Therapeutic Reviews

Management of Allergic Rhinitis: Focus on Intranasal Agents

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The clinical manifestations of allergic rhinitis are the result of an immune-mediated process after exposure of a sensitized individual to airborne allergens. The primary symptomatology includes nasal congestion, rhinorrhea, nasal and conjunctival pruritus, and sneezing. Principles of management include allergen avoidance, palliative therapy, immunotherapy, and pharmacotherapy. Oral decongestants stimulate α-adrenergic receptors in the nasal cavity, resulting in vasoconstriction and decreased edema. Oral antihistamines block histamine$_1$ (H_1) receptors, and may relieve rhinorrhea, sneezing, and nasal and conjunctival pruritus. Topical decongestants have a local effect on adrenergic receptors in the nasal mucosa, resulting in rapid, marked vasoconstriction. Intranasal corticosteroids inhibit mediator release from mast cells and basophils, and reduce edema of the nasal mucosa. Dexamethasone sodium phosphate, beclomethasone dipropionate, and flunisolide are currently available for intranasal administration. Cromolyn sodium inhibits allergen-induced degranulation and mediator release from sensitized cells, and is useful primarily as a prophylactic agent. Several agents, including the corticosteroids budesonide and flucortin butylester, the mast cell-stabilizing agent nedocromil sodium, the antichololinergic agent ipratropium bromide, and the H_1 receptor antagonist levocabastine are being investigated for intranasal use in the management of allergic rhinitis. **(Pharmacotherapy 1989;9(6):338–350)**

OUTLINE

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Rhinitis denotes a condition involving inflammation of the nasal mucosa in response to various stimuli, and may be considered under two headings: allergic and nonallergic. Allergic rhinitis is an immunologic process that can produce symptoms during specific periods (seasonal) or throughout the year (perennial).[1–4] Nonallergic rhinitis collectively refers to vasomotor rhinitis and nonallergic rhinitis with eosinophilia (NARES). The most commonly observed types of rhinitis and their distinguishing characteristics are shown in Table 1.[5–11] Therapeutic management of allergic rhinitis is varied, and emphasis currently is on topically active pharmacologic agents administered by the intranasal route.

Allergens are airborne, water-soluble proteins present primarily in pollen and mold spore carriers. After they are inhaled, these proteins are readily extracted from their natural carrier sources, faciliating their deposition on nasal epithelial surfaces. In temperate climates, the most important environmental allergens are tree pollens in the spring, grass pollens in late spring and summer, and ragweed pollen in the late summer and fall.[12] The onset and severity

Table 1. Types of Allergic and Nonallergic Rhinitis

Variable	Seasonal	Perennial	NARES[a]	Vasomotor
Onset	Childhood	Childhood	Nonspecific	Adult
Cause	Pollens	Animal dander, house dust, mold spores	Unknown	nervous system disorder
Family history of allergy	Common	Common	Coincidental	Coincidental
Occurrence of symptoms	Seasonal	Throughout the year	Sporadic; throughout the year	Worse in changing seasons
Laboratory tests				
Eosinophilia	Present	Present	Present	Absent
Serum IgE	Elevated	Elevated	Normal	Normal
Skin tests	Positive	Positive	Negative	Negative
Symptoms				
Sneezing	Frequent	Frequent	Sporadic	Sporadic
Rhinorrhea	Profuse, watery	Profuse, watery	Profuse, watery	Moderate, watery
Nasal pruritus	Marked	Marked	Moderate	Minimal
Nasal polyps	Common	Common	Occasional	Rare
Congestion	Moderate	Moderate	Minimal	Marked
Lacrimation	Common	Common	Common	Rare
Therapeutic response to				
Decongestants[b]	Fair	Fair	Fair	Poor
Steroids[b]	Good	Good	Good	Poor
Cromolyn[b]	Good	Good	None	Poor
Immunotherapy	Good	Good	None	None

[a]Nonallergic rhinitis with eosinophilia.
[b]Administered by the intranasal route.
Adapted from references 5–11.

of symptoms depend on the amount of pollen present in the air, with the highest counts in warm, dry climates. In contrast, mold spores may be airborne throughout the year, and are commonly found in damp, musty places even during the cold winter months.[12]

Estimates suggest that approximately 20% of the population suffers from allergic rhinitis[13–15]; however, the actual number is difficult to assess due to the subjectivity of the symptoms, and to great interpatient differences in perceived severity and desire for medical attention. Peak onset of symptomatic allergic rhinitis occurs in the adolescent years, with equal distribution between the sexes.[6, 7, 14] Seasonal allergic rhinitis (hay fever) is especially common; approximately 75% may be attributed to ragweed pollen, 40% to grass pollen, and 9% to tree pollen.[12] Distinguishing features include seasonal appearance of symptoms, reflecting sensitivity to pollens and fungi. By contrast, the perennial condition results from sensitivity to airborne household particles such as animal dander and house dust mites, which are encountered regularly, as well as to seasonal allergens.

Pathophysiology

The basic nasal functions include filtration, warming and humidification of inspired air, modulation of air flow, odor and taste detection, contribution to vocal resonance, and protection of the lower airways from inhaled microorganisms and toxins.[13, 16, 17] Many of these functions are possible due to the large nasal surface area and tortuous passageways in the folds and turbinates of the nose (Figure 1). The width of the nasal passages is regulated largely by sumpathetic mucosal innervation, especially of the venous sinusoids. Adrenergic stimulation, mediated by norepinephrine, results in vasoconstriction, reduction in size of the erectile vascular tissues, and widening of the airways.[4, 13, 16] Cholinergic stimultion, mediated by acetylcholine, stimulates nasal secretions and also produces some vasodilatation, vascular engorgement, and narrowing of the airways.[4, 13, 16] A normal side-to-side, alternating pattern, or nasal cycle, occurs in which the mucous membrane of one airway swells, while that of the other side may shrink. This cyclic change generally occurs every 1–4 hours, and is mediated by reciprocal sympathetic innervation of the erectile tissue, the total nasal resistance remaining constant.[16] In the case of rhinitis, however, the nasal cycle may occur entirely differently, or may not occur at all.[16]

Sharp, angular turns inside the nose encourage particle deposition from inspired air. The majority of particles trapped in the nasal passages are swept

up by the mucociliary system and transported away from the nasal region at an average rate of 8–9 mm/minute.[4] The sneeze mechanism helps expel inhaled particles, using nasal secretions as a vehicle. Vibrissae present in the anterior nares can effectively trap nearly all particles larger than 15 μm, although filtering capacity falls to 80% for 5-μ particles and to 0% for those that are 1–2 μm.[4] Impaired ciliary function may be the result of temperature extremes, excessive mucosal dryness, or clinical conditions such as cystic fibrosis and asthma in which excessive secretions overburden ciliary activity.

The mechanisms of allergic response are complex. Initial exposures to airborne allergens stimualte plasma cells in the lymphoid tissue to produce allergen-specific IgE antibodies. These antibodies bind to the surface of mast cells and basophils throughout the body to function as antigen (allergen) receptors. After repeat allergen exposure, allergenic protein molecules are presented to these sensitized cells, especially in the skin, respiratory tract, and gastroinestinal tract. Appropriate allergens bind to cell-bound IgE antibodies, initiating release of various proinflammatory mediators, including histamine, kinins, leukotrienes, chemotactic factors for eosinophils and neutrophils, platelet-activating factor, and several enzymatic activities; tosyl-L-arginine methyl ester (TAME) esterase activity is most often measured.[5, 7, 13, 18–20] These mediators are collectively responsible for itching, influx of cells, increased vascular permeability and fluid leakage, and other tissue effects.

The response to allergen challenge develops in two stages, immediate and late-phase responses. The symptomatology initially present after allergen inhalation in the laboratory generally subsides within 1–3 hours, returning the patient to baseline status.[4] Chemotactic factors released at the site of the initial mast cell degranulation recruit additional mediator cells such as eosinophils, which can participate in later inflammatory responses. Reappearance of nasal symptoms, especially congestion, 3–11 hours (average 4–6 hrs) after the initial episode signals the late-phase response, and, while not entirely explained, involves further release of inflammatory mediators and generation of kinins.[4, 14, 18] Late response symptoms are generally most difficult to treat.[7]

An additonal phenomenon, known as nasal priming, determines that decreasing amounts of allergen are required to elicit a response with continuing exposure (e.g., as a pollen season progresses).[4, 5, 13]

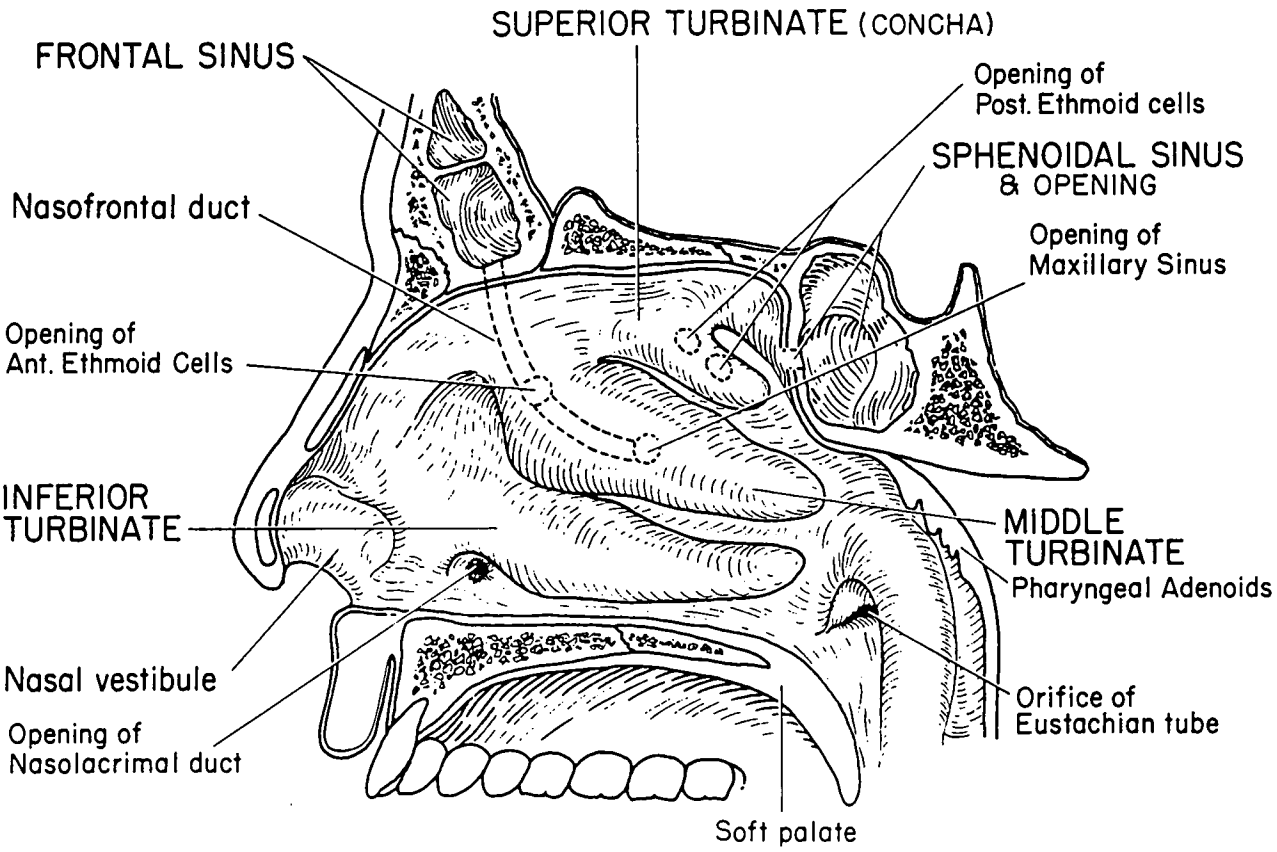

Figure 1. The nose and paranasal sinus. Reprinted with permission from "Medical notes on the common cold," Burroughs Wellcome Co., publication no. P199-2, Research Triangle Park, NC, 1972.

Several investigators have documented an increase in mast cells and basophils in the nasal mucosa during the course of a pollen season.[4, 21] Nasal priming also may explain the increase in responsiveness to unrelated allergens often experienced during a pollen season, as well as to otherwise nonspecific stimuli such as changes in humidity and temperature.

Etiology

The elements required for the development of allergic rhinitis include a genetic predisposition for IgE response to allergens, appropriate initial exposures, and probably, additional determinants of end-organ reactivity.[15] Although specific sensitivities are not genetically transmitted, the predisposition to develop allergic reactions in general (atopy) appears to be inherited. Atopic individuals are likely to develop not only allergic rhinitis but also allergic asthma, atopic eczema, and IgE-mediated food allergies. Insect venom reactions, including systemic anaphylaxis and adverse drug reactions, are at best modestly increased in this risk group.[15]

Nasal symptoms similar to those of allergic rhinitis may be induced by medications, including reserpine, hydralazine, guanethidine, methyldopa, prazosin, propranolol and other ß blockers, certain antidepressants and antipsychotics, estrogens, cocaine, and alcohol.[7, 15, 22, 23] Aspirin and other nonsteroidal antiinflammatory agents also may produce flushing, rhinorrhea, and intense wheezing in susceptible individuals.[7, 15, 22] Other factors that may lead to obstruction of the nasal airways include respiratory infections, irritant dusts or chemical fumes, tobacco smoke, perfumes, strong odors, rising from bed in the morning, chilling of the body surface, sexual excitement, menstruation, and pregnancy.[4]

Clinical Findings

After initial exposure of atopic individuals to sensitizing allergens, symptoms generally develop within 2-3 years, often escalate in severity for 2–3 years, and then plateau.[4, 7] The severity of symptoms may fluctuate in later life and often diminishes during the sixth or seventh decade, although spontaneous, complete remissions are uncommon if exposure continues.[3, 4] Allergic rhinitis is seldom problematic in elderly patients, which may reflect age-related changes in the nasal mucosa and decreased immunologic responsiveness in this population.[3, 4]

The primary symptoms of allergic rhinitis include nasal congestion, paroxysms of repetitive sneezing, clear rhinorrhea, lacrimation, and nasal, conjunctival, and pharyngeal pruritus. These symptoms may further involve mucous membranes of the middle ears and paranasal sinuses, resulting in ear popping, mildly impaired hearing, and a sensation of pressure over the cheeks and forehead. Other nonspecific symptoms include irritability and fatigue (often the effect of sleep loss or sedating medications), as well as variations in appetite. Chronic mouth breathing often begets snoring and excessive dryness of the mouth and throat. Increasingly severe symptoms such as wheezing and loss of olfaction may develop; secondary infection is common. Children often demonstrate the so-called allergic salute, a maneuver in which the hand deflects the tip of the nose upward, presumably to open the passages and relieve nasal itching. Repeated over time, this results in a transverse crease about 2 cm above the nasal tip.[24, 25] Young sufferers also develop "allergic shiners," or edematous, dark circles under the eyes due to chronic venous congestion.[24, 25]

Several developmental complications may occur in children with allergic rhinitis. Chronic mouth breathing may result in recession of the mandible and malocclusions, as well as hyperplasia of pharyngeal lymphoid tissue.[24, 26, 27] A high, arched palate and gross overbite are also common.[17, 26] Frequent episodes of otitis media may complicate allergic rhinitis, especially in pediatric patients. Several studies support a correlation between histamine- or allergen-induced nasal changes and eustachian tube obstruction; however, the role of nasal allergy in otitis media is still a focus of investigation.[28] Nasal polyps may complicate allergic rhinitis, especially when bacterial infection is associated. In turn, polyps may obstruct normal sinus drainage and promote bacterial infection (i.e., sinusitis).[10] A definite association exists between the occurrence of severe or untreated allergic rhinitis and the later development of asthma, although estimates of the risk differ among authorities.[13, 29]

Diagnosis

Since individuals with allergic rhinitis exhibit the classic symptoms only on an intermittent basis, diagnosis is often difficult. The most useful information is generally obtained from the clinical history, from which the chronology and severity of specific complaints and their response to therapeutic management may be determined. The differential diagnosis for allergic rhinitis should include the processes listed in Table 2.[17, 23]

Several simple, noninvasive diagnostic tests are available, including fiberoptic rhinoscopy of the nasal region. This allows direct inspection of the entire nasal mucosa, which appears pale, swollen, and bluish gray in patients with rhinitis.[15, 30] Rhinoscopy is also effective for identifying mucosal and anatomic changes, such as edematous turbinates, nasal polyps, and septal deviation, and may be especially useful in infants and children. Roentgenograms are of value primarily to assess nasal mucosal hypertrophy and sinusitis, as well as to detect nasal polyps.[6, 15]

In vivo diagnostic procedures include allergen skin testing and nasal provocation testing. The purpose of skin testing is to identify specific allergen

Table 2. Differential Diagnosis of Rhinitis

Primary	Allergic rhinitis with eosinophilia: seasonal or perennial rhinitis
	Nonallergic rhinitis with eosinophilia: vasomotor or atrophic rhinitis
Secondary	Anatomic deviations: nasal septal deviation, nasal polyps, primary nasal mastocytosis, adenoidal hypertrophy, choanal atresia, impacted foreign body, cerebrospinal fluid leak
	Infectious: bacterial, viral, or fungal infection
	Endocrine disorder: hypothyroidism, pregnancy
Other	Congenital syphilis, Crohn's disease, vasculitic disease, cystic fibrosis

Adapted from references 17, 23.

sensitivities by intradermal injection of dilute allergen extracts. Various types are used, including the epicutaneous, or prick test, for screening large numbers of potential allergens. This may be followed by the more sensitive intradermal test, using allergens that cause a positive response to epicutaneous injection. A positive skin test reaction may be noted within 10–30 minutes, and is manifested by a large wheal and flare at the injection site.[31] Skin testing may be of predictive value for future development of symptomatic disease, and is routinely performed in all patients prior to the initiation of immunotherapy.[31] Advantages are the rapidity of response and relatively low patient discomfort; disadvantages include a 5–35% false positive rate, a false negative or reduced response caused by a number of drugs, and a risk of anaphylaxis.[31]

The nasal provocation or challenge test involves controlled introduction of histamine, methacholine, or specific allergens by atomizer into the nasal cavity. In sensitive individuals, this challenge produces a vigorous reaction marked by sneezing, nasal congestion, and rhinorrhea.[30] This form of testing is not pleasant for the patient, and may cause significant discomfort in the nasopharynx. It may be indicated when the results of skin testing or in vitro testing conflict with clinical assessment, or to monitor the onset and duration of immunotherapy.

In vitro testing methods include examination of a nasal smear and measurement of serum IgE concentrations. Staining of the nasal smear highlights eosinophils and other cell types present. Evaluation of serum IgE may be accomplished by the radiollergosorbent (RAST) test, Phadiatop method, or enzyme-linked immunosorbent assay (ELISA); these methods can help ascertain both the concentration and the allergen specificity of IgE present in the serum.[32,33] In vitro test results correlate well with those obtained by other diagnostic methods, and may be used when skin testing is not feasible, such as in patients with eczema.

Treatment

General Principles

The primary goal in managing allergic rhinitis is to achieve maximum symptomatic relief with minimum adverse effects. The principles of management include allergen avoidance, pharmacotherapy, and immunotherapy.

Minimizing patient exposure to offending allergens is not always easily accomplished, especially in the case of airborne agents from natural sources. Patients should note that pollen prevalence is highest in warm, sunny, dry weather and lower during damp or cold periods. Strategies for avoiding outdoor allergens center on keeping windows closed (feasible through use of air-conditioning units with appropriate filters) and precautions during lawn and garden work. For brief, predictable outdoor exposures, felted fiber masks (e.g., 3M Pollen Mask) may give substantial protection. Avoidance of indoor allergens is facilitated by careful house cleaning, keeping dogs and cats outside as much as possible, and use of zippered plastic encasings over mattresses, box springs, and pillows. Obvious dust collectors such as thick carpeting, heavy draperies, and uncleaned venetian blinds should be eliminated, especially in the bedroom. Electrostatic precipitators are often recommended, but remain to be proved clinically useful.[34]

Palliative therapy may include air humidification and nasal irrigation with sodium chloride solutions, especially in extremely dry climates or as an adjunct in treating secondary infection. Nasal irrigations soothe the inflamed mucosa, help clear tenacious mucus, and improve olfaction.[35–39] Two approaches are available for nasal irrigation: commercial buffered sodium chloride preparations such as NaSal, Saline X, Ayr, and Ocean, which are sprayed into each nostril several times daily as needed, and isotonic sodium chloride solutions made from one-fourth teaspoon of iodine-free salt in 7 oz warm water, instilled with a bulb syringe or Water-Pik as needed.[37,38]

Despite its long history of proved value in the management of nasal allergy, immunotherapy is reserved primarily for severe cases of rhinitis and patients refractory to standard pharmacotherapy.[15] Immunotherapy seeks to decrease the allergic response through a series of subcutaneous injections providing increasing doses of specific allergen extracts. The injections result in production of IgG-blocking antibodies to the administered allergens, which reduce mast cell and basophil degranulation and diminish the inflammatory response after allergen exposure. Both magnitude and duration of the therapeutic response are directly related to the cumulative dose of allergen administered.[15] Immunotherapy can provide substantial, long-lasting symptomatic relief to patients with allergic rhinitis; however, it seldom provides a permanent cure, and includes a low but definite risk of anaphylactic reac-

Table 3. Nasal Decongestant Products

Product[a]	Strengths Available	Adult Dose (drops/sprays per nostril)	Age 6–12 yrs (drops/sprays per nostril)	Age 2–6 yrs (drops/sprays per nostril)
Catecholamines				
Epinephrine HCl	0.1%	2–3 as needed	2–3 as needed	NE[b]
Ephedrine SO_4	0.5%	2–3 every 4 hrs	1–2 every 4 hrs	NE
	1.0%	2–3 every 4 hrs	1–2 every 4 hrs	NE
Phenylephrine HCl	0.125%	NR[c]	NR	2–3 every 4 hrs
	0.25%	1–2 every 3–4 hrs	1–2 every 3–4 hrs	NR
	0.5%	1–2 every 3–4 hrs	1–2 every 3–4 hrs	NR
	1.0%	1–2 every 3–4 hrs	NR	NR
Imidazole derivatives				
Naphazoline HCl	0.025%	NR	1–2 every 4–6 hrs	NE
	0.05%	1–2 every 4–6 hrs	NR	NE
Oxymetazoline HCl	0.025%	NR	NR	2–3 every 12 hrs
	0.05%	2–3 every 12 hrs	2–3 every 12 hrs	NR
Tetrahydrozoline	0.05%	NR	NR	2–3 every 3–6 hrs
	0.1%	2–4 every 4–6 hrs	2–4 every 4–6 hrs	NR
Xylometazoline HCl	0.05%	NR	2–3 every 8–10 hrs	2–3 every 8–10 hrs
	0.1%	2–3 every 8–10 hrs	NR	NR
Other				
Propylhexedrine	250-mg nasal inhaler	2 inhalations every 2 or more hrs	2 inhalations every 2 or more hrs	NE
Desoxyephedrine	50 mg nasal inhaler	2 inhalations every 2 or more hrs	2 inhalations every 2 or more hrs	NE

[a]Product should be discontinued after 3–5 days to prevent rebound congestion.
[b]NE = Safety and efficacy data have not been established for use in children less than 6 years of age.
[c]NR = Use of this concentration is generally not recommended by the manufacturers for this age group.
Adapted from references 37–42.

tions at any time during the treatment.[15] The couse of injections must also be repeated before each allergy season, or continued on a maintenance schedule throughout the year.

Oral Decongestants and Antihistamines

Initial pharmacotherapy of rhinitis often includes oral decongestants and emphasizes the use of antihistamines. Oral decongestants are sympathomimetic amines that stimulate α-adrenergic receptors in the nasal mucosa, resulting in vasoconstriction and decreased tissue edema.[37–39] Systemic adverse effects include tachycardia, palpitations, nervousness, tremor, insomnia, and hypertension in predisposed individuals.

Special risks exist in patients with closed-angle glaucoma, bladder outlet obstruction, and impaired gastrointestinal motility.[37–39] Oral decongestants commonly used include ephedrine, pseudoephedrine, phenylephrine, and phenylpropanolamine. These agents minimally suppress rhinorrhea, sneezing, and nasal pruritus, and are therefore best used concurrently with oral antihistamines. Antihistamines inhibit the binding of histamine to H_1 receptors.[37,39] Adverse effects include drowsiness, dizziness, epigastric distress, and anticholinergic effects such as dry mouth, urinary retention, and constipation.[37–39] Popular oral antihistamines for allergic rhinitis include chlorpheniramine, brompheniramine, and triprolidine. Newer agents such as terfendine and astemizole tend to cause significantly less sedation.[37–39] Further discussion of the oral decongestants and antihistamines used in allergic rhinitis is beyond the scope of this article; a thorough review of these agents may be found elsewhere.[37–39]

Topical Decongestants

Topical decongestants are often used as initial intranasal therapy for allergic rhinitis (Table 3).[37–42] The catecholamine and imidazole derivatives act preferentially on α-adrenergic receptors in the mucosa, causing marked vasoconstriction and decreased edema.[37–40] Propylhexedrine and desoxyephedrine indirectly stimulate α-adrenergic receptors by a mechanism similar to that of amphetamine.[41,42] Improvements in nasal ventilation and control of rhinorrhea generally occur within 5–10 minutes of topical decongestant application. The catecholamine derivatives provide a rapid effect of short (average 4 hrs) duration, while the imidazole products offer a rapid effect with a substantially longer (9–12 hrs) duration. Propylhexedrine and desoxyephedrine have a very short (1–2 hrs) duration and are therefore less desirable.

Adverse reactions to these agents include sneezing, nasal burning, mucosal dryness, and, rarely, bleeding.[38,39] Patients may experience nasal irritation due to product pH or the presence of additives such as antioxidants and preservatives. Systemic side effects after intranasal administration are generally rare, since the amount of drug absorbed is relatively small and metabolism is rapid.[38]

Prolonged therapy (>3–5 days) or excessive application of the topical decongestants can result in mucosal ischemia, edema, and rebound congestion, collectively known as rhinitis medicamentosa.[10,37,43] This phenomenon has not been associated with oral decongestants.[39] It is treated by immediate discontinuation of the topical decongestant. Isotonic sodium chloride preparations may offer symptomatic relief, and some patients may require a brief course of intranasal corticosteroid therapy.[37]

Topical decongestants are useful for short-term, symptomatic relief and control of rhinorrhea, but do not effectively inhibit the nasal response to allergens. They may be used on initiation of intranasal corticosteroid or cromolyn sodium therapy to improve nasal penetration of these agents. The longer-acting imidazole products require less frequent dosing and are therefore more convenient; they are also less likely to cause rebound congestion when applied in an appropriate dosage for a short course of therapy.[40] Patients should be cautioned not to use topical decongestants, especially the highly concentrated, long-acting preparations, for more than 3–5 consecutive days, and should be advised against exceeding the recommended dosage.[37,40] Several topical decongestant products can be used in children over 2 years of age, provided the appropriate concentration is selected and administered according to manufacturers' recommendations (see Table 3).[37–42]

Corticosteroids

The development of potent corticosteroids for intranasal administration has been a major advance in the management of allergic rhinitis. The therapeutic effect produced by these agents is not completely understood, but is thought to involve inhibition of allergen-induced mediator release from mast cells and basophils, inhibition of mast cell and basophil accumulation on the nasal mucosal surface, reduction in the number of eosinophils present in nasal secretions, inhibition of leukocyte chemotaxis, inhibition of prostaglandin and leukotriene generation, and direct vasoconstriction.[37,38,44,45] Intranasal corticosteroid therapy has been shown to inhibit both the early and late inflammatory responses after allergen challenge.[44,46]

Dexamethasone sodium phosphate (Decadron Turbinaire) was introduced in 1968 as the first corticosteroid with an intranasal dosage form. While it was effective in relieving the symptoms of allergic rhinitis,[44,47] side effects resulting from significant systemic absorption of active drug with suppression of the hypothalmic-pituitary-adrenal (HPA) axis significantly limited its use.[48–51] Fortunately, several topically active hydrocortisone derivatives with maximized antiinflammatory potency and highly lipophilic structures have subsequently been synthesized; these include beclomethasone dipropionate, flunisolide, and the investigational agents budesonide and flucortin butylester.[52,53]

The antiinflammatory activities of beclomethasone dipropionate (BDP) and flunisolide are, respectively, 5000 and 3000 times greater than that of hydrocortisone.[38,44] Both agents are indicated for treatment of seasonal and perennial allergic rhinitis and normal nonallergic rhinitis with eosinophilia, and for the prevention of recurrent nasal polyps.[47,54–57] They also effectively reduce inflammation and stabilize the nasal mucosa in rhinitis medicamentosa.[37,38,47]

Both BDP and flunisolide are rapidly absorbed from the nasal mucosa and the gastrointestinal tract after intranasal administration and partial swallowing of the dose. Drug that is swallowed undergoes a rapid first-pass hepatic metabolism to relatively inactive metabilites. Drug absorbed from the nasal mucosa initially avoids the first-pass metabolism, but is ultimately metabolized in the liver. These agents are highly bound to plasma proteins. The serum elimination half-life is approximately 15 hours for BDP[38,44] and 1–2 hours for flunisolide[58]; serum levels, however, do not correlate with the local intranasal effect.

Adverse effects with intranasal BDP and flunisolide include nasal burning, irritation, sneezing, congestion, minor headache, and infrequent nosebleeds. Other adverse effects may include transient lightheadedness and reversible loss of taste and smell.[58] Spraying the aerosol toward the nasal septum rather than the turbinates may result in hemorrhagic crusting of the septum; rare cases of nasal mucosal ulceration have been reported.[59] Septal perforations due to unknown causes have been reported with these drugs,[60–62] the effect being preceded in some instances by severe nasal crusting and bleeding. No significant metaplastic or atrophic changes in the nasal mucosa have been seen after up to 5 years of use for either agent.[44,47,58,63–66] Nasal candidiasis is rare.[58,64,65,67] Both BDP and flunisolide produce a dose-dependent decrease in nasal ciliary beating frequency in vitro; further investigation is needed to evaluate their potential effects on mucociliary clearance in vivo.[58,68,69] Unlike dexamethasone, neither drug produces overt suppression of the HPA axis when administered in recommended dosages for prolonged courses.[58,65,66,71,71]

Recommended dosages of BDP and flunisolide are shown in Table 4.[38,54–58,72–75] Clinicians generally initiate therapy at the higher dosages in order to provide early maximum suppression of symptoms. Dosages should be adjusted based on clinical re-

Table 4. Products Currently Available for Intranasal Therapy of Rhinitis

Generic Name	Trade Name	Recommended Dosage	Available From
Dexamethasone	Decadron phosphate Turbinaire	Adults: 2 sprays/nostril 2–3 times daily	100-μg/spray; freon-propelled
		Children 6–12 yrs[a]: 1–2 sprays/nostril 2 times daily	
Beclomethasone dipropionate	Beconase, Vancenase	Adult and children >12 yrs: 1 spray/nostril 2–4 times daily, or 2 sprays/nostril 2 times daily	42-μg/spray; freon-propelled
		Children 6–12 yrs[a]: 1 spray/nostril 3 times daily	
	Beconase AQ, Vancenase AQ	Adults and children >6 yrs[a]: 1–2 sprays/nostril 2 times daily	42-μg/spray; metered pump
Flunisolide	Nasalide	Adults: 2 sprays/nostril 2–3 times daily	25-μg/spray; metered pump
		Children 6–14 yrs[a]: 1 spray/nostril 3 times daily, or 2 sprays/nostril 2 times daily	
Cromolyn sodium	Nasalcrom	Adults and children >6 yrs[a]: 1 spray/nostril 3–6 times daily	4% nasal solution; 5.2 mg/spray

[a]Safety and efficacy data have not been established for use in children less than 6 years of age.
Adapted from references 38, 51, 54–58, 72–76.

sponse and patient tolerance, and should be reduced to the lowest maintenance level possible once symptoms have been controlled. Use of higher than recommended dosages has not provided additional benefit, and it increases the risk of systemic adverse effects.[54-57] Relief of symptoms usually begins within 2–3 days of initiating therapy; maximum response may require 2–3 weeks in some patients.[37, 65]

It is essential that patients understand the rate of response to be expected from intranasal steroids and that these products require regular use for maximum benefit. Therapy should be continued throughout the expected season for hay fever, and may be required on a long-term basis for perennial allergic rhinitis. Patients who are receiving inhalation BDP for asthma and who also require intranasal BDP for management of rhinitis may receive total daily doses that exceed generally recommended doses; prescribers should be aware of the potential for increased systemic steroid side effects.

The major difference among the intranasal corticosteroid preparations is the delivery system. Beconase and Vancenase are generically equivalent, each delivering 42 μg of BDP per spray.[54, 55] Metered-dose spray preparations of these agents use freon as an aerosol propellant, which promotes excessive drying, crusting, and occasional minor bleeding of the mucosa.[37, 54, 55, 57] The force of the aerosal spray is also not well tolerated by many patients.[37, 77-79] Nasalide is a finger-operated mechanical nasal pump spray that delivers an aqueous suspension of drug.[56, 57, 80] Propylene and polyethylene glycol are included in the formulation to facilitate spreading of the liquid over the nasal mucosa.[47, 56, 80] The pump spray system is generally better tolerated; however, the acidic pH and high (20%) propylene glycol content of Nasalide produces considerable stinging and burning in many patients.[37, 58, 80] A recent report from Canada describes improved patient acceptability with an investigational formulation of flunisolide (Rhinalar) containing less (5%) propylene glycol.[80]

Aqueous formulations of BDP are now available (Beconase AQ, Vancenase AQ) in pump spray delivery systems similar to Nasalide but with a more acceptable pH. The aqueous products have been shown to be as effective as the pressurized sprays in alleviating the symptoms of rhinitis, are better tolerated, and are generally preferred over the pressurized spray products.[77-80]

The recommended dosage of Beconase AQ and Vancenase AQ for adults and children above 6 years of age is 1–2 sprays in each nostril twice daily.[74, 75] While not endorsed by manufacturers, children under 6 years of age with allergic rhinitis have been successfully treated with BDP 1 spray per nostril 3 times daily,[81] or flunisolide 2 sprays per nostril 2 times daily.[82] Although either formulation of BDP would be reasonable for use in the pediatric population, an aqueous preparation may be better tolerated. All patients receiving intranasal corticosteroids should be carefully monitored both for therapeutic response and adverse effects, including clinical changes in the nasal mucosa and bleeding.

Budesonide is a synthetic, nonhalogenated corticosteroid with relative antiinflammatory activity comparable to that of BDP and flunisolide. It is currently available in Europe (Rhinocort) as a metered-dose nasal inhaler for allergic rhinitis.[44] Budesonide has been shown to be effective, compared to placebo, in treating seasonal and perennial nasal allergy, vasomotor rhinitis, and nasal polyposis.[83-87] It appears to be most effective in reducing nasal congestion, rhin-

Table 5. Comparative Efficacies of the Intranasal Agents

Comparison	Daily Dose (μg/)	Results
BDP vs FLU	400/200	BDP = FLU[95]
BDP vs FLU	400/200	BDP = FLU[96]
BDP vs FLU	400/200	BDP = FLU[97]
BDP vs FLU	400/200	BDP = FLU[98]
BDP vs FLU	400/200	BDP = FLU[99]
BDP vs BUD	400/400	BDP = BUD[100]
BDP vs BUD	400/400	BUD > BDP[101]
BDP vs BUD	400/400[a]	BUD > BDP[102]
FLU vs BUD	200/400	FLU = BUD[103]
BDP vs CRO	400/31.2 mg[b]	BDP > CRO[104]
BDP vs CRO	400/10 mg	BDP > CRO[105]
FLU vs CRO	200/31.2 mg[b]	FLU > CRO[106]
BDP vs FLU or CRO	336/200/41.6 mg	BDP = FLU > CRO[107]
BUD vs CRO	400/26 mg[b]	BUD > CRO[108]
FLU vs LEV	200/0.4 mg	FLU = LEV[109]

[a]Both regimens were administered on an as-needed basis.
[b]Cromolyn used was a 2% solution; current formulation contains 4% cromolyn.
BDP = beclomethasone dipropionate; FLU = flunisolide; CRO = cromolyn sodium; BUD = budesonide; LEV = levocabastine sodium.

orrhea, and sneezing. The drug is rapidly and completely absorbed from the nasal mucosa. Absorbed drug is rapidly inactivated by liver enzymes, with a hepatic extraction ratio of 90% and a serum elimination half-life of 2 hours.[88] Adverse effects include nasal stinging, minor sore throat, dry nose, and slight nasal bleeding.[83, 87] One case of contact eczema involving the nasal mucosa and surrounding tissues was reported after the use of Rhinocort.[89] Budesonide produces few systemic adverse effects and has not caused demonstrable adrenal suppression.[84, 86, 88] Unlike BDP and flunisolide, it has minimal effect on the frequency of nasal ciliary beats.[90] No morphologic changes in the nasal mucosa have been observed after its use for up to 1 year, and no cases of intranasal candidiasis have been reported.[84, 87] Budesonide is administered by freon-propelled, metered-dose spray, delivering approximately 50 μg per actuation. The recommended dosage is 2 sprays twice daily into each nostril (400 μg/day), which may be reduced to 1 spray per nostril twice daily after symptomatic response.[86, 87]

Flucortin butylester is also a synthetic, lipophilic, hydrocortisone derivative with potent topical antiinflammatory activity. It is available in West Germany as a powder for nasal insufflation, with lactose added as an excipient to facilitate dispersion.[91] A special hand-activated device (Rhinolater) delivers 0.5 mg of flucortin per actuation into a plastic Venturi tube from which the drug is intranasally inhaled without the assistance of an aerosal propellant.[91] Flucortin appears effective in treating seasonal and perennial allergic rhinitis, as well as nonallergic rhinitis, at daily dosages of 2–8 mg given in 2–4 equally divided intranasal doses.[91–94] Symptomatic relief was reported to appear early and progress during the course of therapy.[93] After intranasal administration, flucortin is metabolized by nonspecific tissue esterases to metabolites with little or no glucocorticoid activity, thereby producing little risk of systemic corticosteroid effects.[92, 93] Reported adverse effects include irritation of the mucous membranes, postnasal drip, sneezing, nasal crusting, headache, and nausea.[92, 93] No systemic adverse effects have been reported, and HPA axis suppression has not been observed at dosages 20–80 times the normal daily dose.[93]

Studies have compared the relative efficacies of intranasal corticosteroids for rhinitis (Table 5).[95–103] As BDP and flunisolide have shown comparable therapeutic efficacy,[95–99] the decision to use either agent is generally based on prescriber and patient preference. Budesonide appears equally effective as, and in some cases more effective than, BDP and flunisolide in the treatment of rhinitis,[100–103] and may soon offer a therapeutic alternative to currently available agents.

Mast Cell Stabilizers

Cromolyn sodium is a derivative of the natural product khellin. Its mechanism of action in allergic rhinitis is to stablize mast cell membranes, apparently by inhibiting calcium transmembrane flux and thereby preventing antigen-induced degranulation. It is more effective in stabilizing mast cells than basophils, and therefore may not completely relieve symptoms.[37, 38, 110] Cromolyn does not inhibit the binding of IgE to mast cells or interfere with the interaction between cell-bound IgE and antigen.[38]

Cromolyn can be effective in reducing sneezing, rhinorrhea, and nasal pruritus, is minimally useful in nonallergic types of rhinitis, and has little effect on mucociliary transport.[15, 38, 110–112] It often prevents the symptoms of both seasonal and perennial allergic rhinitis, and diligent prophylaxis can significantly re-

duce both immediate and late symptoms after allergen exposure. Tachyphylaxis due to the intranasal effects of cromolyn has not been reported; it may be more difficult to achieve maximum therapeutic response once symptoms have developed.[38, 110]

Less than 7% of an intranasal dose of cromolyn is absorbed systemically.[110] Absorbed drug is rapidly excreted unchanged in urine and bile, with a serum elimination half-life of 1–2 hours. The remainder of the dose is swallowed, with minimal gastrointestinal absorption, and excretion primarily in the feces.[38, 110, 111] Adverse effects occur in less than 10% of patients, and most commonly include sneezing, nasal stinging, nasal burning, transient headache, and an unpleasant aftertaste.[38, 76, 110, 111] Patients may also experience mucosal irritation due to the preservatives benzalkonium chloride and ethylenediaminetetraacetic acid. Cromolyn is effective and well tolerated in both adults and older children; however, safety during pregnancy and in children under 6 years of age has not been positively established.[76, 110]

Cromolyn is currently available as a 4% nasal solution (Nasalcrom) in a pump spray delivery system. The recommended initial dosage for adults and children 6 years of age and older is 1 spray (5.2 mg) in each nostril 3–4 times daily, increasing as needed up to 6 times daily.[72, 110, 111] Although not recommended by the manufacturer, cromolyn has been administered to children under 6 years of age as 1 inhalation per nostril 3–4 times daily, with careful monitoring for therapeutic response.[113] Nasal passages should be cleared to the best extent possible prior to administration. For management of seasonal rhinitis, treatment should begin 2–4 weeks prior to contact with offending allergens, and should continue throughout the period of exposure. Due to the delayed onset of effect, concurrent decongestant or antihistamine therapy may be indicated. It is essential for patients to understand the rate and extent of repsonse to be expected from intranasal cromolyn, and that, since the product is prophylactic, it must be used on a regular basis for maximum benefit.

Several studies have compared the therapeutic efficacy of cromolyn nasal solution to that of the intranasal corticosteroids in allergic rhinitis (see Table 5).[104–108] Results from open, parallel studies of 3–8 weeks' duration showed BDP and flunisolide to be more effective than cromolyn in controlling symptoms.[106, 107] A double-blind, crossover study in patients with perennial allergic rhinitis also found BDP superior to cromolyn after 4 weeks of therapy.[104] Finally, budesonide demonstrated a superior therapeutic effect to cromolyn in controlling nasal symptoms after 3 weeks of therapy in patients with seasonal rhinitis.[108]

Similar to cromolyn sodium, nedocromil sodium is an investigational mast cell-stabilizing agent.[114] Several placebo-controlled studies have demonstrated the efficacy of nedocromil sodium 1% nasal spray in preventing symptoms of allergic rhinitis.[115–117] The recommended dosage is 1 spray (1.3 mg) in each nostril 2 times daily.[115–117] Adverse effects include slight nasal irritation and stinging, sneezing, and unpleasant taste.[115–117] Like cromolyn, nedocromil is recommended primarily for prophylactic use, and therapy should be initiated 2–4 weeks prior to significant seasonal allergen exposure.

Miscellaneous Agents

Ipratropium bromide (Atrovent) is a topically active derivative of atropine available in the United States as a metered-dose inhaler for oral administration in the management of chronic bronchitis and reactive airways disease. The drug is also available in Europe as a nasal spray for topical administration in the management of nasal hypersecretion.[6] By blocking acetylcholine-mediated responses, ipratropium decreases tissue concentrations of cyclic guanosine monophosphate, resulting in reduced volume of nasal secretions and some minor degree of vasoconstriction.[118, 119] Administered intranasally from the inhaler both with and without a special nasal adaptor, ipratropium has been shown rapidly and effectively to reduce mucosal hypersecretion provoked by methacholine challenge,[119] and effectively to decrease rhinorrhea in patients with perennial allergic,[120, 121] vasomotor,[122–124] and viral rhinitis.[125] It has no effect on basal mucus secretion, sneezing, or nasal congestion, and it does not affect the nasal mucociliary transport system.[9, 118, 119, 121, 122, 126] It reduces excessive secretions for 8 hours or more after intranasal administration.[118, 121]

Ipratropium's quaternary ammonium structure results in minimal absorption after topical administration.[121] The recommended dosage is 2 sprays (20 μg/spray) into each nostril 4 times daily.[118, 121] Adverse effects include nasal irritation, nasal stuffiness, mucosal dryness, headache, and dry or sore throat.[118, 120, 122, 124] Extremely high dosages (400 μg 4 times daily) have been associated with systemic anticholinergic effects such as dizziness, blurred vision, nausea, abdominal pain, constipation, and urinary retention.[121] No significant adverse effects have been reported with long-term therapy.[118,123] Although neither the nasal spray nor the nasal adaptor for the oral metered-dose inhaler is currently available in the United States, ipratropium has the potential to be a useful agent for managing conditions that produce nasal hypersecretion. An adaptor for the oral metered-dose inhaler can be made by cutting the tip off a rubber baby bottle nipple and placing it over the mouthpiece; the spray can then be directed into the nasal passages.

Levocabastine, a selective H_1 receptor antagonist, is currently under investigation for use in allergic rhinitis based on prior successful topical use in allergic conjunctivitis and allergic rhinoconjunctivitis.[127] Topical use of antihistamines may avoid the sedation observed with systemic therapy and provide

higher drug concentrations at the primary site of action. Compared to placebo, 2 metered sprays (0.05 mg/spray) of levocabastine per nostril have been shown significantly to reduce rhinorrhea and sneezing, but not nasal obstruction, in nasal allergen provocation tests.[120, 129] Levocabastine, administered as 2 sprays per nostril 4 times daily for 3 months, effectively reduced rhinorrhea and sneezing in patients with both perennial allergic and nonallergic rhinitis.[130] In an open, parallel, comparative study, no significant difference in response was observed between maintenance regimens of intranasal flunisolide and levocabastine after 4 weeks of therapy in patients with seasonal rhinitis.[109] No adverse effects have been reported.[109, 120-130] While levocabastine promises to be a useful agent,[128-130] its therapeutic role in allergic rhinitis remains to be determined.

Summary

Allergic rhinitis is a very common disease, with the potential to cause great discomfort and diminished quality of life. Allergen avoidance, the most effective approach in preventing rhinitis, is often difficult or unfeasible to accomplish. The goal of pharmacotherapy is to use the fewest medications and lowest dosages to control symptoms adequately, taking into consideration patient age, tolerance, and therapeutic response. Patients must be monitored regularly for adverse effects, including clinical changes in the nasal mucosa.

Palliative measures in the management of allergic rhinitis include air humidification and sodium chloride nasal spray preparations. Initial pharmacotherapy generally includes oral antihistamines and decongestants to control acute symptoms; these agents are especially useful in the presence of ocular pruritus and lacrimination. Congestion and rhinorrhea respond well to topical decongestants; however, these preparations must be discontinued after 3–5 days to prevent rebound congestion. Patients who have adverse effects or inadequate reponse to initial therapy, or who require extended treatment, should be considered for intranasal corticosteroid or cromolyn sodium therapy. Although beneficial as a prophylactic agent prior to the onset of a major allergen season, cromolyn sodium has not been as effective as topical corticosteroids once the symptoms of rhinitis develop. Since the currently available intranasal corticosteroids (BDP and flunisolide) are comparable in therapeutic efficacy, product selection is based primarily on patient response and tolerance. The newer aqueuos, pump sprays seem to be most acceptable to patients. Intranasal ipratropium bromide can effectively decrease rhinorrhea and nasal hypersecretion, and may soon be available in the United States. Other investigational agents, including the corticosteroids budesonide and flucortin, and the mast cell-stabilizing agent nedocromil, show promising results in clinical trials.

References

1. **Mathews KP.** Allergic and nonallergic rhinitis, nasal polyposis, and sinusitis. In: Kaplan AP, ed. Allergy. New York: Churchill Livingstone, 1985:323–66.
2. **Ricketti AJ.** Allergic rhinitis. In: Patterson R, ed. Allergic diseases: diagnosis and management, 3rd ed. Philadelphia: JB Lippincott, 1985:207–31.
3. **Mygind N.** Essential allergy. Oxford: Blackwell, 1986:277–350.
4. **Norman PS.** Allergic rhinitis. J Allergy Clin Immunol 1985;75:531–45.
5. **Fagin J, Friedman R, Fireman P.** Allergic rhinitis. Pediatr Clin North Am 1981;28:797–806.
6. **McNamara RM.** Approach to rhinitis. Emerg Med Clin North Am 1987;5:279–92.
7. **Druce HM, Kaliner MA.** Allergic rhinitis. JAMA 1988;259:260–3.
8. **Mullarkey MF, Hill JS, Webb DR.** Allergic and nonallergic rhinitis: their characterization with attention to the meaning of eosinophilia. J Allergy Clin Immunol 1980;65:122–6.
9. **Jacobs RL, Freedman PM, Boswell RN.** Nonallergic rhinitis with eosinophilia (NARES syndrome). J Allergy Clin Immunol 1981;67: 253–62.
10. **Jacobs RL.** Nonallergic chronic rhinitis syndromes. Immunol Allergy Clin North Am 1987;7:93–103.
11. **Anggard A.** Vasomotor rhinitis: pathophysiological aspects. Rhinology 1979;17:31–5.
12. **Weber RW.** Allergens. Primary Care 1987;14:435–45.
13. **Settipane GA.** Allergic rhinitis—update. Otolaryngol Head Neck Surg 1986;94:470–5.
14. **Berman BA.** Allergic rhinitis: mechanisms and management. J Allergy Clin Immunol 1988;81:980–4.
15. **Conner BL, Georgitis JW.** Practical diagnosis and treatment of allergic and nonallergic rhinitis. Primary Care 1987;14:457–73.
16. **Druce HM.** Nasal physiology. Ear Nose Throat J 1986;65:201–5.
17. **Stafford CT.** Allergic rhinitis. Postgrad Med 1987;81:147–57.
18. **Smith TF.** Allergy and pseudoallergy: an overview of basic mechanisms. Primary Care 1987;14:421–33.
19. **Naclerio R, Proud D, Peters S, Kagey-Sobotka A. Lichtenstein L, Norman P.** The role of inflammatory mediators in allergic rhinitis. Ear Nose Throat 1986;65:206–12.
20. **Okuda M, Watase T, Mezawa A, Liu CM.** The role of leukotriene D4 in allergic rhinitis. Ann Allergy 1988;60:537–40.
21. **Viegas M, Gomez E, Brooks J, Davies RJ.** Changes in nasal mast cell numbers in and out of the pollen season. Int Arch Allergy Appl Immunol 1987;82:275–6.
22. **Coman WB.** Allergic rhinitis and sinusitis. Aust Fam Physician 1986;15:694–9.
23. **Middleton E.** Chronic rhinitis in adults. J Allergy Clin Immunol 1988;81:971–5.
24. **Pearlman DS.** Chronic rhinitis in children. J Allergy Clin Immunol 1988;81:962–6.
25. **McDonald TJ.** Nasal disorders in children. Postgrad Med 1987;81: 65–74.
26. **Sassouni V, Friday GA, Shnorhokian H, et. al.** The influence of perennial allergic rhinitis on facial type and a pilot study of the effect of allergy management on facial growth patterns. Ann Allergy 1985; 54:493–7.
27. **Shapiro PA.** Effects of nasal obstruction on facial development. J Allergy Clin Immunol 1988;81:967–71.
28. **Fireman P.** Nasal allergy: a risk factor for middle ear disease. Ann Allergy 1987;58:395–400.
29. **Hagy GW, Settipane GA.** Risk factors for developing asthma and allergic rhinitis. J Allergy Clin Immunol 1976;58:330–6.
30. **Schumacher MJ.** Advances in tests for the evaluation of rhinitis. Immunol Allergy Clin North Am 1987;7:15–35.
31. **Evans R, Summers RJ.** Classical approaches to the diagnosis of allergy. Ear Nose Throat J 1986;65:34–40.
32. **Duc J, Peitrequin R, Pecoud A.** Value of a new screening test for respiratory allergy. Allergy 1988;43:332–7.
33. **Negrini AC, Troise C, Voltolini S.** ELISA in diagnosis of respiratory allergy. Allergy 1985;40:238–41.
34. **Nelson HS, Hirsch ST, Ohman JL, et al.** Recommendations for the use of residential air-cleaning devices in the treatment of allergic respiratory diseases. J Allergy Clin Immunol 1988;82:661–9.
35. **Nuutinen J, Holopainen E, Haahtela T, Ruoppi P, Silvasti M.** Balanced physiological saline in the treatment of chronic rhinitis. Rhinology 1986;24:265–9.
36. **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.
37. **Broide D, Schatz M, Zeigler R.** Current status of pharmacotherapy in the treatment of rhinitis. Ear Nose Throat J 1986;65:222–6.
38. **Meltzer EO, Schatz M.** Pharmacotherapy of rhinitis—1987 and beyond. Immunol Allergy Clin North Am 1987;7:57–91.
39. **Bryant BG, Cormier JF.** Cold and allergy products. In: Handbook of

nonprescription drugs, 8th ed. Washington, DC: American Pharmaceutical Association, 1986:127–74.
40. **Empey DW, Medder KT.** Nasal decongestants. Drugs 1981;21: 438–43.
41. **Anonymous.** Nasal decongestants. In: Kastrup EK, Olin BR eds. Facts and comparisons. St. Louis: JB Lippincott, 1988:184–86.
42. **Anonymous.** Vasoconstrictors. In: McEvoy GK, ed. Drug information 1988. Bethesda, MD: American Society of Hospital Pharmacists, 1988:1580–92.
43. **Blue JA.** Rhinitis medicamentosa. Ann Allergy 1968;26:425–9.
44. **Siegel SC.** Topical intranasal corticosteroid therapy in rhinitis. J Allergy Clin Immunol 1988;81:984–91.
45. **Okuda M, Sakaguchi K, Ohtsuka H.** Intranasal beclomethasone: mode of action in nasal allergy. Ann Allergy 1983;50:116–20.
46. **Pipkorn U, Proud D, Lichtenstein LM, Kagey-Sobotka A, Norman PS, Naclerio RM.** Inhibition of mediator release in allergic rhinitis by pretreatment with topical glucocorticosteroids. N Engl J Med 1987; 316:1506–10.
47. **Norman PS.** Review of nasal therapy: update. J Allergy Clin Immunol 1983;72:421–32.
48. **Chervinsky P.** Dexamethasone aerosol in perennial allergic rhinitis. Ann Allergy 1966;24:150–2.
49. **Michels MI, Smith RE, Heimlich EM.** Adrenal suppression and intranasally applied steroids. Ann Allergy 1967;25:569–74.
50. **Kimmerle R, Rolla AR.** Iatrogenic Cushing's syndrome due to dexamethasone nasal drops. Am J Med 1985;79:535–7.
51. **Merck Sharp & Dohme.** Decadron Phosphate Turbinaire package insert. West Point, PA; 1985 April.
52. **Brattsand R, Thalen A, Roempke K, Kallstrom L, Gruvstad E.** Development of new glucocorticosteroids with a very high ratio between topical and systemic activities. Eur J Respir Dis 1982; 122(suppl):62–73.
53. **Wihl JA.** Recent progress in the treatment of nasal allergy; intranasal steroid treatment. Rhinology 1984;22:27–31.
54. **Glaxo Inc.** Beconase products information. Research Triangle Park, NC; 1988 Aug.
55. **Schering Corp.** Vancenase product information. Kenilworth, NJ; 1988 July.
56. **Syntex Inc.** Nasalide package insert. Palo Alto, CA; 1986 Dec.
57. **Anonymous.** Intranasal corticosteroid aerosols for noninfectious rhinitis. Med Lett Drugs Ther 1981;23:101–2.
58. **Pakes GE, Brogden RN, Heel RC, Speight TM, Avery GS.** Flunisolide: a review of its pharmacological properties and therapeutic efficacy in rhinitis. Drugs 1980;19:397–411.
59. **Doble N.** Reaction to beclomethasone dipropionate nasal spray. Br Med J 1985;290:518.
60. **Schoelzel EP, Menzel ML.** Nasal sprays and perforation of the nasal septum. JAMA 1985;253:2046.
61. **Soderberg-Warner ML.** Nasal septal perforation associated with topical corticosteroid therapy. J Pediatr 1984;105:840–1.
62. **LaForce C, Davis V.** Nasal septal perforation in patients using intranasal beclomethasone dipropionate. J Allergy Clin Immunol 1985; 75:186.
63. **Mygind N, Sorensen H, Pedersen CB.** The nasal mucosa during long-term treatment with beclomethasone dipropionate aerosol. Acta Otolaryngol 1978;85:437–43.
64. **Knight A, Kolin A.** Long-term efficacy and safety of beclomethasone dipropionate aerosol in perennial rhinitis. Ann Allergy 1983;50:81–4.
65. **Brogden RN, Heel RC, Speight TM, Avery GS.** Beclomethasone dipropionate. Drugs 1984;28:99–126.
66. **Clayton DE, Kooistra JB, Geller M, et al.** Short-term efficacy trial and twenty-four-month follow-up of flunisolide nasal spray in the treatment of perennial rhinitis. J Allergy Clin Immunol 1981;67:2–7.
67. **Siegel SC, Katz RM, Rachelefsky GS, et al.** Multicentric study of beclomethasone dipropionate nasal aerosol in adults with seasonal allergic rhinitis. J Allergy Clin Immunol 1982;69:345–53.
68. **Stafanger G.** In vitro effect of beclomethasone dipropionate and flunisolide on the mobility of human nasal cilia. Allergy 1987;42: 507–11.
69. **Spock A.** The effect of topical agents on ciliary activity of nasal mucosa. J Allergy Clin Immunol 1984;73:142.
70. **Turkeltaub PC, Norman PS, Johnson JD, Crepea S.** Treatment of seasonal and perennial rhinitis with intranasal flunisolide. Allergy 1982;37:303–11.
71. **Horowitz M, Burnet RB.** The effect of intranasal beclomethasone dipropionate on adrenal function. Med J Aust 1979;2:660–1.
72. **Munch E, Gomez G, Harris C, et al.** An open comparison of dosage frequencies of beclomethasone dipropionate in seasonal allergic rhinitis. Clin Allergy 1981;11:303–9.
73. **Nuutinen J, Ruoppi P, Sorri M, Suonpaa J, Vainio – Mattila J.** Two-dose beclomethasone dipropionate aerosol in the treatment of seasonal allergic rhinitis. Rhinology 1983;21:165–72.
74. **Glaxo Inc.** Beconase AQ product information. Research Triangle Park, NC; 1988 Aug.
75. **Schering Corp.** Vancenase AQ product information. Kenilworth, NJ; 1988 July.
76. **Fisons Corp.** Nasalcrom package insert. Bedford, MA; 1985 March.
77. **Orgel HA, Meltzer EO, Kemp JP, Welch MJ.** Clinical, rhinomanometric, and cytologic evaluation of seasonal allergic rhinitis treated with beclomethasone dipropionate as aqueous nasal spray or pressurized aerosol. J Allergy Clin Immunol 1986;77:858–64.
78. **Boyd G, Langan CE, Langan JJ.** Beclomethasone dipropionate in seasonal allergic rhinitis: a comparison of two preparations. Practitioner 1985;229:823–5.
79. **Sidwell S.** A comparison of the efficacy and tolerance of an aqueous beclomethasone dipropionate nasal spray with the conventional pressurized spray. Curr Med Res Opin 1983;8:659–64.
80. **Greenbaum J, Leznoff A, Schulz J, Massa J, Tobe A, Miller D.** Comparative tolerability of two formulations of Rhinalar (flunisolide) nasal spray in patients with seasonal allergic rhinitis. Ann Allergy 1988;61:305–10.
81. **Short AC, Weinberg EG.** Beclomethasone dipropionate aerosol in treatment of perennial allergic rhinitis in children. Arch Dis Child 1977;52:486–88.
82. **Gale AE, Solomon E, Tao BK.** Intranasal topical flunisolide therapy in children with seasonal allergic rhinitis. Clin Allergy 1980;10: 527–33.
83. **Pipkorn U, Rundcrantz H, Lindquist S, Lindquist N.** Budesonide – a new nasal steroid. Rhinology 1980;18:171–5.
84. **Balle VH, Pedersen U, Engby B.** The treatment of perennial rhinitis with a new, non-halogenated, topical, aerosol packed steroid, budesonide. Acta Otolaryngol 1982;94:169–73.
85. **Warland A, Moller P, Lindquist N.** Budesonide – a new steriod for intranasal use. Allergy 1981;36:425–8.
86. **Lindquist N, Balle VH, Karma P, et al.** Long-term safety and efficacy of budesonide nasal aerosol in perennial rhinitis. Allergy 1986;41: 179–86.
87. **Clissold SP, Heel RC.** Budesonide. Drugs 1984;28:485–518.
88. **Edsbacker S, Andersson KE, Ryrfeldt A.** Nasal bioavailability and systemic effects of the glucocorticoid budesonide in man. Eur J Clin Pharmacol 1985;29:477–81.
89. **Meding B, Dahlberg E.** Contact allergy to budesonide in a nasal spray. Contact Dermatitis 1986;14:253–4.
90. **Duchateau GS, Zuidema J, Merkus FW.** The in vitro and in vivo effect of a new non-halogenated cortocosteroid – budesonide – aerosol on human ciliary epithelial function. Allergy 1986;41:260–5.
91. **Horak F, Matthes H.** The protective action of flucortin butylester (FCB) in the nasal antigen provocation test: a controlled double-blind, crossover study. Ann Allergy 1982;48:305–8.
92. **Arbesman C, Bernstein IL, Bierman CW, et al.** Multi-center, double-blind, placebo-controlled trial of flucortin butyl in perennial rhinitis. J Allergy Clin Immunol 1983;71:597–603.
93. **Hartley TF, Lieberman PL, Meltzer EO, Noyes JN, Pearlman DS, Tinkelman DG.** Efficacy and tolerance of flucortin butyl administered twice daily in adult patients with perennial rhinitis. J Allergy Clin Immunol 1985;75:501–7.
94. **Moesgaard-Nielsen V, Vinther B, Illum P, Harvig H.** Perennial rhinitis treated with a new steroid: flucortin butylester (FCB). Rhinology 1986;24:175–9.
95. **McAllen MK, Portillo PR, Parr EJ.** Intranasal flunisolide, placebo and beclomethasone dipropionate in perennial rhinitis. Br J Dis Chest 1980;74:32–6.
96. **Sahay JN, Chatterjee SS, Engler C.** A comparative trial of flunisolide and beclomethasone dipropionate in the treatment of perennial allergic rhinitis. Clin Allergy 1980;10:65–70.
97. **Aasand G, Etholm BO, Skjostad M, Volden J.** Flunisolide nasal spray compared to beclomethasone dipropionate in the treatment of seasonal rhinitis. Rhinology 1982;20:205–11.
98. **Sipila P, Sorri M, Ojala K, Palva A.** Comparative trial of flunisolide and beclomethasone dipropionate nasal sprays in patients with seasonal allergic rhinitis. Allergy 1983;38:303–7.
99. **Langrick AF.** Comparison of flunisolide and beclomethasone dipropionate in seasonal allergic rhinitis. Curr Med Res Opin 1984;9: 290–5.
100. **Pipkorn U.** Hay fever treatment with budesonide and beclomethasone dipropionate twice daily – a clinical comparison. Rhinology 1983;21:335–40.
101. **Pipkorn U, Rundcrantz H.** Budesonide and beclomethasone dipropionate in hay fever – a single-blind comparison. Eur J Respir Dis 1982;63:211–20.
102. **Vanzieleghem MA, Juniper EF.** A comparison of budesonide and beclomethasone dipropionate nasal aerosols in ragweed-induced rhinitis. J Allergy Clin Immmunol 1987;79:887–92.
103. **Pipkorn U, Geterud A.** A comparative trial testing budesonide and flunisolide nasal sprays in patients with seasonal allergic rhinitis. Ann Allergy 1984;52:183–6.
104. **Hilas J, Booth RJ, Sommerfield S, Morton R, Avery J, Wilson JD.** A comparative trial of intranasal beclomethasone dipropionate and

sodium cromoglycate in patients with chronic perennial rhinitis. Clin Allergy 1980;10:253–8.
105. **Tandon MK, Strahan EG.** Double-blind crossover trial comparing beclomethasone dipropionate and sodium cromoglycate in perennial allergic rhinitis. Clin Allergy 1980;10:459–62.
106. **Brown HM, Engler C, English JR.** A comparative trial of flunisolide and sodium cromoglycate nasal sprays in the treatment of seasonal allergic rhinitis. Clin Allergy 1981;11:169–73.
107. **Welsh PW, Stricker WE, Chu CP, et al.** Efficacy of beclomethasone nasal solution, flunisolide, and cromolyn in relieving symptoms of ragweed allergy. Mayo Clin Proc 1987;62:124–34.
108. **Bjerrum A, Illum P.** Treatment of seasonal allergic rhinitis with budesonide and disodium cromoglycate. Allergy 1985;40:65–9.
109. **Bende M, Pipkorn U.** Topical levocabastine, a selective H_1 antagonist, in seasonal allergic rhinoconjunctivitis. Allergy 1987;42:512–15.
110. **Schwartz HJ.** The effect of cromolyn on nasal disease. Ear Nose Throat J 1986;65:449–56.
111. **Anonymous.** Cromolyn sodium nasal spray for hay fever. Med Lett Drugs Ther 1983;25:89–90.
112. **Nelson BL, Jacobs RL.** Response of the nonallergic rhinitis with eosinophilia (NARES) syndrome to 4% cromolyn sodium nasal solution. J Allergy Clin Immunol 1982;70;125–8.
113. **Shore L.** Disodium cromoglycate (Rhynacrom) in the treatment of nasal allergy in children. S Afr Med J 1972;46:279.
114. **Gonzales JP.** Brogden RN. Nedocromil sodium. Drugs 1987;34: 560–77.
115. **Rhuno J, Denburg J, Dolovich J.** Intranasal nedocromil sodium in the treatment of ragweed-allergic rhinitis. J Allergy Clin Immunol 1988;81:570–4.
116. **Sipila P, Sorri M, Pukander J.** Double-blind comparison of nedocromil sodium (1% nasal spray) and placebo in rhinitis caused by birch pollen. Clin Otolaryngol 1987;12:365–70.
117. **Corrado OJ, Gomez E, Baldwin DL, Clague JE, Davies RJ.** The effect of nedocromil sodium on nasal provocation with allergen. J Allergy Clin Immunol 1987;80:218–22.
118. **Borum P.** Nasal disorders and anticholinergic therapy. Postgrad Med J 1987;63:61–8.
119. **Sanwiker S, Schmitz PI, Dieges PH.** The effect of locally applied ipratropium aerosol on the nasal methacholine challenge in patients with allergic and non-allergic rhinitis. Ann Allergy 1986;56:162–5.
120 **Sjogren I, Juhasz J.** Ipratropium in the treatment of patients with perennial rhinitis. Allergy 1984;39:457–61.
121. **Kirkegaard J, Mygind N, Molgaard F, et al.** Ordinary and high-dose ipratropium in perennial nonallergic rhinitis. J Allergy Clin Immunol 1987;79:585–90.
122. **Jokinen K, Sipila P.** Intranasal ipratropium in the treatment of vasomotor rhinitis. Rhinology 1983;21:341–5.
123. **Dolovich J, Kennedy L, Vickerson F, Kazim F.** Control of the hypersecretion of vasomotor rhinitis by topical ipratropium bromide. J Allergy Clin Immunol 1987;80:274–8.
124. **Kazim F, Salvatori VA.** Intranasal Atrovent versus placebo in the treatment of vasomotor rhinitis. Ann Allergy 1986;57:348–54.
125. **Borum P, Olsen L, Winther B, Mygind N.** Ipratropium nasal spray: a new treatment for rhinorrhea in the common cold. Am Rev Respir Dis 1981;123:418–23.
126. **Ohi M, Sakakura Y, Murai S, Miyoshi Y.** Effect of ipratropium bromide on nasal mucociliary transport. Rhinology 1984;22:241–6.
127. **Pipkorn U, Bende M, Hedner J, et al.** A double-blind evaluation of topical levocabastine, a novel specific H_1 antagonist, in patients with allergic conjunctivitis. Allergy 1985;40:491–6.
128. **Pecoud A, Zuber P, Kolly M.** Effect of a new selective H_1 receptor antagonist (levocabastine) in a nasal and conjunctival provocation test. Int Arch Allergy Appl Immunol 1987;82:541–3.
129. **Palma-Carlos AG, Palma-Carlos ML, Rombaut N.** The effect of levocabastine nasal spray in nasal provocation tests. Int J Clin Pharm Res 1988;8:25–30.
130. **Van De Heyning PH, Van Haesendonck J, Creten W, Rombaut N.** Effect of topical levocabastine on allergic and non-allergic perennial rhinitis. Allergy 1988;43:386–91.