Diagnosis and Management of Allergic Rhinitis

Case Study and Commentary, *H. Carter Davidson, MD, PhD, and Suman Golla, MD*

Abstract

- *Objective:* To provide an overview of the approach to diagnosis and management of allergic rhinitis.
- *Methods:* Review of the literature.
- *Results:* Allergic rhinitis affects 20% to 40% of the U.S. population and has a significant impact on patients, their families, and society. The diagnosis can often be ascertained from a history that points to a specific, often seasonal or environmental, trigger. Treatment is often begun without the aid of any testing and based on a diagnosis made on history and physical examination alone. The mainstays of first-line treatment are nonsedating oral antihistamines, nasal corticosteroids, and nasal antihistamine sprays. As an adjunct, mast cell stabilizing antihistamine eye drops may be used. First-line pharmacotherapy should be based on the nature and severity of the patient's symptoms. Allergy testing should be considered when a patient's symptoms are not controlled by routine medical therapies.
- *Conclusion:* Allergy is a significant burden to society. A symptom-based approach to the pharmacologic treatment of allergic rhinitis will yield the most satisfactory control of the patient's major symptoms.

CASE STUDY

Initial Presentation

A 42-year-old woman presents to a clinic complaining of rhinorrhea, nasal congestion, and headache.

History

The patient states that these problems began approximately 3 years ago and began mainly as rhinorrhea, postnasal drip, and itchy, watery eyes. She notes that over the past year her rhinorrhea has worsened and her nasal congestion has become almost year-round. She has always suffered from migraine headaches; however, she describes an increased frequency and a change from a temporal headache to a frontal headache over the past year. Of note, she states that she has never experienced any nasal symptoms of allergy before and only noticed the problem after moving from the Southwest to the Northeast part of the United States. She notices her symptoms are worse in the spring and fall months but lately she is symptomatic in the winter months, with her lowest level of symptoms in the summer. The patient denies any fevers, chills, or constitutional or respiratory symptoms. She has tried oral over-the-counter cold and sinus medications, never used nasal sprays, and has not been tested for allergies.

Physical Examination

On physical examination, the patient's conjunctiva are injected and anterior rhinoscopy reveals pale, boggy mucosa with evidence of polypoid changes of the inferior turbinates and no evidence of nasal septal deviation. There are abundant clear nasal secretions and no evidence of purulent rhinorrhea.

- **How significant is the disease burden of allergic rhinitis?**

Allergic rhinitis affects between 20% and 40% of the U.S. population and its incidence is rising dramatically [1]. In 2007, the World Health Organization estimated that 600 million people worldwide suffer from allergic rhinitis and even more suffer from nonallergic rhinitis [2,3]. The societal burden of allergic rhinitis is significant. An estimated $1.1 to $3 billion is spent annually in the United States on direct costs related to the treatment of allergic rhinitis. In addition, over 6 million days of missed work, 2 million days of missed school, and an astonishing 28 million days of reduced activity are attributed to allergic rhinitis, with total indirect costs of $800 million [4,5]. Furthermore, given that 19% to 38% of patients with allergic rhinitis have coexisting asthma [6] and that conditions such as rhinosinusitis, otitis media with effusion, and sleep disturbances are more prevalent in patients with allergic rhinitis [7], the combined allergic burden was estimated at over $4 billion in 1996 [8]. Ultimately, allergic rhinitis affects both the patient and

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Table 1. Causes of Nonallergic Rhinitis

Environmental irritants
Dust
Second-hand smoke
Odorants (ie, perfumes, chemical fumes)
Weather changes
Humidity and temperature variations
Food
Alcohol consumption
Spicy/hot foods
Medications
NSAIDS, beta blockers
Vasoconstrictive nasal sprays
Erectile dysfunction agents
Oral contraceptives
Emotional triggers
Hormonal variations
Hypothyroidism
Pregnancy

NSAIDs = nonsteroidal anti-inflammatory drugs.

their family members and has a significant impact on daily functioning [9].

- **What is the pathophysiology of allergic rhinitis?**

Pathophysiology

A review of the classification of allergic reactions is necessary for a complete understanding of the basis of allergic testing as well as treatment of allergic disease. Allergic rhinitis and most allergic reactions are classified as a type I hypersensitivity and are mediated by specific IgE antibodies to a particular allergen [10]. In type I hypersensitivity reactions, IgE antibodies are bound to mast cells. Eventual binding of antigen results in crosslinking of mast cell surface IgE and subsequent degranulation of mast cells. Preformed inflammatory mediators, including histamine, leukotrienes, prostaglandins, proteases, and cytokines are released as an immediate response, within seconds to minutes [11]. The collective effects of these inflammatory mediators produce edema, vasodilation, and irritation of nerve endings [12]. Clinically, swelling, itching, congestion, and possibly bronchospasm become the patient's primary symptoms. Collectively, the above mentioned inflammatory mediators constitute the "early phase" of type I hypersensitivity [13]. A "late-phase" of hypersensitivity also exists. Initiated at the time of mast cell degranulation, it is a result of local tissue damage and further release of additional inflammatory mediators, including leukotrienes and prostaglandins from the surrounding tissues. Recruitment of cellular mediators, particularly eosinophils and neutrophils, and subsequent release of these mediators are the hallmark of the "late phase" of type I hypersensitivity [14]. Activation of the immune system by antigens can result in other hypersensitivity cascades but are beyond the scope of this review.

- **How is the diagnosis of allergic rhinitis made?**

Diagnosis

Appreciating the differences between allergic and nonallergic rhinitis is important for an accurate diagnosis. Rhinorrhea, sneezing, nasal irritation, and nasal congestion are symptoms whose causes can be either allergic or nonallergic. Nonallergic rhinitis is defined as rhinitis without an infectious (ie, viral or bacterial rhinosinusitis) or allergic cause and has a plethora of possible causes [15] (**Table 1**). Nonallergic rhinitis is best exemplified in the condition of vasomotor rhinitis, the most common form of nonallergic rhinitis, where the patient's rhinitis may be precipitated by olfactory irritants, temperature changes, or emotional situations [16]. Allergic rhinitis on the other hand is a complex inflammatory disorder of the upper airways and belongs to a spectrum of diseases with a shared IgE-mediated pathway [17]. Activation of the immune system by exposure to the triggering allergen causes the release of inflammatory mediators and the subsequent inflammation which produces the symptomatology of allergy [12]. Therefore, the diagnosis of allergic rhinitis can often be ascertained from a history that points to a specific, often seasonal or environmental, trigger.

Conducting a Comprehensive History

The importance of a thorough history cannot be overestimated. A patient's history of nasal allergy symptoms should be in his or her own words with an attempt to identify the patient's most bothersome symptom. The duration, timing, context, quality, and severity of the symptoms should then be defined. A hallmark of allergic rhinitis is the exacerbation of symptoms due to specific triggers, which often have a seasonal predilection. Therefore, alleviating and aggravating factors must be carefully delineated. Often, this can be achieved best during a second visit after having the patient keep a journal logging the severity and situations surrounding their symptoms. Often omitted but important in the diagnosis as well as the generation of a treatment plan is a thorough occupational history. Additionally, an integral component of the complete history is a review of systems [18]. Triggers of nasal allergy may be restricted to a specific

portion of a patient's environment, and thus a conscientious history including associated symptoms will, with few exceptions, strongly suggest or exclude nasal allergy as a diagnosis. As illustrated in our case, the dominant symptoms of nasal congestion and rhinorrhea are extremely common in allergic rhinitis and can have nonallergic causes, including structural or even malignant conditions. The timing of the initial onset of symptoms concurrent with a recent change in environment as well a seasonal periodicity of symptoms strongly suggests an allergic cause [19].

As mentioned previously, allergy is a systemic disease and thus a complete review of systems may elucidate symptoms that seem unrelated but are in fact systemic manifestations of allergy. Somewhat intuitive as markers of allergy are symptoms such as sneezing and ocular and nasal pruritis; however, symptoms such as fatigue, abdominal pain, and headache are also commonly caused by systemic allergic disease [18]. A careful review of systems may also serve to rule out allergy as a cause and suggest an alternate diagnosis (**Table 2**), preventing delay in diagnosis and treatment of a potentially more serious condition. Additionally, diagnosis of allergic rhinitis carries a significant risk of other comorbid conditions such as sleep-disordered breathing and obstructive sleep apnea, otitis media with effusion, migraines, sinusitis, and asthma [7]. A comprehensive history pertaining to these known conditions can both aid in the diagnosis of allergic rhinitis as well as the diagnosis and treatment of the aforementioned disease conditions.

As a final consideration, a complete past medical history is critical to elucidate related conditions with allergic triggers. Current medications, family history, and social history often aid in the diagnosis of allergy. For example, a history of chronic dermatologic or gastrointestinal conditions may suggest food allergy. Medication side effects may mimic allergic symptoms; most well known may be the condition of rhinitis medicomentosa, caused by the chronic use of vasoconstrictive nasal sprays, but medications such as beta blockers have been shown to reduce the threshold for mast cell degranulation and therefore may serve to exacerbate allergic responses. Family history is important in that 35% of offspring of a single allergic parent and 65% of those with 2 allergic parents will have some allergic symptoms in their lifetime [18]. As mentioned previously, social history may point to allergic triggers specific to a patient's home or work environment, aiding in treatment aimed at avoidance of triggers [20].

Table 2. Differential Diagnosis of Allergic Rhinitis

Nonallergic rhinitis (*see* Table 1)
Gustatory rhinitis
Nasal polyposis
Acute bacterial sinusitis
Viral rhinosinusitis
Anatomic rhinitis
Deviated nasal septum
Turbinate hypertrophy
Adenoid hypertrophy
Sinonasal tumors
Granulomatous rhinitis
Wegeners granulomatosis
Sarcoidosis
Cerebrospinal fluid leak
Kartagener's syndrome

Approach to the Physical Examination

As important as a complete history is a comprehensive physical examination. Initial physical examination, particularly in children, should take note of any facial features known to be classic signs of allergy. Flattened malar eminences, low nasal bridge, open mouth breathing, and a shortened mandible comprise a constellation of facial features known as "adenoid facies." This pattern of facial development occurs with persistent nasal obstruction. Protrusion of front teeth as well as an open mouth at rest and during respiration also suggest allergy. The presence of skin discoloration in the infraorbital region as well as horizontal creases in the lower eyelid skin, known as "allergic shiners" and "Dennie lines," respectively, are stigmata of allergic disease as well. Conjunctival edema and injection due to the downstream effects of histamine release may also be seen [21].

Examination of the external nose and anterior rhinoscopy with nasal speculum are imperative portions of the physical examination. External finding of a supratip crease is caused by frequent manipulation of the nose with the palm of the hand to clear nasal discharge or alleviate nasal itch. Frequent manipulation for a period of 2 years makes this crease permanent. Erythema of the philtrum or obvious nasal crusting may also be present. Anterior rhinoscopy will reveal pale, edematous mucosa of the nasal vault and turbinates, enlargement of nasal turbinates, and clear nasal discharge. In adults or in children whose history is suspicious for nonallergic causes, posterior rhinoscopy should be performed to eliminate other causes of symptoms, especially in patients suffering from significant nasal obstruction or recurrent epistaxis. Findings in the posterior nasal cavity may include cobblestoning of the nasal mucosa or the presence of nasal polyps. Nasal polyps caused by allergic disease are almost universally bilateral, given the systemic nature of the disease [22]. Unilateral polyps should raise the suspicion of malignancy in adults, or foreign body reaction in children. Additionally, nasal polyps in children should prompt a workup for cystic fibrosis [23].

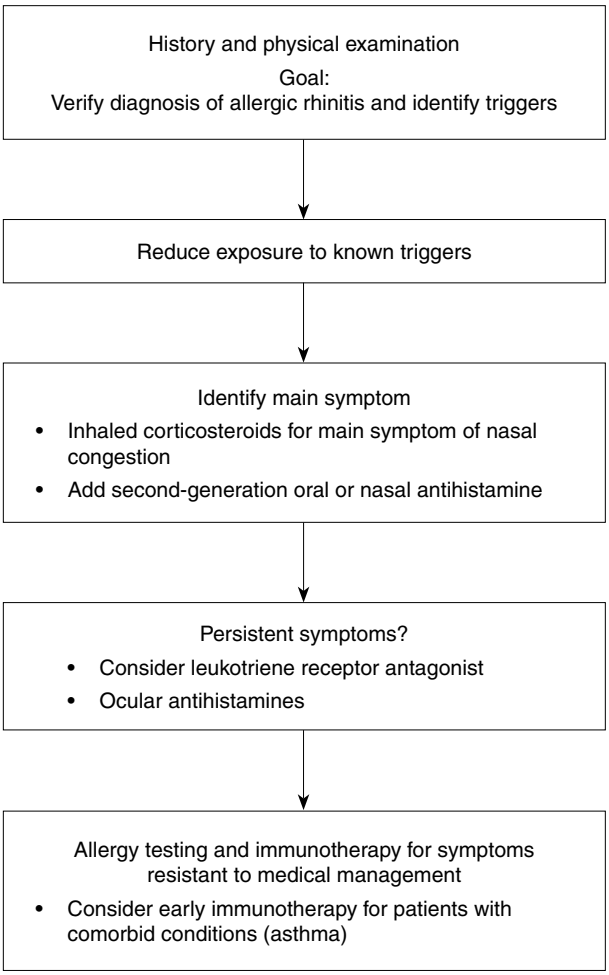

Figure. Algorithm for diagnosis and treatment of allergic rhinitis.

The remainder of the physical examination may reveal other associated findings. Oral cavity examination may reveal high arched palate, halitosis, and dental caries caused by persistent mouth breathing. Oropharyngeal exam may include cobblestoning of the posterior pharynx and cryptic, erythematous tonsils from persistent postnasal drip and hypertrophic lymphoid tissues. Lymphadenopathy from recurrent infections or even hypertrophy of neck musculature from frequent swallowing of nasal secretions may also be present. Otologic exam must also be performed to screen for otitis media with effusion, often associated with nasal allergy [21].

- **How is allergic rhinitis treated?**

Treatment

The treatment of allergic rhinitis is often begun without the aid of any testing and based on a diagnosis made on history and physical examination alone. The mainstays of first-line treatment are nonsedating oral antihistamines, nasal corticosteroids, and nasal antihistamine sprays. As an adjunct, mast cell stabilizing antihistamine eye drops may also be used. Given the relatively low cost of these medications, paucity of side effects, and general effectiveness, the risk-benefit ratio is low [24]. As such, the threshold for a treatment trial is also low [25]. Empiric treatment is advocated in most situations since ancillary testing would not change the initial treatment algorithm.

First-line pharmacotherapy should be based on the nature and severity of the patient's symptoms [26]. Each agent has a unique efficacy in controlling the symptoms of nasal congestion, rhinorrhea, sneezing, itching and other allergic symptoms. Furthermore, an algorithm-based treatment plan has been supported in a randomized controlled trial as more efficacious in controlling symptoms and improving patient quality of life than physician-chosen therapy [27] (**Figure**). Delineated below are the agents used most commonly in the treatment of allergic rhinitis, including their effectiveness in controlling the most common symptoms of allergic rhinitis as well as their side-effect profile.

Antihistamines

The early allergic response is largely a result of histamine release. Oral antihistamines have been a mainstay of treatment since their advent in the 1930s [28]. Though effective in alleviating the histamine-driven symptoms of ocular and nasal pruritis, sneezing, and rhinorrhea, the major drawback of first-generation antihistamines has been their propensity to cross the blood–brain barrier, producing the side effect of sedation. Furthermore, antihistamines generally are not efficacious in controlling nasal congestion, the major symptom of allergic rhinitis [29]. Second-generation antihistamines do not cross the blood–brain barrier and have been shown as efficacious in the control of allergic symptoms as their sedating counterparts. Antihistamines are now available in oral and topical forms and both preparations are useful as first-line treatment for mild or intermittent allergic rhinitis [30,31].

Intranasal Corticosteroids

Topical corticosteroids are the most effective agents for the treatment of moderate to severe allergic rhinitis [12]. At present, second-generation antihistamines are still considered first-line agents for mild allergic rhinitis due to their favorable side-effect profile; however, intranasal corticosteroids are also considered safe for first-line treatment in severe allergic rhinitis [16]. Concern over systemic side effects has

been diminished by recent studies demonstrating no significant systemic side effects; however, concern over growth inhibition in children still exists [32–34]. The majority of intranasal steroids have been shown to be safe for use in children, with no significant effect on growth [35]. Some discussion of side effects of nasal corticosteroids is justified. The most common side effect is epistaxis [36]; however, other minor side effects include nasal irritation, burning, sore throat, and foul taste [37]. Nasal corticosteroids do not have a mechanism of action that prevents the immune response to allergen but instead attenuate the effects of an allergic response; however, their mechanism of action in controlling allergic symptoms is not fully understood. The end effect of corticosteroid treatment is the blockade of proinflamatory cytokine release and a subsequent decrease in vessel permeability and recruitment of proinflamatory cells. For this reason, intranasal corticosteroids are best at controlling the symptom of nasal congestion [38]. A comparison of symptom control has shown nasal corticosteroids superior to oral antihistamines in control of nasal congestion and sneezing but equally efficacious in the control of ocular symptoms [29]. Nasal antihistamines performed similarly to oral preparations in a separate meta-analysis [39].

Leukotriene Receptor Antagonists

Leukotrienes are one of the many inflammatory mediators released during an allergic response, and monoleukast, a leukotriene receptor antagonist, has been shown to decrease the daily symptom scores of patients suffering from allergic rhinitis [40]. The effects of leukotriene receptor antagonists on daily symptom scores are superior to placebo but not superior to antihistamines or nasal corticosteroids [41]. Leukotriene receptor antagonists are most useful as adjunctive therapy, but no clear data exists on combination therapy with either nasal corticosteroids or antihistamines.

Other Pharmacotherapy

Like antihistamines and leukotriene inhibitors, inhibitors of mast cell degranulation have the ability to prevent a portion of the allergic response. Cromolyn sodium is available over the counter in the United States and has been shown to effectively control symptoms of sneezing, pruritis, and rhinorrhea. Despite its theoretic efficacy, clinical use is hampered by its frequent dosing as well as a need to administer prior to antigen exposure for maximum effect. Therefore, utility is limited to use in mild allergy with an identifiable trigger with preemptive treatment [42]. Nasal decongestants are also used in the treatment of allergic rhinitis. As mentioned, nasal congestion is a prominent symptom for a majority of patients and is often difficult to treat. Acute episodes of nasal congestion, times of intense allergen exposure, and exacerbations of symptoms associated with episodes of acute sinusitis may all be treated with oral or topical decongestants. However, caution must be exercised when topical decongestants are used for greater than a 5-day duration due to the risk of rebound rhinitis [43]. As well, the systemic side effects of oral decongestants cannot be overlooked, especially in patients with hypertension, cardiovascular disease, and benign prostatic hypertrophy. Finally, anticholinergics have shown efficacy in the control of refractory rhinorrhea [44].

- **When is allergy testing and immunotherapy indicated?**

Allergy Testing

Allergy testing should be considered when a patient's symptoms are not controlled by routine medical therapies. The negative predictive value of allergy testing is not strong enough to warrant avoidance of treatment in patients with a history otherwise strongly suggestive of allergic disease; therefore, testing should be utilized after traditional medical therapy has failed to control disease symptoms [45]. The major goal of allergy testing is the identification of specific antigen triggers, thus allowing allergen avoidance and allergen-specific immunotherapy.

Allergy testing can be performed either in vitro or in vivo. In vitro testing is based on detection of surrogate markers of allergic response [46]. In vitro allergy testing measures the level of antigen-specific IgE in a patient's blood. This form of testing verifies that a patient has been previously sensitized to an allergen in question. Measurement of a patient's total IgE level may be useful if elevated, prompting further allergy testing. However, a normal total IgE screen does not rule out an elevation of an antigen-specific IgE. The classic in vitro allergy test is a radioallergosorbent test (RAST), but this has largely been replaced by the nonradioactive enzyme-linked immunosorbant assay (ELISA) [46]. Both tests are based on the same principle of detecting allergen-specific IgE by exposing the patient's serum to a known concentration of antigen bound to solid support. The detection methods differ but are beyond the scope of this discussion. There are situations in which in vitro testing is preferred to in vivo testing (eg, very young children who cannot tolerate skin testing, patients with severe anaphylactic reactions to in vivo testing, or patients with dermatologic conditions). In general, in vivo testing is more sensitive, while in vitro assays are more specific.

In vivo assays can be broken down into skin testing or intradermal testing (IDT) [46]. Skin testing can be performed by patch testing, scratch testing, and skin prick testing. Patch testing is difficult to reproduce and forms of skin irritation can be mistaken for allergic response. Scratch testing has

a problematic low sensitivity and specificity and therefore both testing methods are generally not recommended forms of allergy testing. Skin prick testing is more sensitive and specific and allows for rapid screening of multiple antigens. Skin prick testing also has the advantage of testing a serial dilution of antigen, thus giving a safe dose appropriate for starting IDT as well as determining a starting dose for immunotherapy [46]. IDT has the highest sensitivity and reproducibility compared with other testing methods but carries the highest risk of anaphylaxis due to the vascularity of the dermis [47]. Again, IDT involves the injection of progressively dilute antigen and helps determine a starting immunotherapy dose, but it should always be preceded by skin endpoint testing to decrease the risk of anaphylaxis.

Immunotherapy

After medical management, allergen avoidance, and environmental controls have failed to control disease, immune modulation through immunotherapy is a treatment option. Immunotherapy is the most specific treatment for allergic rhinitis. Immunotherapy has been shown to decrease medication use as well as symptoms in patients [48,49]. The drawbacks of immunotherapy include the necessity of determining a specific antigen trigger as well as a commitment to at least 1 year of therapy. The identification of multiple allergen triggers can make immunotherapy difficult or impossible to administer. Furthermore, considerable caution must be exercised in patients with uncontrolled asthma, beta blocker usage, and in patients with immunocompromised states.

Case Follow-up

The patient was diagnosed with allergic rhinitis. The seasonal nature of her symptoms as well as the triggers of tree pollen and fresh cut grasses elucidated on further questioning pointed to the diagnosis. The patient was started on a nasal steroid spray and at her 6-week follow-up visit she reported less nasal congestion and partial relief of her rhinorrhea. A nasal antihistamine spray was later added for her persistent rhinorrhea. She has not undergone allergy testing given that her symptoms are well controlled.

SUMMARY

Allergy is a significant burden to society on many levels. The individual symptom burden, decreased productivity, and extensive health care costs make the diagnosis and treatment of allergic disease exceedingly important. The diagnosis of allergic rhinitis should be based largely on appropriate history and physical examination, and in vitro and in vivo methods of allergy testing should be used only when necessary. Awareness of associated comorbid conditions is also important in the workup and complete treatment, of the patient with allergic rhinitis. Furthermore, a symptom-based approach to pharmacologic treatment of allergic rhinitis will yield the most satisfactory control of the patient's major symptoms.

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