating" ones by the higher incidence of drowsiness associated with the former at the doses used to control allergic symptoms. In part, this difference is due to the speed with which antihistamines cross the blood–brain barrier – i.e., rapidly in the case of the sedating agents and slowly in the case of the nonsedating agents. The sedative potential of the newer agents is limited further by their specificity for binding to peripheral H_1-receptors. Sedating antihistamines, in contrast, affect central H_1-receptors and receptors of other types (e.g., muscarinic cholinergic, α-adrenergic, and tryptaminergic) (67). This may contribute to their sedative and other side-effects (67). Sedating agents' effect on central H_1-receptors may be especially relevant, as histaminergic transmission originating from the posterior hypothalamus sustains waking arousal (68). In short, by having a reduced capacity to cross the blood–brain barrier and specifically blocking H_1-receptors, the nonsedating agents are less able to cause CNS effects and associated adverse reactions. (See subsequent discussion of CNS effects.)

Efficacy. Table 4 presents selection criteria for 10 of the antihistamines most commonly used in Europe. Studies have shown that the newer nonsedating antihistamines produce moderate to

Table 4 Selection criteria for oral antihistamine

	cetir	lora	terf	fexo	ebas	aste	mequi	chlor	hydro	dmm
Clinical efficacy										
SAR	+++	+++	+++	+++	+++	+++	++	++	+++	+++
PAR	++	++	++	N/A	++	++	++	?	++	++
Urticaria	+++	+++	+++	N/A	N/A	+++	?	?	+++	+++
Others	Eczema	Eczema							Eczema	Eczema
Onset of action	<1 h	<1 h	1–2 h	1 h	?	>2 h	?	<1 h	?	<1–2 h
Duration	24 h	24 h	>12 h	>12 h	24 h	7–9 days	12 h	−12 h	4–12 h	>24 h
Tachyphylaxis	No	No	No	?	?	No	?	Possibly	No	Yes
Anti-H_1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Somnolence	Yes	No	No	No	No	No	Yes	Yes	Yes	Yes
Alcohol additive effect	Yes	No	No	No	No	No	?	Yes	Yes	Yes
Enhanced cardiovascular effect with										
Ketoconazole	No	No	Yes	No	No	Yes	?	?	No	No
Erythromycin	No	No	Yes	No	?	Yes	?	?	No	No
Anticholinergic effect	No	No	No	No	No	No	Yes	Yes	No	Yes
Weight gain	No	No	No	No	?	Yes	No	?	No	No
Food effect	No	No	No	?	?	Yes	?	?	No	No
Dose reduction										
Renal dysfunction	Yes	No	No	Yes	Yes	No	?	?	Yes	Yes
Liver dysfunction	Yes	Yes	Yes	No	Yes	Yes	?	?	Yes	Yes

cetir: cetirizine; lora: loratadine; terf: terfenadine, fexo: fexofenadine; ebas: ebastine, SAR: seasonal allergic rhinitis, aste: astemizole, mequi: mequitazine, chlor: chlorpheniramine; hydro: hydroxyzine, dmm: dimethindemaleate; PAR: perennial allergic rhinitis.

excellent symptom response in up to 67% of patients with seasonal allergic rhinitis (69), making them as effective as, if not more effective than, the older (i.e., sedating) agents (70, 71). As a group, the newer agents demonstrate comparable efficacy (72, 73). A comparison of loratadine and astemizole in patients with seasonal rhinitis found equivalent efficacy in the two (72). Cetirizine has been shown to lessen nasal blockages (74).

Although the use of antihistamines in asthma is still controversial, the new nonsedating agents seem to offer some benefit for allergic patients with concomitant asthma. Data indicate that terfenadine (75, 76) and loratadine alone (77), and combined with pseudoephedrine (55), astemizole (78), certirizine (79), and azelastine (80) exhibit modest bronchodilating effects (75), reduce bronchial sensitivity to histamine (55), and guard against exercise- (78) and antigen-induced bronchospasm. Such effects may require higher than currently recommended doses, however. Loratadine (55), cetirizine (56), and terfenadine (57) have been shown to reduce asthma symptoms in rhinitic patients with seasonally induced asthma when taken over weeks or months, though this evidence is disputed. Together, such findings suggest that timely and appropriate use of antiallergy therapy may help prevent lower airway symptoms in susceptible patients if used in an adjunctive manner. Moreover, they dispel the fallacy that antihistamines are contraindicated in asthmatic patients.

CNS effects. Sedating antihistamines can exacerbate the cognitive and functional problems caused by untreated allergic rhinitis (81). Among their most troubling CNS effects are fatigue, sedation, and performance impairment (81).

Patient reports of unusual daytime drowsiness have been noted in 25–50% of users of sedating antihistamines (82) – e.g., diphenhydramine, pyrilamine, brompheniramine, chlorpheniramine, triprolidine, hydroxyzine, promethazine, and cyproheptadine. By contrast, when given at the recommended doses, the "nonsedating" antihistamines – astemizole, ebastine, fexofenadine, loratadine, and terfenadine – cause no more drowsiness than placebo.

Confusion exists as to the sedating properties of two new agents, acrivastine and cetirizine. Both medications have been associated with significantly more reports of daytime drowsiness than placebo at recommended doses: acrivastine, 8 mg, 11% versus 6% (82); cetirizine, 10 mg, 9% to 25% versus 6% (83).

Although the lower dose (5 mg) of cetirizine is no more sedating than placebo (83), it has been shown that, if allowed, more than 80% of cetirizine users will titrate the dose upward, to achieve symptom relief (84).

After repeated dosing, some patients may become tolerant of the sedating effects of antihistamines (85). However, it is unwise to depend upon tolerance to abolish the antihistamine-

induced sedation and performance impairment that commonly occurs for at least 1 week after the medication is started (86). It is generally agreed that tolerance is a highly idiosyncratic phenomenon that is not universal, complete, or predictable. Virtually all antihistamines are equally effective in relieving allergy symptoms (see "Efficacy" section). Consequently, before recommending a particular antihistamine, physicians must weigh the benefits of that agent against its drawbacks. The lower cost of the older "sedating" antihistamines, and their general availability without prescription, may argue in their favor, but their use can no longer be recommended. The nonsedating agents offer the potential long-term benefits of safety and improved performance at work or in school compared to sedating antihistamines, and greater therapeutic compliance owing to their longer half-life and the need for less frequent dosing (81, 82).

Consequences of CNS effects. Unfortunately, one's subjective sense of sleepiness or impairment is an unreliable gauge of whether it is safe to operate heavy machinery while taking sedating antihistamines. This is because impairment can occur without the patient's awareness (87, 88). These factors have important safety implications in areas such as building construction, manufacturing, public transportation, and automobile driving. Simulated and real-life driving studies verify that these agents can impair performance significantly (87, 89, 90). In one study, lane weaving by drivers given triprolidine 10 mg (sustained release), was comparable to that in persons with a blood alcohol level of 0.05%; moreover, at 3–4 h after drug use, the drivers stopped reporting any sense of being impaired (87) (Fig. 4). Another study found that the effects of a single 10-mg dose of cetirizine resembled those of alcohol (72 g/kg lean body mass), and that the

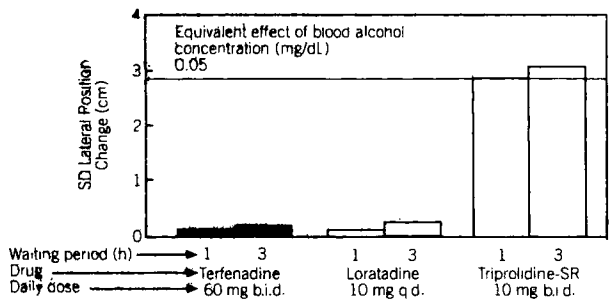

Fig. 4. Effect of sedating and nonsedating antihistamines on driving performance. This study measured effect of single doses of terfenadine (60mg), loratadine (10 mg), and triprolidine (10 mg controlled release form) on driver's ability to keep car within lane boundaries. Specific parameter measured was change in lateral position (lane weaving) at 1 and 3 h after dosing, SD = standard deviationSR=sustained release.

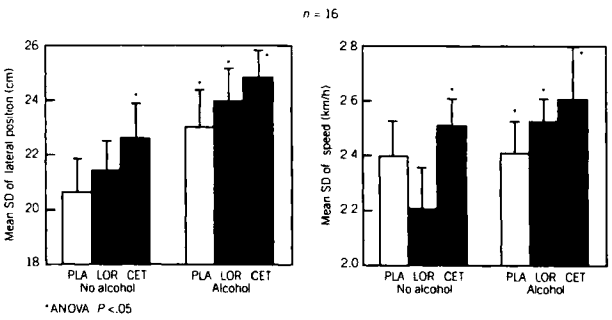

Fig. 5. Effect of antihistamines and alcohol on driving performance. This study measured effect of single doses of loratadine (10 mg) and cetirizine (10 mg), with and without alcohol, on actual driving in healthy volunteers. Parameters measured were changes in lateral position (lane weaving) and speed maintenance over 100-km highway circuit. CET: cetirizine; LOR: loratadine; PLA: placebo; SD: standard deviation. (Adapted with permission from Ramaekers et al. 1992.)

impairment appeared to be greater when alcohol and cetirizine were taken together (91) (Fig. 5). By contrast, no psychomotor deficits have been observed in drivers given loratadine (87, 91), or in individuals tested while taking astemizole (92); nor does the use of alcohol with these agents produce an additive effect. Studies have also shown that terfenadine did not impair psychomotor performance or reaction time (65), and that ebastine at 10, 20, or 30 mg given for 5 days did not impair driving performance compared to triprolidine 10 mg (93).

Besides causing psychomotor problems, sedating antihistamines also adversely affect cognition and functional performance (6, 88, 94, 101), compromising sustained attention and cerebral processing speed in adults (97) and children (95). The effects of nonsedating agents on somnolence, cognition, and performance, by contrast, are comparable to those of placebo (70, 95, 96, 102). Specific findings to date include the following:

- *performance on a digit symbol substitution test* – impaired by diphenhydramine (50 mg t.i.d.), but not by loratadine (10 mg q.d. and 40 mg q.d.) (99)
- *visual/motor coordination* – impaired by promethazine, chlorpheniramine, and clemastine, but not by terfenadine (101, 115)
- *clerical skills* – 8/12 skills impaired by diphenhydramine; none by loratadine (96)
- *learning in children with seasonal rhinitis* – impaired by diphenhydramine (50 mg) compared to nonallergic, unmedicated children, with the impairment in allergic children offset partly by loratadine (10 mg) (6).

Nonallergic, unmedicated children performed significantly better on tests of learning ability than atopic children given placebo, diphenhydramine, or loratadine; performance among atopic children was

best among subjects receiving loratadine and worst among those receiving diphenhydramine. This suggests that the learning problems associated with allergy are augmented by sedating antihistamines and offset somewhat by nonsedating agents.

Cardiovascular effects. Two nonsedating agents – terfenadine and astemizole – have been found to cause malignant ventricular arrhythmias, such as torsades de pointes (103, 104), when patient factors or drug interactions result in greatly elevated serum drug levels (105, 106). Although rare, these phenomena can delay cardiac repolarization and prolong the QT interval through blockage of a K rectifier channel, resulting in possible sudden death. At least 11 case reports involving 20 patients have been published in which patients taking astemizole experienced torsades de pointes, QT prolongation, and sometimes other cardiac effects (67). Eight such reports affecting 22 patients have appeared for terfenadine (67). Acrivastine, cetirizine, fexofenadine and loratadine appear to be the least likely of the newer antihistamines to be arrhythmogenic (67). The risk of cardiac arrhythmias can be minimized by reviewing the medical and pharmacologic risk factors for torsades de pointes *before* prescribing terfenadine or astemizole for any individual. Drug interactions associated with the potential for cardiotoxicity are a major concern of clinicians, as patients frequently fail to report all of the medications they are taking. Concomitant administration of certain antifungal agents (especially ketoconazole and itraconazole) or macrolide antibiotics (particularly erythromycin), along with terfenadine or astemizole, inhibit metabolism of these two antihistamines through competition for hepatic P450 enzymes. This results in increased plasma concentrations of these antihistamines. Coadministration of terfenadine or astemizole in users of such medications is thus strictly contraindicated. Hepatic dysfunction and preexisting cardiovascular disease also are risk factors for cardiovascular complications with these antihistamines.

Because the causes of QT prolongation are additive (106), patients with more risk factors have a potentially greater chance of developing ventricular arrhythmias while taking either terfenadine or astemizole. The use of these drugs *at recommended doses* without the aforementioned concomitant medications by patients *lacking known risk factors* carries a low risk of an adverse cardiac event. Still, such low-risk patients taking terfenadine or astemizole should be warned not to increase antihistamine doses without consulting their physician.

Drug interactions

Cytochrome P450 enzymes are responsible for the metabolism of many drugs. All of the currently available nonsedating antihistamines are metabolized by the cytochrome P450 hepatic enzyme system. Cytochrome P450 3A4 is involved in the metabolism of terfenadine, and erthromycin attenuates the metabolic effect of CYP3A4. Loratadine is metabolized primarily by CYP3A4 and secondarily by CYP2D6.

Other considerations. Side-effects involving the digestive tract (e.g., loss of appetite, nausea, vomiting, epigastric distress, and constipation or diarrhea) are among the most common for all antihistamines. Many of the older agents are associated with significant anticholinergic or antimuscarinic side-effects, such as dryness of the mouth and respiratory passages, urinary retention or frequency, palpitation, blurred vision, hypotension, headache, and tingling or weakness of the hands (58). Use of astemizole can cause weight gain. In a comparative trial with loratadine, weight gain was significantly greater with astemizole ($P<0.012$) (72). This side-effect may argue against astemizole's use in selected individuals.

Oral decongestants

Nasal blockage is a major factor in perennial rhinitis, and a possible incitement to related airway disorders such as OME and chronic sinusitis. Topical steroids are the agents of choice for nasal blockage (see subsequent section, "Intranasal steroids"); however, leukotriene antagonists or oral decongestants also control this symptom. Examples of the last class of agents include pseudoephedrine, phenylpropanolamine, and phenylephrine. These α-adrenergic agonists constrict blood vessels supplying the nasal mucosa, thereby decreasing congestion; they do not control the itching, sneezing, or rhinorrhea associated with upper-respiratory allergies. When such symptoms coexist with significant blockage, optimal management requires the use of intranasal steroids. Another option is a combination decongestant/antihistamine medication (see next section).

α-Adrenoreceptor agonists are stimulatory agents that constrict vascular beds throughout the body, not just in the nose. This raises the potential for significant systemic side-effects – e.g., hypertension, palpitations, tachycardia, and extrasystole, as well as restlessness, insomnia, and headache. As side-effects are dose-related, clinicians must choose the prescribed dosage carefully to prevent aggravating or "unmasking" hypertension. Patients should

be cautioned against increasing dosages on their own. As a rule, oral decongestants should be avoided in patients who have cardiovascular disease, thyrotoxicosis, glaucoma, or diabetes.

Antihistamine/decongestant combinations

Medications that combine an antihistamine with a long-acting oral decongestant offer another option for managing nasal blockage. The value of this practice has been proven in trials using formulations containing pseudoephedrine and either loratadine (107), acrivastine (108), or chlorpheniramine (109). Such combinations may be especially beneficial for patients at risk of chronic, allergen-induced eustachian tube obstruction, a condition that may favor the development of OME (109). Combined antihistamine/decongestants can provide greater overall symptom relief than possible with either agent alone (107, 108), though the tradeoff may be a higher incidence of adverse events (110). Nevertheless, combination agents decrease the number of drugs patients must take, a fact which may facilitate therapeutic compliance in selected individuals.

Oral corticosteroids

Oral corticosteroids and systemic injected depot preparations carry a high risk of systemic side-effects. Consequently, the only justification for their use in chronic rhinitis is to improve nasal patency in patients with severe or urgent blockage, so that topical therapy can proceed. Even then, systemic steroids should be given only by a specialist, and only to patients who lack contraindications to their use. These agents generally should not be used in children or pregnant women. A course of systemic steroids may be needed to gain control of nasal polyps, after which the patient can be managed with topical steroids (44). In addition, oral corticosteroids can rapidly relieve anosmia associated with polyps and, by opening the nasal passages, facilitate the access of locally acting nasal corticosteroids.

Alternate-day dosing may improve the risk/benefit ratio of oral corticosteroids, but studies proving this point have yet to be undertaken.

Topical nasal sprays

Various topical agents are now available for relieving the symptoms and, in some cases, addressing the underlying pathology, of chronic rhinitis. The benefits, appropriate usage, and drawbacks of specific agents are discussed in this section. General limitations of topical treatments are reviewed in Table 5.

Table 5. Limitations of topical agents

The value of any topical agent in the treatment of allergic or nonallergic rhinitis syndrome may be limited by several factors:

Physical anomalies. Severe septal deviation or enlarged turbinates may impede direct delivery of topical agents to the nasal mucosa.

Poor therapeutic compliance. Compliance studies have shown that patients generally prefer taking pills to using medicinal sprays (50).

Slow therapeutic onset. In the case of intranasal steroids and cromolyn sodium, a slower onset of action may leave some patients frustrated and noncompliant.

Patient handicaps. In particular, children and elderly persons may find it difficult to aim sprays or manipulate inhalers.

Intranasal steroids

Intranasal steroids can relieve most of the symptoms of seasonal and perennial allergic rhinitis (112–117). They are more effective than cromolyn sodium (17). Intranasal steroids are probably the most effective drug for all symptoms but they are particularly effective on nasal blockage (117–119).

Topical steroids are the agents of choice for relieving nasal blockage. They permit direct delivery to the nasal mucosa, thus minimizing systemic side-effects. The following specific actions are noteworthy:

- inhibition of both the early and late hypersensitivity response to allergens (111)
- reduction of the number of eosinophils in the nasal mucosa (112, 113)
- substantial inhibition of the nasal secretory response (114)
- reduction of mast cells and T cells
- desensitization of nasal irritant receptors (114).

Appropriate use. Intranasal steroids may be used to:

- relieve seasonal or perennial allergic rhinitis, when the main complaint is moderate to severe nasal blockage
- treat NARES (only effective therapy at present)
- shrink small nasal polyps, or manage patients with polyps once control is gained through a course of oral steroids (44)
- prevent polyp recurrence after surgery
- reduce the risk of chronic sinusitis, OME, or bronchial asthma in allergic patients with a history of these complications.

Drawbacks. Side-effects of intranasal steroids are generally minor and local, e.g., irritation, burning, and reactive sneezing, which usually disappear after several days; and nasal dryness followed by blood-stained crusts (124). In rare cases, treatment has to be stopped due to epistaxis. A few reports of septal perforation following intranasal steroid use have been published (124, 125). Some adverse

effects (e.g., mucosal drying) can be avoided by using sprays with an aqueous base.

The risk of systemic side-effects is very small, with one published report of a posterior cataract after intranasal steroid use and one report of children's growth being inhibited while taking an adult dose of budesonide (124). It is prudent to use the lowest efficacious dose in children and pregnant women (124).

Once-daily usage probably is sufficient for all glucocorticoids if the nose is patent and dry when the spray is used (124). Some patients or agents may require multiple daily dosing, however, or multiple sprays per nostril.

Patients should be informed that onset of action is delayed compared with that of antihistamines and decongestants, and requires a few days for patients with seasonal allergic rhinitis (124).

Many patients are reluctant to use steroids in any form, and parents may be especially hesitant to sanction their use in children. Individuals should be reassured that intranasal steroids are much safer than oral corticosteroids and that the former should not be equated with the latter.

Antiallergic drugs

Cromolyn sodium

This anti-inflammatory agent has been proved safe and effective for the treatment of allergic rhinitis (126, 127), although in one comparative study (17) it proved less effective than intranasal corticosteroids. Owing to its control of both early- and late-phase hypersensitivity responses, cromolyn can relieve nasal itching, sneezing, hypersecretion, and nasal blockage. Its need for frequent administration (four to six times daily [126], with possible reduction to two to three times daily in periods of low antigen load [127]), may impede therapeutic compliance.

Appropriate use. Cromolyn sodium is best used for the prevention of allergic symptoms. Given its wide safety margin, it often is prescribed for elderly patients, children, and pregnant women with seasonal or perennial allergies. It has virtually no utility in nonallergic rhinitis syndromes. The ocular formulation of cromoglycate is very effective in controlling eye symptoms.

Nedocromil sodium

Like cromolyn, nedocromil sodium controls both the early- and late-phase allergic reaction. Unlike cromolyn, nedocromil can both prevent an allergic reaction and control a reaction in progress (126). Nedocromil has significantly improved symptoms of rhinorrhea, congestion, itching, and sneezing (126). It is about 10 times more potent than cromolyn sodium. Recommended dosing is two to four times daily (126).

Appropriate use. Like cromolyn, nedocromil sodium is very effective at blocking symptoms when used immediately prior to an anticipated allergen exposure (126).

Topical antihistamines

Both nasal challenge studies (128, 129) and those involving seasonal exposures (130) indicate that topical antihistamines can inhibit allergen-induced nasal symptoms, including sneezing and rhinorrhea. Side-effects are local – e.g., stinging and itching in the nose and, occasionally, the throat – with the incidence ranging from 7% to 30% of patients (128–131). Azelastine has been shown to lessen nasal blockage, although reported side-effects include burning in the nose and altered taste (132). The lack of major improvement in nasal blockage (128, 129) in some other studies, however, suggests that congestion entails more than the direct effect of histamine on receptors on the capacitance vessels of the nasal mucosa.

Levocabastine is a potent antihistamine available as nasal spray and eye-drops. Minute amounts applied topically are sufficient to result in an antiallergic effect.

Appropriate use. On the basis of their safety profile, topical antihistamines may be used to relieve ocular or nasal symptoms in patients with mild to moderate seasonal allergies. When patients have severe ocular symptoms, specific topical preparations for ocular application should be used. Azelastine (133) and levocabastine (134, 135), for example, have been found to be nonsedating.

Decongestant sprays

Topical nasal decongestants constrict the smaller arterioles of the nasal passages, thus reducing blood flow and relieving mucosal edema. These agents can relieve nasal congestion rapidly and effectively, and generally are available without a prescription. This probably explains their popularity among patients with perennial forms of allergic or nonallergic rhinitis. Unfortunately, the overuse of decongestant sprays can cause rebound nasal congestion and rhinitis medicamentosa. Moreover, like oral sympathomimetics, topical sprays are associated with systemic side-effects such as cardiac arrhythmias and exacerbation of hypertension (136). Thus,

patients who overuse decongesting nose-drops should be assessed for hidden allergic nasal disease.

Appropriate use. The primary use for topical decongestants in chronic rhinitis is to open severely blocked nasal passages, so that slower acting drugs (e.g., cromolyn or intranasal steroids) can reach the necessary nasal passages to provide ongoing symptom control. Their potential for causing rebound congestion is such, however, that these agents should *never be used for more than 3 consecutive days.*

Intranasal anticholinergics

Ipratropium bromide, an anticholinergic drug, acts on the glandular cholinergic receptors in the nose to control excessive watery rhinorrhea (137). Rhinorrhea generally improves within 30 min, and remains in check for 8–12 h. There is no improvement, however, in nasal blockage, sneezing, or itching.

Nasal dryness, the main local side-effect of topical anticholinergics, may be alleviated by adjusting the dose. Although rarely required, high doses of these agents may cause systemic side-effects.

Appropriate use. Intranasal anticholinergics may be used to relieve the excessive rhinorrhea associated with allergic or nonallergic rhinitis syndromes – e.g., gustatory or idiopathic rhinitis ("skier's nose"). The latter, perennial form of rhinitis entails little if any nasal blockage, and tends not to respond to other treatments. Intranasal anticholinergics also may help relieve the rhinorrhea associated with common colds (138).

Wetting agents

Various symptoms of perennial rhinitis – e.g., nasal stuffiness, sneezing, rhinorrhea, and nose-blowing – may improve with the use of saline or propylene-and-polyethylene glycol sprays. In one trial, patients also showed decreased eosinophil counts with propylene-and-polyethylene glycol spray (139). Symptom amelioration also may be accompanied by an improvement in nasal airway resistance and nasal biopsy findings (139). Although wetting agents act slowly, their lack of side-effects makes them attractive therapeutic options for some patients.

Appropriate use. Wetting agents are indicated for the relief of mucosal irritation or dryness, the prevention of mucosal atrophy, and the removal of encrusted or thickened mucus. They also may be used immediately before intranasal steroid dosing, to prevent or mitigate drug-induced local side-effects.

Management of poor responders

When the use of any of these medications results in poor control of chronic rhinitis, physicians have several options:

- *Determine whether there has been therapeutic noncompliance.* If so, try to ascertain the reason – e.g., poor symptom control, inconvenient dosing schedule, high medication cost. Once the cause is known, engage the patient in therapeutic decision-making, as this may enhance treatment satisfaction and compliance.
- *Adjust drug doses.*
- *Try one or two other therapeutic agents.*
- *Consider combination therapy.* See section below, "Principles of combination therapy".
- *Investigate whether allergen exposure has increased.*
- *Reconsider the diagnosis.* For example, consider whether the patient may have an immune system defect (e.g., IgA deficiency).
- *Re-evaluate the patient for structural defect of the nose.*
- *Re-evaluate the patient for complications of allergic rhinitis.* Likely complications include asthma, chronic sinusitis, nasal polyps, and OME.
- *Review environmental control measures.*
- *Refer the patient to a rhinitis specialist.*

Principles of combination therapy

Two or more antiallergy medications may be prescribed if a single agent fails to relieve adequately a patient's symptoms. Combination therapy generally is indicated in the following situations.

When symptoms are moderately severe, severe, or diverse

Patients with severe nasal symptoms often benefit from taking both an antihistamine/decongestant *and* a topical nasal steroid. When patients have severe ocular symptoms, specific topical preparations for ocular application should be used. In a study comparing solo and combined drug use in patients with seasonal rhinoconjunctivitis, Juniper et al. found that a) nasal symptoms responded better to beclomethasone alone than to astemizole monotherapy, b) ocular symptoms were relieved more effectively by astemizole alone than by beclomethasone monotherapy, and c) the combination provided the best relief of ocular symptoms (121).

When symptoms are intense or long-lasting

Patients who suffer from perennial rhinitis with seasonal exacerbations may benefit from using intranasal steroids on a continual basis and employing "rescue" antihistamines as needed.

When rhinitis is complicated by a concomitant illness

Persons with allergic rhinitis and asthma might require a nasal corticosteroid *and* a bronchodilator to control their upper and lower airway problems.

Rationale for immunotherapy

Reliance on specific immunotherapy (SIT) varies from country to country. Physicians in the south of Europe are more inclined to offer SIT, while a decreasing number of patients receive this therapy in Scandinavia and the UK (141).

Immunotherapy used to be viewed as indicated only for patients responding inadequately to, or developing side-effects from, drug therapy (141). Current recommendations are to consider SIT for a broader range of patients (see Table 6). SIT, unlike pharmacotherapy, modifies the immune system and plays a preventive role in asthma development. It is used in conjunction with drug therapy but should reduce the need for symptomatic pharmacotherapy. The efficacy of SIT for grass pollen, ragweed pollen, and house-dust mites is very well established (141, 142). Results are best when the patient has a single allergic sensitivity rather than allergies to multiple substances. It must be stressed, however, that SIT should be undertaken only by physicians working in facilities equipped to handle possible adverse reactions (urticaria, laryngeal edema, bronchospasm, and anaphylaxis). Although its safety under these conditions is good, a careful risk/benefit analysis is required for each patient before injections commence.

Some experts believe that children may be especially responsive to SIT (142). Although childhood allergies show a strong tendency toward spontaneous improvement, SIT may hasten this effect in a greater percentage of cases. Disagreement exists, however, about the age at which SIT may be started (141, 142).

Noninjective immunotherapy is another option to consider. Nasal, sublingual, and oral immunotherapy have been demonstrated to be safe and effective (143). Perhaps the most encouraging thing about SIT is that it holds out the possibility – at present, more than conventional pharmacologic therapy – of "curing" seasonal allergies and even preventing the progression to asthma (141, 142).

Table 6. Specific immunotherapy for allergic rhinitis (142)

Indications
• Evidence of IgE-mediated disease, with allergens as the likely major triggers
• Patients with rhinitis or asthma caused by allergens for which the clinical efficacy and safety of SIT have been documented by placebo-controlled, double-blind studies
• Patients requiring daily pharmacotherapy for longer periods (e.g., preventive treatment during a pollen season or perennially)
• Inadequacy of drug therapy or intolerable side-effects
• Inability of patient to avoid allergen
• Lack of symptom control with appropriate observation of avoidance measures
• Seasonal allergies for 2 consecutive years
• Perennial allergies of at least 6 months' duration
• Limited number of allergen sensitivities (1–2 preferably)
• Compliant patient
Contraindications
• Concurrent therapy with drugs likely to impede treatment of anaphylaxis (e.g., β-blockers or other adrenergic blockers)
• Contraindication to adrenaline (epinephrine)
• Significant medical or immunologic disease
• Multiple allergies
• Lack of suitable allergen extracts
• Uncontrolled asthma (except in UK, where immunotherapy is not indicated in asthma)
• Noncompliant patient

Diagnosis and treatment in special populations

Children

A variety of genetic and environmental factors favor the development of respiratory allergies in children (Table 7). Allergy should be considered in the differential diagnosis when children have asthma, IgE levels exceeding 100 IU/ml at age 6, or a maternal history of allergy (11). These were found on logistic regression to be risk factors for development of allergic rhinitis by age 6 in the Tucson Children's Respiratory Study, which followed 747 healthy children from birth to age 6 (11). Presence of dogs as household pets and serum IgE exceeding 100 IU/ml were significant risk factors for development of atopic (*vs* nonatopic) allergic rhinitis (11). Wheezing in infancy usually implies no increased risk of asthma or allergies, but for the minority (14%) of children in whom wheezing persists at age 6, this symptom may signal a predisposition to asthma (144). A prospective study following 826 children from birth to age 6 years found that risk factors for persistent wheezing were elevated serum IgE at 9 months old and a maternal

Table 7. Risk factors for development of childhood allergies

Risk factor	Comment
Genetics	
Positive family history of allergy (11, 142)	Maternal history of physician-diagnosed allergy: significant risk of development of allergic rhinitis (11). Positive family history: significant risk of development of allergic symptoms, asthma, and eczema (145)
Birth factors	
Male sex	Significant for asthma and positive skin prick test (142)
Maternal smoking	Significant for asthma (145). Mother smoking pack or more of cigarettes a day in the child's first year of life means significant risk of onset of allergic rhinitis at <6 months (11)
Birth weight <2.5 kg	Significant for allergic symptoms, asthma, food tolerance, positive skin prick test (145)
Season of birth	Spring, summer, autumn birth, significant risk of development of asthma. Autumn birth, significant risk of development of allergic rhinitis (145)
Pollen	
Pet dander	Significant for allergic rhinitis in one study (11); presence of cats or dogs nonsignificant for risk of respiratory allergies in another study (145)
Mold spores	
House-dust mites	Exposure >10 μg/ml Der p 1/g before age 1 year, especially for asthma (risk raised ~fivefold)
Cockroaches	
Latex	In hospital settings
Family factors	
Low socioeconomic status	Significant for development of allergic rhinitis (145)

Sources: Wright et al. (11), Report of BSACI (142) and Sporik R, Holgate ST, Platts-Mills TAE, Cogswell JJ. Exposure to house-dust mite allergen (*Der p* I) and the development of asthma in childhood. N Engl J Med 1990;323:502-7.

history of asthma (144). Preventive therapy may be especially relevant for these children. Special concern is also indicated for those with severe or persistent nasal polyps. Such children should be referred to a specialist, as polyps in the very young may be associated with cystic fibrosis or primary ciliary dyskinesia.

Allergen avoidance

Environmental control assumes particular importance in children with allergic rhinitis, as considerable evidence shows that chronic respiratory symptoms are associated with significant early exposure to allergens (11, 145). The Tucson Children's Respiratory Study of 747 6-year-olds found that 42% had allergic rhinitis, and half of them had been diagnosed with this condition in their first year of life (11). Accordingly, it is important to instruct parents about environmental control measures and the need to implement them early in the course of their child's disease. Early avoidance not only improves symptoms, but also may affect the natural history of nasal allergy and related disorders such as OME. Moreover, if implemented aggressively at home, it has the added benefit of possibly preventing similar allergies in any siblings that the patient may have.

Pharmacotherapy

When drug therapy is needed, a conservative approach to selection is warranted. Nonsedating oral antihistamines are a good choice for children, owing to their lack of CNS side-effects and ease of use. Moreover, once- or twice-daily administration eliminates the need for dosing during school hours. Pediatric formulations of the nonsedating antihistamines generally are available throughout Europe.

Cromolyn sodium, nedocromil, or intranasal steroid sprays, although safe and effective, may be difficult for small children to use. This can lead to compliance problems. Moreover, cromolyn must be dosed at least four times a day, whereas nedocromil is used twice a day. Intranasal steroids usually are given at half the adult dose, once daily in the morning. As a rule, systemic steroids and topical vasoconstrictors should be avoided in very young children.

The elderly

Perennial rhinitis in the elderly is generally idiopathic in nature (42), with the underlying cause being autonomic imbalance, alteration in muscarinic receptors, or the sequelae of previously treated nasal disorders. Almost invariably, the only symptom of nasal hyperresponsiveness in older persons is profuse rhinorrhea. Treatment with ipratropium bromide, an anticholinergic drug, has been shown to be effective in some cases (146).

For elderly persons with true allergic rhinitis, treatment plans must take into account age, concomitant illnesses, and the use of other pharmacologic agents. Nonsedating topical or oral antihistamines are a reasonable choice for this population. Older antihistamines are best avoided, not only because of their sedative properties, but also because of the potential for urinary retention, problems with visual accommodation, and CNS impairment. Because of their sympathomimetic effects, oral vasoconstrictors (e.g., phenylephrine, phenylpropanolamine, or pseudoephedrine) are generally contraindicated or need to be used with considerable caution in patients with diseases that frequently occur in the elderly such as hypertension,

coronary artery disease, diabetes, glaucoma, or prostate hypertrophy. Finally, elderly patients may require lower doses of certain antihistamines owing to slowed hepatic metabolism. Moreover, because they often take multiple prescription and nonprescription medications, the elderly also run a greater risk of drug interactions than most other patients.

Pregnant women

Pregnancy-associated hormones affect the nasal mucosa, and may indirectly affect the nose through increasing circulating blood volume (146). As a result, some women with allergic rhinitis experience an exacerbation of symptoms, especially congestion, during pregnancy. This phenomenon generally starts toward the end of the first trimester and resolves rapidly after parturition. Other women experience the apparent onset of allergic rhinitis during pregnancy (147).

Although pharmacologic agents may help control nasal symptoms in pregnant women, clinicians should prescribe them cautiously, bearing the following facts in mind:

- Despite its probable safety in pregnant women, clinical experience with loratadine is still relatively limited.
- The safety of diphenhydramine remains uncertain (148).
- All oral antihistamines are excreted in breast milk.
- In the USA, pseudoephedrine is approved for use in pregnancy at recommended dosages, and is widely prescribed in this population.
- Owing to their overall safety, saline wetting agents and cromolyn sodium may be used to relieve congestion during pregnancy. In some European countries, topical antihistamines are recommended for the treatment of allergic rhinitis during pregnancy (149).
- If cromolyn proves ineffective, intranasal steroids may be tried. Their use at recommended doses has not been associated with teratogenicity or other adverse effects in pregnant women (38).

Unfortunately, nasal congestion in pregnant women is often refractory to medical therapy. In such cases, patients may obtain some relief by using an external nasal dilator and saline douches. Under no circumstances should immunotherapy be started during pregnancy, though continuation of maintenance doses is safe (38).

Athletes

Physical exercise causes vasoconstriction that lasts for about 1 h after exertion stops. However, endurance athletes (e.g., long-distance runners or cyclists) may experience long-lasting rebound congestion after a brief period of improved nasal patency. This rebound effect may impair athletic performance.

When managing allergic rhinitis in competitive athletes, physicians must be careful to avoid prescribing medications with doping properties or therapy that may adversely affect performance. Nonsedating antihistamines and topical steroids are generally the best choices for serious athletes. The International Olympic Committee and other international regulatory authorities prohibit sympathomimetic decongestants (e.g., phenylpropanolamine and pseudoephedrine). In large enough quantities, these agents can act as psychostimulants as strong as *d*-amphetamine. Immunotherapy is recommended for athletes who wish to avoid being dependent on anti-allergy medications, though discomfort at the injection site may impede physical performance for several days at a time.

Patient education and therapeutic compliance

The successful management of chronic rhinitis depends greatly on how well patients cooperate with the therapeutic program. Educating patients about their disease and its management can promote that cooperation. It has been shown, for example, that allergic symptoms can be well controlled and a reasonable quality of life maintained when patients are given the appropriate medications, education, and written instructions *before* the pollen season commences (150).

Specifically, patients benefit from knowing or understanding the following:

- *How and why rhinitis develops.*
- *Simple avoidance measures that can minimize exposure to allergens or rhinitis triggers.* The Appendix provides a handout about allergen control measures for patients in primary care.
- *Complications and related airway diseases that can develop from poor allergy control.* Patients who understand the scope of their disease are apt to take it seriously and thus comply better with therapy. This, in turn, may help minimize their risk of developing related airway diseases.
- *How specific medications work, and how to use nasal sprays correctly.* Patients must understand that antihistamines and intranasal steroids are most effective when taken on a regular basis and not as needed. For those who require two or more medications, an explanation of how each drug works provides a rationale for their use and may aid compliance.

- *The necessity for prophylactic medication.* Patients should be informed that early use of medication can prevent the onset of severe symptoms. Individuals with seasonal symptoms should start treatment at the outset of the spring or autumn seasons or in late summer. Those with perennial allergies need to take medication in advance of specific exposures – for example, before visiting a relative who keeps indoor pets.
- *The side-effects associated with prescribed medications.* Patients should be told about common side-effects of particular pharmacologic agents, and what to do in the event of their occurrence.
- *Possible drug interactions.* Patients should understand the importance of informing their physician of all the medications they are taking, both prescription and nonprescription. Because of the risk of torsades de pointes, this is especially vital for users of terfenadine or astemizole. For the same reason, patients taking either of the latter two agents should also be instructed not to increase the dosage without consulting their physician.
- *The appropriate use of topical decongestants.* The risks and consequences of overuse should be discussed.

Reinforcing educational points

Simply written instructions help to reinforce key messages. Still, clinicians should ascertain whether patients truly understand what they have been told. Consider having patients repeat instructions rather than merely asking whether everything is clear. Reviewing key points with patients during subsequent office visits is advisable, especially when therapeutic goals are not being met.

Patient compliance and satisfaction

Building a trusting alliance with patients is important in gaining their cooperation with therapy. In part, trust is established by attending to patients' concerns and preferences. Specifically, patients should be asked the following types of questions:

- How does rhinitis affect you daily?
- What medications or measures have you tried to reduce your symptoms?
- What do you expect from anti-allergy therapy?
- Do you anticipate any problems from treatment?
- Do you have any preferences in medications?

Asking patients about their opinions and experiences in these matters fosters empathy and trust, and so encourages compliance.

Other pathways to improved compliance include the following:

- Prescribing drugs with a longer half-life, so that less frequent dosing is possible.
- Choosing combination agents when more than one medication is needed to control symptoms.
- Selecting pharmacologic agents with few side-effects.
- Educating patients about their disease and its management (see prior section about patient education). For example, allergic patients who appreciate that poor compliance may increase the risk of asthma may be more motivated to follow pharmacologic and avoidance protocols.
- Selecting medications that target what the patient considers to be his or her most troubling symptoms.
- Impressing upon patients that compliance improves disease control and quality of life. Allergists and immunologists find that compliance can be good, even when patients are not symptomatic, because failure to take medications or practice avoidance guarantees the return of symptoms.

In conclusion, therapeutic intervention in allergic rhinitis aims to relieve symptoms, improve long-term outcome and quality of life, and encourage patient satisfaction with medical management. Patients who are compliant with therapy generally obtain better symptom relief and feel more satisfied with their care.

References

1. Marshall PS. Allergy and depression: a neurochemical threshold model of the relation between the illnesses. Psychol Bull 1993;113:23-43.
2. Marshall PS, Colon EA. Effects of allergy season on mood and cognitive function. Ann Allergy 1993;71:251-8.
3. Avner SE, Kinsman RA. Psychologic factors and allergic diseases. In: Bierman CW, Pearlman DS, editors. Allergic diseases from infancy to adulthood. Philadelphia, PA: WB Saunders, 1988:300-17.
4. Klein GL, Ziering RW, Girsh LS, Miller MF. The allergic irritability syndrome: four case reports and a position statement from the Neuroallergy Committee of the American College of Allergy. Ann Allergy 1985;55:22-4.
5. Sly RM. Allergy and school problems. In: Bierman CW, Pearlman DS, editors. Allergic disease of infancy, childhood and adolescence. Philadelphia, PA: WB Saunders, 1980: 746-50.
6. Vuurman EF, van Veggel LM, Uiterwijk MM, Leutner D, O'Hanlon JF. Seasonal allergic rhinitis and antihistamine effects on children's learning. Ann Allergy 1993;71:121-6.
7. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. Clin Exp Allergy 1991;21:77-83.
8. Juniper EF, Guyatt GH, Dolovich J. Assessment of quality of life in adolescents with allergic rhinoconjunctivitis: development and testing of a questionnaire for clinical trials. J Allergy Clin Immunol 1994;93:413-23.

9. Bousquet J, Bullinger M, Fayol C, Marquis P, Valentin B, Burtin B. Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire. J Allergy Clin Immunol 1994;94:182-8.
10. Sibbald B, Rink E. Epidemiology of seasonal and perennial rhinitis: clinical presentation and medical history. Thorax 1991;46:895-901.
11. Wright AL, Holberg CJ, Martinez FD, Halonen M, Morgan W, Taussig LM. Epidemiology of physician-diagnosed allergic rhinitis in childhood. Pediatrics 1994;94: 895-901.
12. Pollart SM, Chapman MD, Fiocco GP, Rose G, Platts-Mills TAE. Epidemiology of acute asthma: IgE antibodies to common inhalant allergens as a risk factor for emergency room visits. J Allergy Clin Immunol 1989;83:875-82.
13. Davis WE, Templer JW, Lamear WR, Davis WE Jr, Craig SB. Middle meatus antrostomy: patency rates and risk factors. Otolaryngol Head Neck Surg 1991;104:467-72.
14. Bernstein JM. The role of IgE-mediated hypersensitivity in the development of otitis media with effusion. Otolaryngol Clin North Am 1992;25:197-211.
15. Tomonaga K, Kurono Y, Mogi G. The role of nasal allergy in otitis media with effusion: a clinical study. Acta Otolaryngol (Stockh) 1988;458(suppl):41-7.
16. Anderson HR. Increase in hospital admissions for childhood asthma: trends in referral, severity, and readmissions from 1970 to 1985 in a health region of the United Kingdom. Thorax 1989;44:614-19.
17. Corren J, Adinoff AD, Buchmeier AD, Irvin CG. Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. J Allergy Clin Immunol 1992;90:250-6.
18. Watson WTA, Becker AB, Simons FER. Treatment of allergic rhinitis with intranasal corticosteroids in patients with mild asthma: effect on lower airway responsiveness. J Allergy Clin Immunol 1993;91:97-101.
19. Foresi A, Pelucchi A, Gherson G, Mastropasqua B, Chiapparino A, Testi R. Once daily intranasal fluticasone propionate (200 mg) reduces nasal symptoms and inflammation but also attenuates the increase in bronchial responsiveness during the pollen season in allergic rhinitis. J Allergy Clin Immunol 1996;98:247-82.
20. Naclerio RM. Allergic rhinitis. N Engl J Med 1991;325: 860-9.
21. Naclerio RM, Proud D, Peters S, Sobotka AK, Lichtenstein L, Norman P. The role of inflammatory mediators in allergic rhinitis. Ear Nose Throat J 1986;65: 206-12.
22. Connell JT. Quantitative intranasal pollen challenges. III. The priming effect in allergic rhinitis. J Allergy 1969;43: 33-44.
23. Weller PF. The immunobiology of eosinophils. N Engl J Med 1991;342:1110-18.
24. Altman LC, Gleich GJ. Eosinophils. Immunol Allergy Clin North Am 1990;10:263-71.
25. Yukawa T, Read RC, Kroegel C, et al. The effects of activated eosinophils and neutrophils on guinea pig epithelium *in vitro*. Am J Respir Cell Mol Biol 1990;2:341-53.
26. Cook RM, Ashworth FR, Musgrove NRJ. Eosinophil- and neutrophil-mediated injury of human lung fibroblast cells. Int Arch Allergy Appl Immunol 1987;139:428-31.
27. Vignola AM, Crampette L, Mondain M, et al. Inhibitory activity of loratadine and descarboethoxyloratadine on expression of ICAM-1 and HLA-DR by nasal epithelial cells. Allergy 1995;50:200-3.
28. Montefort S, Feather IH, Wilson SJ, et al. The expression of leukocyte-endothelial adhesion cells is increased in perennial allergic rhinitis. Am J Respir Cell Mol Biol 1992;7:393-8.
29. Wegner CD, Gundel RH, Reilly P, Haynes N, Letts LG, Rothlein R. Intercellular adhesion molecule-1 (ICAM-1) in the pathogenesis of asthma. Science 1990;247:456-9.
30. Djukanovic R, Roche WR, Wilson JW, et al. Mucosal inflammation in asthma. Am Rev Respir Dis 1990;142: 434-57.
31. Ciprandi G, Pronzato C, Ricca V, Bagnasco M, Canonica GW. Evidence of intercellular adhesion molecule-1 expression on nasal epithelial cells in acute rhinoconjunctivitis caused by pollen exposure. J Allergy Clin Immunol 1994;94:738-46.
32. Ciprandi G, Buscaglia S, Pesce G, et al. Minimal persistent inflammation is present at mucosal level in patients with asymptomatic rhinitis and mite allergy. J Allergy Clin Immunol 1995;96:971-9.
33. Greve JM, Davis G, Mejer AM, et al. The major human rhinovirus receptor is ICAM-1. Cell 1989;56:839-47.
34. Staunton DE, Merluzzi VJ, Rothlein R, Barton R, Marlin SD, Springer TA. A cell adhesion molecule, ICAM-1, is the major surface receptor for rhinoviruses. Cell 1989; 56:849.
35. Johnston SL, Pattemore PK, Sanderson G, et al. A longitudinal study of the role of viral infections in exacerbations of asthma in school children in the community. BMJ 1995; 310:1225-9.
36. Johnston SL, Pattemore PK, Sanderson G, et al. Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. BMJ 1995;310:1225-8.
37. Seminario MC, Squillace D, Bardin PG, Fraenkel DJ, Gleich GJ, Johnston SL. Increased levels of eosinophil, a major basic protein in nasal secretions in rhinovirus infection [Abstract]. J Allergy Clin Immunol 1995;95:259.
38. Lemanske RF Jr, Dick EC, Swenson CA, Vrtis RF, Busse WW. Rhinovirus upper respiratory infection increases airway hyperreactivity and late asthmatic reactions. J Clin Invest 1989;83:1-10.
39. Fraenkel DJ, Bardin PG, Sanderson G, Lampe F, Johnston SL, Holgate ST. Lower airways inflammation during rhinovirus colds in normal and in asthmatic subjects. Am J Respir Crit Care Med 1995;151:879-86.
40. International Rhinitis Management Working Group. International consensus report on the diagnosis and management of rhinitis. Allergy 1994;49 Suppl 19:1-34.
41. Moneret-Vautrin DA, Hsieh V, Wayoff M, Guyot JL, Mouton C, Maria Y. Nonallergic rhinitis with eosinophilia syndrome a precursor of the triad: nasal polyposis, intrinsic asthma, and intolerance to aspirin. Ann Allergy 1990;64: 513-18.
42. Lusk RP, Lazar RH, Muntz HR. The diagnosis and treatment of recurrent and chronic sinusitis in children. Pediatr Clin North Am 1989;36:1411-21.
43. Raphael G, Hauptschein Raphael M, Kaliner M. Gustatory rhinitis: a syndrome of food-induced rhinorrhea. J Allergy Clin Immunol 1989;83:110-15.
44. Jacobs RL. Nonallergic chronic rhinitis syndromes. Immunol Allergy Clin North Am 1987;7:93-103.
45. Platts-Mills TAE, Hayden ML, Chapman MD, Wilkins SR. Seasonal variation in dust mite and grass-pollen allergens in dust from the houses of patients with asthma. J Allergy Clin Immunol 1987;79:781-91.
46. Mabry RL. Rhinitis of pregnancy. South Med J 1986; 79:965-71.
47. Snyder RD, Snyder LB. Intranasal cocaine abuse in an allergist's office. Ann Allergy 1985;54:489-92.
48. Gupta OP, Bhatia PL, Agarwal MK, Mehrotra ML, Mishr SK. Nasal, pharyngeal, and laryngeal manifestations of hypothyroidism. Ear Nose Throat J 1977;56:349-56.
49. Edfors-Lubs M-L. Allergy in 7000 twin pairs. Acta Allergol 1971;26:249-85.

50. Fergusson DM, Horwood LJ, Shannon FT. Parental asthma, parental eczema, and asthma and eczema in early childhood. J Chron Dis 1983;36:517-24.
51. Gerrard JW, Vickers P, Gerrard CD. The familial incidence of allergic disease. Ann Allergy 1976;36:10-15.
52. Kelloway JS, Wyatt RA, Adlis SA. Comparison of patients' compliance with prescribed oral and inhaled asthma medications. Arch Intern Med 1994;154:1349-52.
53. Cohn JR, Pizzi A. Determinants of patient compliance with allergen immunotherapy. J Allergy Clin Immunol 1993;91: 734-7.
54. Spector SL. Is your asthmatic patient really complying? Ann Allergy 1985;55:552-6.
55. Corren J, Fourre J, Harris A. Treatment of allergic rhinitis with loratadine plus pseudoephedrine in patients with mild asthma: effects on lower airway symptoms and function. 1997 (in press).
56. Dijkman JH, Hekking PRM, Molkenboer JF, et al. Prophylactic treatment of grass pollen-induced asthma with cetirizine. Clin Exp Allergy 1990;20:483-90.
57. Rafferty P, Jackson L, Smith R, Holgate ST. Terfenadine, a potent histamine H_1- receptor antagonist in the treatment of grass pollen sensitive asthma. Br J Clin Pharmacol 1990; 30:229-35.
58. Garrison JC. Histamine, bradykinin, 5-hydroxytryptamine, and their antagonists. In: Goodman Gilman A, Rall TW, Nies AS, Taylor P, editors. Goodman Gilman's Pharmacological basis of therapeutics. 8th ed. Oxford: Pergamon Press, 1990:575-99.
59. Miadonna A, Milazzo N, Lorini M, Marchesi E, Tedeschi A. Inhibitory effect of the H_1 antagonist loratadine on histamine release from human basophils. Int Arch Allergy Immunol 1994;105:12-17.
60. Berthon B, Taudou G, Combettes L, et al. *In vitro* inhibition, by loratadine and descarboxyethoxyloratadine, of histamine release from human basophils, and of histamine release and intracellular calcium fluxes in rat basophilic leukemia cells (RBL-2H3). Biochem Pharmacol 1994;47:789-94.
61. Bousquet J, Lebel B, Chanal I, Morel A, Michel F-B. Antiallergic activity of H_1-receptor antagonists assessed by nasal challenge. J Allergy Clin Immunol 1988;82:881-7.
62. Eda R, Sugiyama H, Hopp RJ, Bewtra AK, Townley RG. Effect of loratadine on human eosinophil function *in vitro*. Ann Allergy 1993;71:373-8.
63. Eda R, Townley RG, Hopp RJ. Effect of terfenadine on human eosinophil and neutrophil chemotactic response and generation of superoxide. Ann Allergy 1994;73:154-60.
64. Naclerio RM. The effect of antihistamines on the immediate allergic response: a comparative review. Otolaryngol Head Neck Surg 1993;108:723-30.
65. Canonica GW, Ciprandi G, Pronzato C, et al. Topical azelastine reduces eosinophil activation and intercellular adhesion molecule expression on nasal epithelial cells: an antiallergic activity. J Allergy Clin Immunol 1997 (in press).
66. Ciprandi G, Pronzato C, Ricca V, Varese P, Del Giacco GS, Canonica GW. Terfenadine exerts antiallergic activity reducing ICAM-1 expression on nasal epithelial cells in patients with pollen allergy. Clin Exp Allergy 1995;25:871-8.
67. Passalacqua G, Bousquet J, Bachert C, et al. Position paper. The clinical safety of H_1-receptor antagonists. An EAACI position paper. Allergy 1996;51:666-75.
68. Schwartz JC, Arrang JM, Garbarg M, Pollard H, Ruat M. Histaminergic transmission in the mammalian brain. Physiol Rev 1991;71:1-51.
69. Horak F, Bruttmann G, Pedrali P, et al. A multicentric study of loratadine, terfenadine, and placebo in patients with seasonal allergic rhinitis. Arzneimittelforschung Drug Res 1988;38:124-8.
70. Kaliner MA, Check WA. Non-sedating antihistamines. Allergy Proc 1988;9:649-63.
71. Kemp JP, Bahna SL, Chervinsky P, et al. A comparison of loratadine, a new nonsedating antihistamine, with clemastine and placebo in patients with fall seasonal allergic rhinitis. Am J Rhinol 1987;1:151-4.
72. Chervinsky P, Georgitis J, Banov C, Boggs P, Vande Stouwe R, Greenstein S. Once daily loratadine versus astemizole once daily. Ann Allergy 1994;73:109-13.
73. Monroe EW. The role of antihistamines in the treatment of chronic urticaria. J Allergy Clin Immunol 1990;86:662-5.
74. Berman BA. Perennial allergic rhinitis: clinical efficacy of a new antihistamine. J Allergy Clin Immunol 1990;86: 1004-8.
75. Taytard A, Beaumont D, Pujet JC, Sapene M, Lewis PJ. Treatment of bronchial asthma with terfenadine: a randomised controlled trial. Br J Clin Pharmacol 1987;24:743-6.
76. Spector SL, Lee N, McNutt B, et al. Effect of terfenadine in asthmatic patients. Ann Allergy 1992;69:212-16.
77. Dirksen A, Engel T, Frølund L, Heinig JH, Svendsen UG, Weeke B. Effect of a non-sedative antihistamine (loratadine) in moderate asthma: a double-blind controlled clinical crossover trial. Allergy 1989;44:566-71.
78. Clee MD, Ingram CG, Reid PC, Robertson AS. The effect of astemizole on exercise-induced asthma. Br J Dis Chest 1984;78:180-3.
79. Spector SL, Nicodemus CF, Corren J, et al. Comparison of the bronchodilatory effects of cetirizine, albuterol, and both together versus placebo in patients with mild-to-moderate asthma. J Allergy Clin Immunol 1995;96:174-81.
80. Busse WW, Middleton E, Storms W, et al. Corticosteroid-sparing effect of azelastine in the management of bronchial asthma. Am J Respir Crit Care Med 1996;153:122-7.
81. Meltzer EO. Comparative safety of H_1-antihistamines. Ann Allergy 1991;67:625-33.
82. Physicians' desk reference. 49th ed. Montvale, NJ: Medical Economics Data, 1996.
83. Falliers CJ, Brandon ML, Buchman E, et al. Double-blind comparison of cetirizine and placebo in the treatment of seasonal rhinitis. Ann Allergy 1991;66:257-62.
84. DuBuske L. Dose-ranging comparative evaluation of cetirizine in patients with seasonal allergic rhinitis. Ann Allergy 1995;74:345-54.
85. Schweitzer PK, Muehlbach MH, Walsh JK. Sleepiness and performance during three-day administration of cetirizine or diphenhydramine. J Allergy Clin Immunol 1994;94:716-24.
86. Simons FER. H_1-receptor antagonists. Comparative tolerability and safety. Drug Safety 1994;10:350-80.
87. O'Hanlon JF. Antihistamines and driving performance: The Netherlands. J Respir Dis 1988;9 Suppl 7A:S12-S17.
88. Seidel WF, Cohen S, Bliwise NG, Dement WC. Cetirizine effects on objective measures of daytime sleepiness and performance. Ann Allergy 1987;59:58-62.
89. Volkerts ER, van Willigenburg APP, van Laar MW, Maes RAA. Does cetirizine belong to the new generation of antihistamines? An investigation into its acute and subchronic effects on highway driving, psychometric test performance and daytime sleepiness. Hum Psychopharmacol 1992;7:227-38.
90. Aso T, Sakai Y. Effects of terfenadine on actual driving performance. Jpn J Clin Pharmacol Ther 1988;19:681-8.
91. Ramaekers JG, Uiterwijk MMC, O'Hanlon JF. Effects of loratadine and cetirizine on actual driving and psychometric test performance, and EEG during driving. Eur J Clin Pharmacol 1992;42:363-9.
92. Hindmarch I, Bhatti JZ. Psychomotor effects of astemizole and chlorpheniramine, alone and in combination with alcohol. Int Clin Psychopharmacol 1987;2:117-19.

93. Brookhuis KA, De Vries G, De Waard D. Acute and subchronic effects of the H_1-histamine receptor antagonist ebastine in 10, 20, and 30 mg dose, and triprolidine 10 mg on car driving performance. Br J Clin Pharmacol 1993; 36:67-70.
94. Kemp JP, Buckley CE, Gershwin ME, et al. Multicenter, double-blind, placebo-controlled trial of terfenadine in seasonal allergic rhinitis and conjunctivitis. Ann Allergy 1985;54:502-9.
95. Simons FER, Reggin JD, Roberts JR, Simons KJ. Benefit/risk ratio of the antihistamines (H_1-receptor antagonists) terfenadine and chlorpheniramine in children. J Pediatr 1994;124:979-83.
96. Adelsberg BR, D'Amico-Beadon A. The effects of loratadine, diphenhydramine and placebo on worker productivity: results of a double blind trial [Abstract 560]. J Allergy Clin Immunol 1991;87:279.
97. Meador KJ, Loring DW, Thompson EE, Thompson WO. Differential cognitive effects of terfenadine and chlorpheniramine. J Allergy Clin Immunol 1989;84:322-5.
98. Gengo FM, Gabos C. Antihistamines, drowsiness, and psychomotor impairment: central nervous system effect of cetirizine. Ann Allergy 1987;59:53-7.
99. Roth T, Roehrs T, Koshorek G, Sicklesteel J, Zorick F. Sedative effects of antihistamines. J Allergy Clin Immunol 1987;80:94-8.
100. Nicholson AN, Smith PA, Spencer MB. Antihistamines and visual function: studies on dynamic acuity and the pupillary response to light. Br J Clin Pharmacol 1982;14:683-90.
101. Clarke CH, Nicholson AN. Performance studies with antihistamines. Br J Clin Pharmacol 1978;6:31-5.
102. Neves-Pinto RM, Moreira Lima G, da Mota Teixeira R. A double-blind study of the effects of loratadine versus placebo on the performance of pilots. Am J Rhinol 1992; 6:23-7.
103. Woosley RL, Chen Y, Freiman JP, Gillis RA. Mechanism of the cardiotoxic actions of terfenadine. JAMA 1993;269: 1532-6.
104. Nightingale SL. Warnings issued on nonsedating antihistamines terfenadine and astemizole. JAMA 1992; 266:705.
105. Honig PK, Wortham DC, Zamani K, Cantilena LR. Comparison of the effect of the macrolide antibiotics erythromycin, clarithromycin, and azithromycin on terfenadine steady-state pharmacokinetics and electrocardiographic parameters. Drug Invest 1994;7:148-56.
106. Stratmann HG, Kennedy HL. Torsades de pointes associated with drugs and toxins: recognition and management. Am Heart J 1987;113:1470-82.
107. Hébert J, Bédard P-M, Del Carpio J, et al. Loratadine and pseudoephedrine sulfate: a double-blind, placebo-controlled comparison of a combination tablet (SCH 434) and its individual components in seasonal allergic rhinitis. Am J Rhinol 1988;2:71-5.
108. Meran A, Morse J, Gibbs TG. A cross-over comparison of acrivastine, pseudoephedrine and their combination in seasonal allergic rhinitis. Rhinology 1990;28:33-40.
109. Stillwagon PK, Doyle WJ, Fireman P. Effect of an antihistamine/decongestant on nasal and eustachian tube function following intranasal pollen challenge. Ann Allergy 1987;58:442-6.
110. Henauer S, Seppey M, Huguenot C, Pécoud A. Effects of terfenadine and pseudoephedrine, alone and in combination in a nasal provocation test and in perennial rhinitis. Eur J Clin Pharmacol 1991;41:321-4.
111. Mygind N, Johnsen NJ, Thomsen J. Intranasal allergen challenge during corticosteroid treatment. Clin Allergy 1977;7:69-74.
112. Findlay S, Huber F, Garcia J, Huang L. Efficacy of once-a-day intranasal administration of triamcinolone acetonide in patients with seasonal allergic rhinitis. Ann Allergy 1992;68:228-32.
113. Storms W, Bronsky E, Findlay S, et al. Once daily triamcinolone acetonide nasal spray is effective for the treatment of perennial allergic rhinitis. Ann Allergy 1991; 66:329-33.
114. Wihl J-Å. Topical corticosteroids and nasal reactivity. Eur J Respir Dis Suppl 1982;122:205-10.
115. Fluticasone propionate nasal spray for allergic rhinitis. Med Lett 1995;37:5-6.
116. Orgel HA, Meltzer EO, Bierman CW, et al. Intranasal fluocortin butyl in patients with perennial rhinitis: a 12-month efficacy and safety study including nasal biopsy. J Allergy Clin Immunol 1991;88:257-64.
117. Beswick KBJ, Kenyon GS, Cherry JR. A comparative study of beclomethasone dipropionate aqueous nasal spray with terfenadine tablets in seasonal allergic rhinitis. Curr Med Res Opin 1985;9:560-7.
118. Salomonsson P, Gottberg L, Heilborn H, Norrlind K, Pegelow K-O. Efficacy of an oral antihistamine, astemizole, as compared to a nasal steroid spray in hay fever. Allergy 1988;43:214-18.
119. Munch EP, Søborg M, Nørreslet TT, Mygind N. A comparative study of dexchlorpheniramine maleate sustained release tablets and budesonide nasal spray in seasonal allergic rhinitis. Allergy 1983;38:517-24.
120. Frølund L. Efficacy of an oral antihistamine, loratadine, as compared with a nasal steroid spray, beclomethasone dipropionate, in seasonal allergic rhinitis. Clin Otolaryngol 1991;16:527-31.
121. Juniper EF, Kline PA, Hargreave FE, Dolovich J. Comparison of beclomethasone dipropionate aqueous nasal spray, astemizole, and the combination in the prophylactic treatment of ragweed pollen-induced rhinoconjunctivitis. J Allergy Clin Immunol 1989;83:627-33.
122. Wood SF. Oral antihistamine or nasal steroid in hay fever: a double-blind double-dummy comparative study of once daily astemizole vs twice daily nasal beclomethasone dipropionate. Clin Allergy 1986;16:195-201.
123. Mygind N. Local effect of intranasal beclomethasone dipropionate aerosol in hay fever. BMJ 1973;4:464-6.
124. Mygind N. Glucocorticosteroids and rhinitis. Allergy 1993; 48:476-90.
125. Soderberg-Warner ML. Nasal septal perforation associated with topical corticosteroid therapy. J Pediatr 1984;105:840-1.
126. Mabry RL. Topical pharmacotherapy for allergic rhinitis: new agents. South Med J 1992;85:149-54.
127. Schwartz HJ. The effect of cromolyn on nasal disease. Ear Nose Throat J 1986;65:449-56.
128. Holmberg K, Pipkorn U, Bake B, Blychert L-O. Effects of topical treatment with H_1 and H_2 antagonists on clinical symptoms and nasal vascular reactions in patients with allergic rhinitis. Allergy 1989;44:281-7.
129. Kolly M, Pécoud A. Comparison of levocabastine, a new selective H_1-receptor antagonist, and disodium cromoglycate, in a nasal provocation test with allergen. Br J Clin Pharmacol 1986;22:389-94.
130. Bende M, Pipkorn U. Topical levocabastine, a selective H_1-antagonist, in seasonal allergic rhinoconjunctivitis. Allergy 1987;42:512-15.
131. Mösges R, Spaeth F, Conrad F, Giani G. Azelastin in der allergologischeu praxis. HNO 1995;3:173-6.
132. Grossman J, Halverson PC, Meltzer EO, et al. Double-blind assessment of azelastine in the treatment of perennial allergic rhinitis. Ann Allergy 1994;73:141-6.

133. McTavish DB, Sorkin EM. Azelastine. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential. Drugs 1989;38:778-800.
134. Arriaga F, Rombaut N. Absence of central effects with levocabastine eye drops. Allergy 1990;45:552-4.
135. Rombaut N, Bhatti JZ, Curran S, Hindmarch I. Effects of topical administration of levocabastine on psychomotor and cognitive function. Ann Allergy 1991;67:75-9.
136. Kobayashi RH, Kiechel F III, Kobayashi ALD, Mellion MB. Topical nasal sprays: treatment of allergic rhinitis. Am Fam Physician 1994;50:151-7.
137. Mygind N, Borum P. Anticholinergic treatment of watery rhinorrhea. Am J Rhinol 1990;4:1-5.
138. Spector SL. The common cold: current therapy and national history. J Allergy Clin Immunol 1995;95:1133-8.
139. Spector SL, Toshener D, Gay I, Rosenman E. Beneficial effects of propylene and polyethylene glycol and saline in the treatment of perennial rhinitis. Clin Allergy 1982; 12:187-96.
140. Mösges R, Spaeth J. A novel therapy concept for the treatment of allergic rhinitis. In: Mösges R, Schlöndorff G, editors. Rhinitis, asthma, polyposis nasi. Zülpich: Biermann, 1996.
141. European Academy of Allergology and Clinical Immunology. Immunotherapy. In: Malling H-J, Weeke B, editors. EAACI Position Papers. Allergy 1993;48 Suppl 14:7-35.
142. Report of BSACI working party. Position paper on allergen immunotherapy. Clin Exp Allergy 1993;23 Suppl 3:1-44.
143. Passalacqua G, Canonica GW. Alternative routes of immunotherapy: a review. J Invest Allergol Clin Immunol 1996;36:81-6.
144. Martinez FD, Wright AL, Taussig LM, et al. Asthma and wheezing in the first six years of life. N Engl J Med 1995;332:133-8.
145. Arshad SH, Stevens M, Hide DW. The effect of genetic and environmental factors on the prevalence of allergic disorders at the age of two years. Clin Exp Allergy 1993;23:504-11.
146. Malmberg H, Grahne B, Holopalnen E, et al. Ipratropium (Atrovent) in the treatment of vasomotor rhinitis of elderly patients. Clin Otolaryngol 1983;8:273.
147. Schatz M, Hoffman CP, Zeiger RS, Mellon M. The course and management of asthma and allergic diseases during pregnancy. In: Middleton E, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, editors. Allergy: principles and practice. Vol II. St Louis, MO: CV Mosby, 1988:1112-31.
148. Briggs GG, Freeman R, Yaffe SJ. Drugs in pregnancy and lactation. 4th ed. Baltimore, MD: Williams & Wilkins, 1994.
149. Heppt W. Pharmacotherapy of allergic rhinitis. HNO 1997 (in press).
150. Juniper EF, Willms DG, Guyatt GH, Ferrie PJ. Aqueous beclomethasone dipropionate nasal spray in treatment of seasonal (ragweed) rhinitis. Can Med Assoc J 1992; 147:887-92.