Allergic Rhinitis

5

Niharika Rath and Salman Aljubran

Contents

N. Rath · S. Aljubran (✉)
Department of Allergy and Immunology, Children's Mercy Hospital, Kansas City, MO, USA
e-mail: nrath@cmh.edu; saaljubran@cmh.edu

M. Mahmoudi (ed.), *Allergy and Asthma*,
https://doi.org/10.1007/978-3-030-05147-1_5

Abstract

Allergic rhinitis is an allergen-induced response leading to inflammation of the nasal membranes. This is a common disorder increasing in prevalence in the Western Hemisphere and negatively impacts quality of life in affected individuals. Allergic rhinitis can significantly impair productivity and social functioning in both children and adults due to the bothersome symptoms of this disease. Indoor and outdoor exposures can lead to symptoms of allergic rhinitis. Pollens, mold spores, pet, and pest exposures are the cause of symptoms in most patients. Primary symptoms of allergic rhinitis are sneezing, rhinorrhea, nasal congestion, and itching. Allergy testing in the forms of skin test and in vitro blood test is necessary to confirm the diagnosis, keeping in mind that history-guided testing is essential. Treatment options vary depending on the patient age and preference. These options include allergen avoidance, pharmacotherapy, and allergen immunotherapy. Therefore, the goal is treatment directed toward improvement of symptoms and quality of life.

Keywords

Allergic rhinitis · Rhinitis · Immunotherapy · Histamine · Antihistamine · Allergy testing · AIT

5.1 Introduction

Rhinitis is inflammation of the nasal epithelium characterized by sneezing, itching, rhinorrhea, and congestion. Allergic rhinitis, also known commonly as hay fever, is caused by an allergic response mediated by immunoglobulin E (IgE). Approximately 10–25% of people suffer from allergic rhinitis, and it can be a debilitating disease due to the interference with quality of life (Corren 2014). Allergic rhinitis affected 60 million people in the United States in 2013, 40% of whom were in the pediatric population (Gentile et al. 2015). Each year, this affected population has 7 or more days of allergic rhinitis or conjunctivitis symptoms leading to loss of productivity and compromised quality of life. Socioeconomic costs are substantial (Borish 2016). Chronic nasal dysfunction results in impaired school performance and decreased productivity, as well as complications from the chronic inflammation leading to other disorders such as middle ear disease and sinusitis (Corren 2014). Children and adolescents are proportionally more commonly affected than adults, but symptoms and treatment are generally the same in both pediatric and adult groups (Marcdante and Kliegman 2015). Treatment options are varied and include avoidance, pharmacotherapy, and allergen immunotherapy. Allergic rhinitis can be well managed with proper guidance regarding precautions and treatment.

5.2 Epidemiology

The incidence and prevalence of allergic rhinitis has increased significantly, especially in Western countries, over the past few decades. Overall disease prevalence is 15–20%. However, accurate estimates around the world are difficult to obtain due to variability of geographic pollen counts and difficulty in recognizing the symptoms by both patient and physician. Peak prevalence occurs in early teen years, around 13–14 years of age. Most patients diagnosed with allergic rhinitis will exhibit symptoms before 20 years of age, with males tending to have an increased incidence in childhood although this equalizes later in adolescence. Studies have shown the incidence is higher in developed countries and in adolescents compared to children. However, allergic rhinitis decreases in prevalence with advancing age in adults (Ricketti and Cleri 2009). It is postulated that exposures in early childhood can result in an increased risk of allergic rhinitis development. Specifically, development of allergic rhinitis is associated with air pollution levels and maternal smoking history (Corren 2014). There is also a higher incidence in upper level socioeconomic groups, ethnicities other than Caucasian, those with greater exposure to high indoor allergen

concentrations, and patients with greater serum IgE concentrations (Ricketti and Cleri 2009). There is a decreased risk of developing allergic rhinitis in patients with a higher number of siblings, patients living in a farm environment, and those eating a Mediterranean diet (Corren 2014). About 50% of patients with allergic rhinitis have associated allergic conjunctivitis, both occurring as a result of an allergen trigger.

5.3 Anatomic and Allergic Pathophysiology

The clinical definition of allergic rhinitis is a nasal disorder induced by an IgE-mediated inflammatory reaction of the membrane of the nose after exposure to an allergen. Although seasonal allergic rhinitis can occur in infants, it is unusual due to an individual requiring two or more seasons of exposure to a seasonal antigen in order to develop an allergic response (Ricketti and Cleri 2009). Aeroallergen sensitization can occur in the first 2 years of life if there is a significant atopic family history, but classic seasonal allergic rhinitis symptoms such as pruritus, rhinorrhea, and congestion generally do not develop until 2–7 years of age (Garcia-Lloret 2011).

5.3.1 Nasal Anatomy and Pathophysiology

Six major functions of the nose differentiate it from other sensory organs of the body. It is an olfactory organ, but it is also an important part of speech and phonation, an airflow passageway, a way to humidify and warm inspired air and a noxious particle filter for inspired air. Significantly, the nose is also involved in allergic and immunologic responses (Ricketti and Cleri 2009).

Air is heated and humidified by the vascularized nasal turbinate mucosa as the air passes through the nasal airway. Large cavernous vascular sinusoids on the turbinates contribute to this heating and humidification of inspired air. When these sinusoids are dilated, they cause congestion. This can occur in both allergic and non-allergic types of disease (Scadding et al. 2012). These blood vessels are controlled by the autonomic nervous system. The sympathetic process leads to vascular constriction and decreased secretion, whereas the parasympathetic effect leads to vascular dilation and increased secretions. Due to the large amount of vasculature in the nasal mucosa, changes can lead to obstruction. The normal nasal cycle involves congestion and decongestion of the mucosa, but abnormalities in this cycle due to allergic symptoms lead to changes in this cycle and emphasize congestion (Ricketti and Cleri 2009).

The filtering role of nasal mucosa is also critical to overall health. Nasal secretions contain bacteriostatic enzymes that work at an optimal pH of 7, as do the cilia. In addition to enzymes, these secretions contain immunoglobulin A (IgA) and protein, providing lubrication and protection. Large particles are filtered by hairs within the nostrils. Cilia beat at a steady frequency leading to a streaming mucus blanket that contains the filtered materials, moving the captured debris toward the pharynx to be swallowed or expectorated (Ricketti and Cleri 2009). Mucus is secreted by goblet and serous cells in the epithelium and by nasal glands. The secretion is controlled by parasympathetic nerves, but sympathetic stimuli and reflexes can also enhance secretion (Scadding et al. 2012).

Nasal sensation is primarily through the trigeminal nerve, and sensory fibers are stimulated by inflammatory mediators like histamine and bradykinin. Stimulation leads to release of neuropeptides, therefore increasing vascular permeability and activating submucosal gland release. This results in sensations of itching, rhinorrhea, and burning involved in the rhinitis response (Joe and Liu 2015).

5.3.2 Nasal Allergic Pathophysiology

Allergen exposure in the mucus membranes affects the overall response because of immune involvement of the nose. Mediator release from nasal mast cells and basophils is an important part of the immediate-type allergic reaction. Allergic

rhinitis patients have IgE antibodies that bind to high-affinity receptors on mast cells and basophils; low-affinity receptors on other cells can also bind to IgE. Sensitization to an allergen is needed to trigger an IgE response, which occurs by the allergen interacting with an antigen-presenting cell (APC) such as a macrophage, dendritic cell, B cell, or epithelial cell. Most APCs process the allergen and fragments and are presented with class II major histocompatibility class (MHC) molecules to T-helper cells. This results in cytokine release by the T-helper cell. Switching from a type 1 T-helper cell (Th1) response to a type 2 (Th2) phenotype is an early event of the allergic sensitization process and is the initiating factor for allergic inflammation. Two major Th2 pathways that lead to this inflammation are cytokine secretion and isotype switching of B cells to secrete IgE and the secretion of eosinophil growth factor IL-5 (Ricketti and Cleri 2009).

After IgE antibodies specific for an allergen are secreted, they bind to high-affinity receptors on mast cells and basophils. The allergic response occurs when nasal reexposure to the allergen causes cross-linking of the specific IgE on the mast cell surface and inflammatory mediator release such as histamine, prostaglandins, and bradykinin. These cause the vasodilation, increased vascular permeability, increased secretion, and afferent nerve stimulation that lead to rhinitis symptoms (Ricketti and Cleri 2009). Cytokines are also generated in this response. Physical examination, therefore, would show swollen nasal mucosa with clear secretions consistent with the induction of these vasoactive mediators (Borish 2016).

Nasal mast cells are located in the nasal lamina propria as connective tissue mast cells, although some are epithelial and known as mucosal mast cells. Superficial nasal epithelium in patients with allergic rhinitis has significantly more mast cells and basophils when compared to non-allergic patients (Ricketti and Cleri 2009). The lamina propria is highly vascular with significant permeability amenable to access by pharmacologic agents. The capillary network is extensive and fenestrated, allowing for rapid fluid transit (Scadding et al. 2012). T-helper cells, eosinophils, neutrophils, and basophils accumulate with continued allergic response. Eosinophils release proteins that disrupt the respiratory epithelium leading to further mast cell mediator release and hyperresponsiveness. Eosinophils increase during seasonal exposure and correlate with the severity of disease in nasal scrapings. Basophils, lymphocytes, eosinophils, and neutrophils infiltrating the nasal cavity lead to the late-phase reaction of allergic rhinitis (Ricketti and Cleri 2009).

5.3.3 Early- and Late-Phase Response

The response to a triggering allergen includes an early and late phase. The early phase, also known as the immediate phase, lasts about 1 h and occurs immediately after exposure. The late phase then begins in 3–6 h with a peak at 6–8 h; it resolves in 12–24 h. Early-phase reactions are sneezing, pruritus, and rhinorrhea, whereas late-phase symptoms involve more nasal congestion. The late phase is exacerbated by factors promoted by the early-phase reaction, with release of inflammatory mediators and cell recruitment in the nasal mucosa (Lang 2010). The release of mediators in the early phase occurs by allergen contact with IgE on mucosal mast cells or basophils (Fischer 2007). Histamine is primarily involved in the early phase, whereas the late phase is associated with other mediators with inflammatory effects. Eosinophils play a large role in the late-phase response including release of leukotrienes which participate in the late-phase congestion. Separation of early- and late-phase responses can be difficult, and a perpetual late-phase response develops in sensitized patients during their allergic seasons or when exposed to perennial triggers (Lang 2010).

5.3.4 Hereditary Association

The influence of inherited and environmental factors in allergic disease continues to be studied. Atopy has been linked to genetic loci on particular chromosomes, identifying family history as a significant risk factor for allergic rhinitis. Risk is low for atopic disease in a patient with absence of

parental family history, increases with one parent or sibling affected, and nearly doubles with biparental family history (Ricketti and Cleri 2009). Identical monozygotic twins have a 40–50% concordance rate, with dizygotic twins having a 25% concordance rate. Studies to identify the specific genes involved are limited at this time, and findings are difficult to interpret due to lack of replication in separate population cohorts (Scadding and Kariyawasam 2012).

5.4 Allergens

Allergic rhinitis occurs due to hypersensitivity to outdoor pollens and mold spores as well as indoor mold spores and animal proteins. Seasonal symptoms are due to specific pollens and mold spores that vary by season, whereas perennial symptoms are associated with indoor mold spores and animal exposures that can occur throughout the year (Borish 2016). Another system to categorize allergic rhinitis involves the terms intermittent or persistent allergic rhinitis as opposed to seasonal or perennial allergic rhinitis. Intermittent allergic rhinitis is defined as symptoms less than 4 days a week or for less than 4 weeks, and persistent allergic rhinitis has symptoms present for more than 4 days a week and more than 4 weeks (Brozek et al. 2017). The specific pollens involved in causing symptoms of rhinitis are airborne, whereas plants depending on insect pollination such as many flowering plants are not involved in allergic rhinitis (Ricketti and Cleri 2009). Outdoor sources of seasonal aeroallergens are weeds, grasses, trees, and outdoor molds such as *Alternaria* spp. and *Cladosporium* spp. In contrast, indoor aeroallergens which are involved in year-round allergic symptoms include house dust mite; pests such as cockroaches, mice, and rats; indoor pets; and indoor molds such as *Aspergillus* spp. and *Penicillium* spp. (Ricketti and Cleri 2009).

Seasons of pollination depend on the particular plants and geographic location. Relative amounts of light determine the pollinating season, and the variability with light is a consistent factor. Variable factors include weather conditions which influence how much pollen is produced in that season (Ricketti and Cleri 2009). In general, trees pollinate in the spring, grasses in late spring to summer, and weeds in late summer to fall (Nelson). March is usually the earliest month in which pollens will appear in the Upper Midwest, Western, and Eastern United States, but again geographic location is critical in determining specific seasons (Ricketti and Cleri 2009). Pollens are able to travel hundreds of miles and result in symptoms remote from the locale of production (Marcdante and Kliegman 2015).

Ragweed is an important pollen because of its potency. It is a significant cause of allergic rhinitis symptoms in the eastern and midwestern portions of the United States, with severe and long-lasting symptoms when compared to symptoms from most other pollens. Symptoms usually begin as early as August in the Midwest, mid-Atlantic, and Southern United States for patients who are highly sensitized. These symptoms can last until a hard winter freeze (Ricketti and Cleri 2009).

Symptoms recur annually depending on the duration of pollination of the specific plant. Symptoms tend to be worse in the morning due to increased airborne pollen release after sunrise; weather factors such as rain can decrease symptoms due to removal of pollen from the air. Dry, windy weather leads to increased pollen distribution and worsening of symptoms. Intensity of symptoms follows the pollen season, although symptoms can persist following the end of pollination season depending on the patient. The lingering effect of the allergic rhinitis symptoms is due to a priming effect, leading to increased reactivity due to repeated exposure to pollen over the prior weeks (Ricketti and Cleri 2009). This is thought to be a nonspecific effect, meaning after disappearance of the pollen from the environment, the patient may react to another allergen that would not cause symptoms in absence of the priming effect. The mechanisms underlying priming are not completely understood, but are thought to be related to increased mast cell and eosinophil numbers with cytokine-induced inflammation (Gentile et al. 2015). Secondary infection can also worsen symptoms of allergic rhinitis, as can irritant effects on already inflamed nasal

membranes. Irritants that are known to cause clinical worsening in these patients are tobacco smoke, paint, newspaper ink, soap powder, and air pollutants.

Mold or fungus is another source of allergen that affects patients with allergic rhinitis and can be due to either indoor or outdoor mold spores. The most commonly identified mold species in the United States are *Alternaria* and *Cladosporium*, which are outdoor allergens that cause the majority of symptoms. Molds are most significant during warmer months, and outdoor molds are not present during winter in regions that develop a frost, due to the killing of the fungi, the source of the spores, in a hard freeze. However, they can begin to appear in the early springtime, which is the earliest some sensitized patients may begin to show symptoms. Mold can be present in damp or musty environments as well as in leaves, barns, moldy hay, or straw. Rarely, ingestion of certain foods such as beer, wine, melons, mushrooms, and certain cheeses with high mold content may also result in symptoms (Ricketti and Cleri 2009).

House dust mites are present in higher humidity environments and practically all climates, resulting in perennial symptoms in sensitized patients. This can be severe, since dust mites are present in bedding and require specific hot water cleaning to remove or pillow and mattress encasements to reduce dust mite allergen production. The chronic exposure to dust mite allergen, with mites found in almost all domestic rooms with fabric or carpet, can result in persistent, significant symptoms (Ricketti and Cleri 2009).

Cockroach infestation in inner city housing, especially apartments, is an important and often overlooked cause of allergic sensitization and symptoms. The allergens are identified in the cockroach's digestive secretions and body parts. Their presence also results in perennial symptoms in sensitized patients.

There are many other allergens involved in allergic rhinitis such as pets and rodents. These are considered perennial allergens like house dust mite and cockroach and will be discussed later in this chapter.

5.5 Classification and Differential Diagnoses to Consider

Allergic rhinitis can be classified into several categories, which are summarized in Table 1. These classifications are seasonal, perennial, intermittent, and persistent. Seasonal allergic rhinitis affects patients in a seasonal manner due to the aeroallergens known as pollen. Patients with seasonal symptoms can have spring, summer, or fall pollen sensitization. Depending on the geographic region, winter pollen exposure can also occur. Patients can have several pollen allergies, resulting in multiple affected seasons. Symptoms during the winter are suggestive of perennial allergen sensitization due to the lack of outdoor pollen during times of frost or freeze. However, in regions without frost or freeze, winter pollen exposure can occur as mentioned above. Perennial allergic rhinitis, in contrast to seasonal allergic rhinitis, occurs year-round without a seasonal preference. This is due to year-round allergens which are primarily indoor, specifically due to house dust mite, cockroach, mold, and pets (Marcdante and Kliegman 2015). Symptoms can acutely worsen with increased exposure to allergen (i.e., close pet contact, cleaning a dusty home). However, in many parts of the world, pollens as well as other allergens are perennial due to the climate. In addition, patients sensitized to multiple triggers may have year-round symptoms due to many seasonal sensitivities and geographic location; this can be confusing since the terms seasonal and perennial may not exclusively apply. These should be considered when classifying a patient. As described in a prior section,

Table 1 Classification of allergic rhinitis

Seasonal allergic rhinitis	Symptoms associated with particular pollen-associated seasons (spring, summer, fall)
Perennial allergic rhinitis	Year-round symptoms, due to non-pollen allergens that are present even in winter
Intermittent allergic rhinitis	Symptoms less than 4 days/week or for less than 4 weeks
Persistent allergic rhinitis	Symptoms more than 4 days/week and for more than 4 weeks

another classification strategy is to use intermittent or persistent allergic rhinitis as opposed to seasonal or perennial allergic rhinitis. Intermittent allergic rhinitis is defined as symptoms less than 4 days a week or for less than 4 weeks, and persistent allergic rhinitis has symptoms present for more than 4 days a week and more than 4 weeks (Brozek et al. 2017). This classification does not specify a particular season in which symptoms are greater or if symptoms are present year-round. Intermittent and persistent allergic rhinitis is also divided into mild, moderate, or severe categories. Mild symptoms do not cause sleep disturbance or an issue with quality of life, whereas moderate to severe symptoms cause interruption of sleep and daily activity, as well as a loss of productivity (Ricketti and Cleri 2009).

Another form of rhinitis is episodic rhinitis, which occurs with intermittent exposure to allergens, commonly indoor allergens encountered in occupational areas, schools, or homes other than the patient's.

5.5.1 Other Causes of Rhinitis

Non-allergic rhinitis is a form of rhinitis that has no relation to allergic triggers. A summary of these differential diagnoses, similarities among them, and common treatments is found in Tables 2 and 3. Incidence of non-allergic rhinitis increases with age, and many patients with allergic rhinitis have some component of non-allergic rhinitis (Joe and Liu 2015). This can be further divided into numerous groups, including infectious rhinitis, which is the most common cause of non-allergic rhinitis in children. Children have on average three to six common cold viruses a year, resulting in episodes of viral rhinitis that usually resolve within 7–10 days. This falls within the category of acute infectious rhinitis and can be identified with associated symptoms of sore throat, fever, poor appetite, and sick contacts (Marcdante and Kliegman 2015). Acute bacterial rhinosinusitis occurs with symptoms of facial pain, persistent purulent nasal discharge, and sometimes fever, often benefiting from treatment with antibiotics (Quillen and Feller 2006). This is in contrast to viral rhinitis, which is milder and is not affected by antibiotics. Chronic bacterial rhinosinusitis usually occurs in older children and adults. This condition has a more indolent course with more than 6 weeks of symptoms, which is also treated with anti-inflammatory therapy with or without antibiotics. Mucopurulent nasal discharge, often yellow or greenish, is usually necessary for the diagnosis. Associated symptoms include facial tenderness, headache, tooth and mouth pain, halitosis, and postnasal drip (Marcdante and Kliegman 2015).

Another form of rhinitis is chronic hyperplastic eosinophilic sinusitis, or CHES, which is an inflammatory disorder with accumulated eosinophils, mast cells, fibroblasts, and Th2 lymphocytes as well as goblet cell metaplasia and mucous gland hypertrophy. The eosinophilic accumulation is the diagnostic feature of this disease. Nasal polyps can complicate this disease. Aeroallergen sensitization may be present but the role of allergens in this disease is unclear. There is a high incidence of asthma in patients with CHES. Symptoms include nasal congestion, rhinorrhea, hyposmia, and facial or sinus pressure. These patients may require surgical treatment, especially if they have nasal polyposis, and patients with more eosinophilic infiltrate have a poorer prognosis (Borish 2016). However, surgery does not cure the disease, and relapse is inevitable without aggressive medical management.

Other infectious etiologies of rhinitis include tuberculosis, syphilis, and fungal infections. Primary nasal tuberculosis is rare, and symptoms involve crusting, occasional epistaxis, nasal congestion, and ulcerative lesions within the nares. Polyp development can also occur. Congenital syphilis can result in *snuffles*, which is the nasal symptom that occurs in infants. Allergic fungal rhinosinusitis involves atopic patients developing an allergic response to fungus growing within the nasal mucus, associated with nasal polyps. The fungus involved are those in the *Dematiaceae* family, for example, *Aspergillus* and *Rhizopus* species (Ricketti and Cleri 2009). The sinus mucosa develops a characteristic eosinophilic inflammation, and bone erosion can occur.

Table 2 Rhinitis differential and common treatments

	Patients affected	Treatment
Allergic rhinitis	All ages	Oral and intranasal antihistamines/decongestants, intranasal corticosteroids/cromolyn
Vasomotor rhinitis	All ages, generally not children	Intranasal corticosteroids, intranasal ipratropium
NARES	All ages, generally not children	Intranasal corticosteroids
Sinusitis (acute, chronic)	All ages	Antibiotics, nasal lavage
Atrophic rhinitis	More common in elderly	Nasal lavage, antibiotics. Avoid decongestants
Rhinitis of pregnancy	Pregnant patients	Intranasal budesonide/cromolyn, oral antihistamine, very brief use of intranasal decongestants
Rhinitis medicamentosa	Patients using intranasal decongestants	Discontinue intranasal decongestant
Occupational rhinitis	All ages (with allergen exposure at work)	Avoid inciting allergen, treat like allergic rhinitis
Physical rhinitis	All ages	Avoid inciting factor, can treat with intranasal ipratropium
Anatomic abnormality	More common in young children unless related to septum or polyps	Referral for potential surgical intervention
Oncologic abnormality	All ages	Referral to oncologic service and potential surgical intervention

Table 3 Common symptoms among the rhinitis differential

Symptoms	Allergic rhinitis	Vasomotor rhinitis	NARES	Sinusitis (acute, chronic)	Anatomic	Oncologic
Sneezing	+	+	+	–	–	–
Pruritus (nasal, oral, etc.)	+	–	+	–	–	–
Congestion	+	+	+	+	+	+/–
Epistaxis	–	–	–	–	+/–	+/–
Rhinorrhea	+	+	+	+	+	+
Bilateral nasal symptoms	+	+	+	+	+/–	+/–

Non-allergic noninfectious rhinitis is also known as vasomotor rhinitis. This is a common cause of rhinitis symptoms with patients presenting for assessment of potential allergic rhinitis. A greater number of patients with non-allergic rhinitis are female, and symptoms are usually perennial (Joe and Liu 2015). With vasomotor rhinitis, patients react to strong irritants such as dust particulates or volatile chemicals. Alcoholic beverages can also act as a trigger, as can barometric pressure changes and cold air. They can also react to strong fumes or odors, such as perfume, cigarette smoke, and chlorine. Symptoms include congestion, rhinorrhea, and limited sneezing with clear nasal discharge (Marcdante and Kliegman 2015).

Non-allergic rhinitis with eosinophils, also known as NARES, is associated with eosinophilia on a nasal cytology. This is seen less frequently in the pediatric population compared to adults. Clear nasal discharge is present in this disorder, as well as perennial symptoms of sneezing, itching, congestion, and occasionally hyposmia. Three stages of evolution appear to occur in NARES, with migration of eosinophils to secretions, retention of eosinophils in the mucosa, and development of nasal polyps (Ricketti and Cleri 2009). Some experts consider NARES an early or mild form of eosinophilic chronic rhinosinusitis discussed above.

Other forms of non-allergic and noninfectious rhinitis include physical rhinitis, gustatory

rhinitis, and reflex rhinitis. Skier's nose is an example of physical rhinitis with response to cold air. Gustatory rhinitis is a response to hot or spicy food, leading to a clear profuse rhinorrhea, sometimes without ingestion but exposure to the aroma. Reflex rhinitis is due to exposure to bright light, usually sunlight, causing a rhinorrhea response.

Atrophic rhinitis is a chronic condition with nasal crusting, purulent discharge, halitosis, and obstruction. This is due to atrophy of the nasal mucosa and underlying bone, leading to a patent nasal cavity with copious foul-smelling discharge. It is most common in areas with prolonged warm seasons such as South Asia and the Middle East; it also occurs more frequently in women. *Klebsiella* is an identified pathogen in this disorder in particular, and symptoms in atrophic rhinitis are severe congestion, altered sense of smell, and a constant malodorous smell. Secondary atrophic rhinitis is more likely to occur in patients with a history of nasal surgery In this case, it is referred to as "empty nose syndrome." It differs from primary atrophic rhinitis in that it is often associated with surgery, radiation, trauma, and chronic granulomatous disease (Corren 2014). This condition may be associated with systemic diseases discussed below.

Rhinitis associated with the workplace is also known as occupational rhinitis, resulting in nasal symptoms following exposures in a particular work environment. This can be allergic or non-allergic in etiology. Those at highest risk of developing occupational rhinitis are laboratory workers, furriers, and bakers due to their specific exposures. Symptomatic worsening during the workweek with improvement over the weekend or vacation away from the job leads to suspecting this diagnosis. Symptoms may persist outside of work when the trigger is absent if mucosal inflammation becomes more established. Depending on the trigger and mechanism, testing may be possible. Those working with irritants or aromatics, such as acids and perfumes, are classified as non-allergic. Allergy testing would not be indicated in this case, and exposure challenge would require an environmental chamber. However, for those exposed to allergic triggers such as grain flour and animal dander, testing can confirm the suspected diagnosis (Corren 2014). It should be noted that occupational rhinitis generally precedes or accompanies the development of occupational asthma, making early diagnosis and removal from the allergen important for asthma prevention as well as symptom improvement (Gentile et al. 2015).

Rhinitis of pregnancy, or hormonal rhinitis, is unrelated to allergic conditions. It was previously attributed to increased concentrations of hormones and mucus hypersecretion on mucosal surfaces in general, presumably for the protection of the cervix and vagina (Corren 2014). Newer data place a higher consideration on decreased alpha adrenergic tone in the venous sinusoids leading to increased vascular pooling of blood or edema caused by leakage of plasma from the vascular bed into the stroma (Ellegård 2006). Seven to thirty percent of pregnant patients will develop rhinitis of pregnancy, defined as new-onset nasal symptoms in absence of another known cause that lasts more than 6 weeks and resolve within 2 weeks after delivery (Ellegård 2006; Finkas and Katial 2016; Scadding et al. 2008). The primary symptom is clear or viscous secretions from the nose. It is often self-limiting, but the symptoms can be aggravating (Scadding et al. 2008). With nasal congestion and rhinorrhea, severe snoring can occur and increases the risk of gestational hypertension, preeclampsia, and intrauterine growth retardation. Rhinitis of pregnancy also increases the risk of obstructive sleep apnea in women predisposed to the disease (Ellegård 2006). Although there is data establishing a link between pregnancy and rhinitis symptoms, there is less information on the menstrual cycle link to rhinitis (Corren 2014). Pregnant patients may also have preexisting allergic rhinitis which can be difficult to distinguish from rhinitis of pregnancy in a patient who has not been previously evaluated.

Rhinitis medicamentosa is a disorder related to overuse of nasal decongestants that cause vasoconstriction due to alpha adrenergic effects, such as phenylephrine or oxymetazoline. This results in a paradoxical effect with continued use, with lessened decongestive benefit and increased sense

of nasal obstruction. The pathophysiology is not fully understood but is thought to be related to alpha adrenergic receptor downregulation, which makes the receptors less responsive to endogenous norepinephrine and exogenous vasoconstrictors (Lang 2010). Cocaine use can also cause this, and this disorder generally does not occur in the younger pediatric population due to limited use of these products. Symptoms are frequent sniffling and rhinorrhea, and physical exam shows red swollen nasal mucosa and minimal discharge. Symptoms will improve with treatment including discontinuation of the offending medication and potentially a short course of oral corticosteroids (Marcdante and Kliegman 2015).

There are also medications with rhinitis symptoms as a side effect including oral estrogens, alpha-blockers, and beta-blockers, as well as psychiatric medications such as benzodiazepines and tricyclic antidepressants. Often, discontinuation of these medications for a few days results in improvement. Aspirin and nonsteroidal anti-inflammatory drugs also may induce rhinitis, though some of the subjects affected have a mild or early development of aspirin-exacerbated respiratory disease (AERD). This condition is associated with development of CHES (see above).

Systemic diseases like cystic fibrosis, polychondritis, Kartagener syndrome or ciliary dysfunction, and hypothyroidism can cause symptoms mimicking allergic rhinitis. Granulomatous diseases such as granulomatosis with polyangiitis, sarcoidosis, and eosinophilic granulomatosis with polyangiitis (previously known as Churg-Strauss vasculitis) are other systemic disorders with rhinitis or nasal symptoms. Subjects with granulomatosis with polyangiitis or polychondritis can develop a depressed nasal bridge (saddle nose deformity) due to necrosis of the cartilage in the nasal septum. Purple discoloration of the nasal tip can be due to sarcoidosis. Hereditary hemorrhagic telangiectasia can present with epistaxis and may be confused with symptoms of allergic rhinitis (Scadding and Scadding 2016). Gastroesophageal reflux can be associated with rhinitis and recurrent ear infections. Cerebrospinal fluid (CSF) rhinorrhea may also mimic allergic rhinitis. This may occur after surgery or a traumatic event and should be ruled out by obtaining beta-2 transferrin levels from the nasal discharge. Beta-2 transferrin is an isomer of transferrin found almost exclusively in CSF. If the fluid is positive for beta-2 transferrin, the patient should be evaluated by neurological specialties immediately to repair the leak and prevent meningitis. Spontaneous, nontraumatic CSF rhinorrhea can also occur and is often persistent, mimicking more common forms of rhinitis (Ricketti and Cleri 2009). Beta-2 transferrin assay of nasal secretions is diagnostic for this condition as well.

Other issues that can cause symptoms similar to allergic rhinitis include anatomic abnormalities. In young children, the most common anatomic abnormality is adenoid hypertrophy leading to obstruction and increased susceptibility to nasopharyngeal infection. Persistent rhinitis can therefore occur, with or without infectious signs and symptoms similar to rhinosinusitis. In infants, congenital choanal atresia may present with signs of congestion and rhinorrhea, especially if distress is noted while feeding. Bilateral choanal atresia generally presents in the neonate with cyanosis occurring in cycles, since infants preferentially breathe nasally. This cyanosis will resolve with crying, since that involves mouth breathing. Choanal atresia can be associated with CHARGE syndrome (coloboma, congenital heart disease, choanal atresia, retardation, genitourinary defects, and ear anomalies). Evaluation for CHARGE syndrome should be considered in any infant with choanal atresia. Unilateral choanal atresia, in contrast, may not present until later in life and may appear as a foreign body due to unilateral discharge and obstruction (Marcdante and Kliegman 2015). Nasal polyps are rare in the pediatric group younger than 10 years of age, but any occurrence in children warrants an evaluation to rule out cystic fibrosis. Another diagnosis to be excluded with a finding of nasal polyps in children is primary ciliary dyskinesia. Polyps can be identified on examination as bilateral gray to white glistening masses that protrude into the nasal airway (Marcdante and Kliegman 2015). They can be associated with clear or purulent nasal discharge as well as a widened nasal bridge and symptoms of congestion or obstruction (Scadding and Scadding 2016). If a

patient presents with changes in the sense of taste or smell, polyps should be considered as well as chronic sinus disease. A foreign body should always be considered in a child, particularly a toddler, due to the tendency of young children to place objects such as food, small toys, and stones in the nose. Symptoms generally include foul smelling, unilateral discharge with purulence. The foreign body can often be noted on examination (Marcdante and Kliegman 2015). Another form of obstruction that can cause symptoms similar to allergic rhinitis is a nasal septum abnormality, such as a deviated septum. In pregnant women, nasal granuloma gravidarum or pregnancy tumor should be considered. This is a rapidly growing benign tumor causing nasal obstruction, which in contrast to rhinitis of pregnancy, is mostly unilateral and causes recurrent nosebleed. It may protrude and be seen from the outside, and it can also resolve without intervention after delivery (Ellegård 2006).

Oncologic causes should be considered in cases of chronic non-allergic rhinitis, especially with other concerning symptoms. Both benign and malignant nasal tumors can cause similar symptoms to allergic rhinitis (Fischer 2007). Encephaloceles are a neoplasm that can occur within the nasopharynx or the nose itself; they are generally unilateral and can have a pulsating quality. They increase in size with any process that increases the pressure in the cerebrospinal fluid, such as crying or straining. Other cancerous lesions can imitate nasal polyps and usually bleed with manipulation, such as carcinomas and sarcomas. Inverted papillomas are a friable and vascular tumor that can involve the nasal septum in addition to the lateral wall of the nose. Angiofibromas are also highly vascular tumors that can arise in the posterior choana of the nasopharynx, especially in preadolescent boys. Without treatment, all of these oncologic processes can result in erosion into surrounding regions (Ricketti and Cleri 2009).

5.6 Diagnosis and Evaluation

Allergic rhinitis is diagnosed by history, physical examination, and allergy testing via skin prick testing or laboratory blood panel. The skin prick testing and laboratory blood panel are best obtained by a clinician with expertise in performing and interpreting these tests, such as an allergist. Obtaining a history with recognition of symptom patterns and associations is the primary factor leading to a diagnosis of allergic rhinitis (Henke 2009).

5.6.1 History, Clinical Symptoms, and Physical Examination

Taking a history in patients with suspected allergic rhinitis is essential to help confirm the diagnosis. All patients may not have all symptoms of the typical allergic patient such as sneezing, rhinorrhea, nasal pruritus, and congestion. Important differentiations need to be made regarding onset and duration of symptoms as well as relation to location (i.e., school, work environments vs. home environment) in order to identify other potential factors such as occupational exposure. Other provoking factors should also be elicited from the patient (Lang 2010). Life events are important, such as acquiring a new pet or moving into a new home. History should be obtained regarding potential allergic conjunctivitis which can be associated with allergic rhinitis. Timing of the symptoms should also be identified regarding a particular season that is worse for the patient than others or if the symptoms are present year-round. Comorbidities should also be identified, such as atopic dermatitis, sleep apnea, gastroesophageal reflux disease, and asthma. A family history of atopic disease should also be sought. A medication list should be reviewed in order to rule out rhinitis as a medication side effect or rhinitis medicamentosa.

Sneezing is the most characteristic symptom of a patient with allergic rhinitis, and rapid succession sneezes are most characteristic. These episodes can be spontaneous or preceded by nasal pruritus and irritation. The nasolacrimal reflex commonly results in ocular symptoms such as tearing. In a sensitized patient, irritant or physical factors can cause frequent sneezing episodes without direct exposure to pollen. For example, a cold air draft can result in local nasal response and a

sneezing paroxysm. Rhinorrhea also occurs and is typically thin, clear discharge. This can be copious, resulting in local skin irritation due to continued production. If purulent discharge is identified, this is unlikely secondary to allergic rhinitis. However, epistaxis can occur since mucus membranes are friable due to the inflammation, and repeated forceful nose blowing or nose picking, especially in children, can lead to recurrent epistaxis. Nasal congestion due to swollen nasal turbinates also occurs and, depending on severity of the congestion, can lead to sinus ostia narrowing with sinus obstruction. Eustachian tube dysfunction can also occur secondary to congestion resulting in earache, decreased hearing, or crackling in the ears. Congestion may be the sole complaint in children, as opposed to symptoms such as rhinorrhea and sneezing. Changes in taste and smell occur with ongoing chronic congestion as well. Cough due to postnasal drip can occur, and this can be a productive or nonproductive cough. Ongoing drainage also leads to constant throat clearing. Nasal pruritus also occurs with partial relief by vigorous rubbing, particularly vertical displacement of the nasal tip. Pruritus is a common theme in allergic rhinitis, and the ears, throat, palate, and face are also frequently affected (Ricketti and Cleri 2009). Allergic conjunctivitis is associated with allergic rhinitis, with ocular signs and symptoms such as erythema, pruritus, and lacrimation. Additional symptoms may include weakness, fatigue, anorexia, and nausea, the latter likely due to postnasal drip and swallowing mucus.

The physical examination should include an evaluation of eyes, ears, nose, throat, and chest. A skin examination should also be performed to assess for rashes with features of atopy such as atopic dermatitis. It should be noted that these findings can be subtle, especially if the patient is affected with seasonal allergic rhinitis, and abnormalities may only be present during acute stages. Findings on eye examination can include "allergic shiners," which are dark periorbital swollen areas often of bluish-purple color possibly caused by venous congestion. Swollen or puffy eyelids from frequent rubbing of the eyes, lacrimation, and conjunctival injection also may occur. Ear examination may demonstrate retracted tympanic membranes or serous otitis media from eustachian tube dysfunction. Classic nasal findings are pale, blue, or gray nasal turbinates that can also be swollen and boggy causing nasal obstruction and mouth breathing with clear rhinorrhea. A transverse nasal crease can be noted across the lower nasal bridge due to frequent rubbing the nose upward and outward with the palm of the hand. This rubbing motion is referred to as the "allergic salute" (Marcdante and Kliegman 2015). Patients may also show a characteristic open mouth breathing pattern due to nasal obstruction reducing nasal breathing. This is sometimes termed the "allergic gape" (Finkas and Katial 2016). Examination of the throat may reveal postnasal drip with clear or white mucus drainage and swollen, non-erythematous tonsils. Direct visualization of the adenoid tissue with pharyngeal mirror or fiber-optic rhinolaryngoscope typically shows a papular appearance of the mucosa, termed cobblestoning, with enlargement of the adenoid tissue. Skin examination should be performed for rashes, typically eczema preferentially on flexor or extensor surfaces of joints, depending on the patient's age. There may be physical findings including residual lichenification, xerosis, or variable pigmentation. Older patients may have had eczema as infants or children, and this would be important history to obtain (Marcdante and Kliegman 2015). All of these findings may not be present during asymptomatic intervals or non-allergic seasons.

Unique findings in children may include a clucking sound from "itching" the soft palate with the tongue due to palatal pruritus. Children are also more likely to suffer from orthodontic abnormalities due to prolonged periods of mouth breathing secondary to nasal congestion. Skin and chest examination are especially important in children with an initial presentation for suspected allergic rhinitis, as they may have an undiagnosed atopic dermatitis or asthma which are more likely with atopy (Marcdante and Kliegman 2015).

Perennial allergic rhinitis and seasonal allergic rhinitis generally present similarly, but due to the chronicity of perennial symptoms, they may seem

more severe, particularly the nasal congestion. Children may have a more constant eye and nose rubbing, mouth breathing, and broadening of the midsection of the nose due to the chronic congestion and rubbing. The transverse nasal crease is generally present in patients with severe, perennial allergic rhinitis. Undiagnosed nasal polyps should be considered in patients with chronic symptoms, but this cannot be specifically related to allergic rhinitis as non-allergic patients develop polyps as well. Nasal secretions in patients with polyps may be more mucoid than clear, and narrowing and elevation of the arch of the palate results in the palatal "Gothic arch" in patients affected early in life (Ricketti and Cleri 2009).

5.6.2 Laboratory Evaluation

Confirmatory testing is not always necessary, and empiric treatment can be started in patients who have mild symptoms (Ferri 2017). Allergy testing often is reserved for those with more severe symptoms or unclear diagnosis; however, it is a consideration in any patient. Specific allergen testing would be needed if immunotherapy is being considered as a treatment option (Quillen and Feller 2006). Testing for allergic rhinitis can be performed by percutaneous skin prick testing (percutaneous testing), intradermal skin testing, or in vitro serum testing. Skin prick testing and intradermal testing provide immediate results; skin testing is generally preferred due to lower cost and immediate results (Lang 2010). There is, however, a concern that intradermal testing does not identify clinical allergy due to greater sensitivity and less specificity. Studies do not show correlation with allergen challenge and intradermal aeroallergen testing; thus, many clinicians do not routinely recommended intradermal testing as part of allergy skin testing. Skin prick testing is a more specific form of allergy testing (Marcdante and Kliegman 2015). The performance of the serum specific IgE testing is similar to skin prick testing, although results are delayed. In vitro specific IgE testing is necessary if skin disease, such as severe eczema or widespread psoriasis, limits opportunity for testing or medications that interfere with histamine response cannot be discontinued.

Saline and histamine controls are necessary for interpretation of skin prick and intradermal testing by providing, respectively, a negative and positive control. If a patient has a positive saline control or a negative histamine test, blood-specific IgE testing should be considered. If a patient has a negative histamine control, it is likely the patient is taking a medication with antihistamine properties. Positive allergen skin prick tests consistently correlate with allergen provocation challenges (Marcdante and Kliegman 2015). There is reproducibility on repeat skin prick testing which makes it a reliable method of diagnosis (Ricketti and Cleri 2009). However, aeroallergen skin testing is not recommended in pregnant patients due to the remote risk of anaphylaxis. This population would be better served with serum testing or returning for skin prick testing after delivery (Finkas and Katial 2016).

A serum test is recommended in patients with abnormal skin conditions that would interfere with the interpretation of the skin test, with history or high risk for anaphylaxis, with residence in areas where good quality extracts for skin testing are not available, and with treatment using medications that would interfere with skin testing. If patients have falsely positive saline controls, serum testing is also indicated (Ricketti and Cleri 2009). There are disadvantages to the blood test such as cost, prolonged time to result, and decreased sensitivity compared to skin prick testing, although the significance of the difference in sensitivity is debatable. There are different tests available for assessing serum IgE to allergens, although radioallergosorbent testing (RAST) is no longer commonly used (Ferri 2017). RAST was the first technique used to measure serum-specific IgE prior to the development of the newer enzyme-labeled anti-IgE. Enzyme assays are now preferred. It is important to note that all laboratory results should be correlated with symptoms. A positive allergen test in a patient with no allergic symptoms is considered sensitization without symptomatic involvement. Therefore, testing in an asymptomatic individual is not recommended (Marcdante and Kliegman 2015).

Specific IgE testing may be positive for allergens that are not clinically important, and it is important to correlate the testing with symptoms. Standardized extract use is desirable for diagnostic purposes. Clinicians should use allergen extracts based on symptoms and seasonality for optimal results (Gentile et al. 2015). Factors as simple as distance between the placements of allergen extract on the skin can affect results. Other factors that affect both results and interpretation are application site, the type of device used for testing, the season, and the extract qualities which can depend on expiration dates and storage conditions (Ricketti and Cleri 2009). Although skin testing can be performed in patients of any age, infants less than 1 year of age may not display a positive reaction due to less overall IgE produced in young children and differences in the skin. The skin differences also apply to elderly patients and subjects with sun damage (Gentile et al. 2015). Serum assays can be used as a supplement to skin testing, as skin testing is considered the diagnostic test of choice by allergy practice parameters. If the skin test is inconclusive, serum-specific IgE tests for confirmation can be performed. However, skin testing with high-quality extracts and proper technique remains the preferred method.

Measurement of serum IgE or blood eosinophils is not routinely recommended in patients undergoing evaluation for allergic rhinitis. Mean concentrations of total serum IgE and blood eosinophils are increased in allergic rhinitis, but there is a significant degree of overlap with values in asymptomatic patients, so the utility of this testing is limited (Corren 2014). A nasal smear with eosinophils via Hansel's stain suggests an allergic diagnosis, but this can also be found in patients with non-allergic rhinitis with eosinophils (NARES) and other non-allergic disorders (O'Connell 2017). However, eosinophilia on nasal smear is often a good predictor of clinical response to nasal corticosteroid therapy (Marcdante and Kliegman 2015). A summary of the common laboratory testing in allergic rhinitis is listed in Table 4.

Table 4 Laboratory evaluation for allergic rhinitis

Specific IgE (pollens, molds, pets, cockroach, house dust mite)	Elevated levels indicate sensitization, must correlate with symptoms for diagnosis
Total IgE	Can be elevated, but nonspecific for allergic rhinitis
Nasal eosinophil smear	Nasal eosinophilia noted in allergic rhinitis but also most nasal polyposis, allergic fungal rhinosinusitis, NARES, local allergic rhinitis
Peripheral eosinophils	Can be elevated, but nonspecific for allergic rhinitis

Radiographic imaging is not necessary for a diagnosis of allergic rhinitis. Computed tomography scan or magnetic resonance imaging may be helpful if an anatomic abnormality is suspected but is not recommended for evaluation of allergic rhinitis (O'Connell 2017). Patients with symptoms unresponsive to medical therapy and atypical for allergic rhinitis may benefit from a computed tomography scan of the paranasal sinuses, which probably is the most accurate test for evaluating inflammation of the sinuses. Standard x-ray imaging is not recommended for sinusitis because of poor sensitivity and specificity (Standring 2016). Findings on any of the abovementioned imaging modalities in allergic rhinitis would be minimal to none (Corren 2014). It is also important to note that radiographs are not necessary to diagnose sinusitis, and the importance of inflammation affecting these images is unclear.

Fiber-optic rhinolaryngoscopy is a procedure utilized for visualization of the nasal airway. This can help rule out other possibilities on the differential for allergic rhinitis and is usually reserved for patients with atypical symptoms or inadequate treatment response. Flexible scopes provide a view of superior and posterior nasal regions such as the septum, nasal turbinates, middle meatus, sphenoethmoid recess, adenoids, and eustachian tube orifices. While flexible scopes are used by most clinicians, rigid scopes are used primarily by otorhinolaryngologists for diagnosis as well as nasal or sinus surgery (Corren 2014). Other

procedures, such as peak nasal inspiratory flow, acoustic rhinometry, and rhinomanometry, can assess nasal airway patency, but the interpretation and reproducibility of results are limiting, and these are not commonly performed except in research (Scadding and Scadding 2016).

A subset of patients may suffer from local allergic rhinitis, or entropy, which is a potential reason for lack of specific IgE findings in the blood or positive skin prick testing but symptoms and signs consistent with allergy. Local allergic rhinitis has specific IgE identified only in the nose. These patients require a nasal allergen challenge to clinically confirm the diagnosis, which is performed in research settings (Corren 2014). The barriers in performing safe, reliable nasal allergen challenges limit the applicability of this procedure for clinical diagnosis.

5.7 Management and Treatment

Medical treatment can ameliorate the symptoms of allergic rhinitis and significantly improve quality of life. Success of the treatment depends on the patient's willingness to adhere to the regimen since deviation can result in recurrence. Other forms of treatment include immunotherapy and environmental control measures. The primary method of management and treatment of allergic rhinitis is avoidance of the offending allergen but requires life style changes that may not be acceptable or affordable.

5.7.1 Avoidance and Environmental Control

Directing avoidance based on results of skin testing or specific IgE blood testing can substantially reduce symptoms and the need for medications. Treatment of allergic rhinitis will be significantly more effective with limiting exposure to the allergen and maximizing control of the environment of the patient. However, in many cases of allergic rhinitis, complete avoidance is not possible due to the broad distribution of the allergens. For example, avoiding outdoor activity in a patient with pollen allergies would be detrimental to social functioning (Gentile et al. 2015). Complete avoidance results in a cure only when there is a single allergen with limited and defined distribution that can be easily controlled, such as an allergy to a household pet. Avoidance of animal allergens, house dust mite, and indoor molds can be accomplished more easily than avoidance of outdoor mold spores and pollens.

The only effective measure for minimizing exposure to animal allergens is removal of the animal from the home. The reason for this is the allergen, derived primarily from the cat or dog saliva and skin gland secretions not the hair or fur, can remain airborne for an extended time after the pet's presence in a particular room or location in the house. Furthermore, the mammalian allergens are sufficiently small to distribute throughout the home via the central heating and air-conditioning system despite standard filtration. However, due to the emotional attachment and personal choice to have a family pet, most households are not willing to take this step. This should still be discussed with the allergic patient's other health issues taken into consideration. Even after a pet's removal from the home, the allergen can persist for several months (Lang 2010). At the very least, pets should be kept out of the allergic patient's bedroom and preferably outside the house. Helpful interventions may include high efficiency particulate air (HEPA) filters, carpet or upholstery removal, frequent washing of bedding, and washing of the animal (Corren 2014).

Indoor mold or fungal growth usually occurs in areas of water intrusion in the living areas. Areas of the home that promote mold growth, such as shower stalls and basements, should be examined and cleaned to reduce exposure to mold spores in allergic subjects. The kitchen and cooking areas are also potential sources of fungal growth. Avoidance of damp, poorly ventilated areas is also recommended; for example, a patient with mold allergy should ideally not reside in a basement or attic (Ricketti and Cleri 2009). HEPA filtration may decrease exposure to allergens and is a consideration if sources cannot be controlled.

House dust mites commonly grow in locations with a humidity greater than 45–50%. Dust mites

are found on all continents except Antarctica; they survive best in warm, humid areas. For patients with house dust mite allergy, it is most practical to focus on making the bedroom as dust mite allergen-free as possible. The microscopic dust mites are found in highest concentrations in carpeting, pillows, mattresses, and upholstered furniture. Mite allergen proteins are large and heavy; therefore, it is less likely that they are transferred long distance via air. Mattress, box spring, and pillow allergen-proof, woven covers to seal against movement of dust mites coupled with frequent washing of bed linens in hot water may be beneficial in reducing exposure and possibly symptom improvement. HEPA filters are ineffective for dust mite allergic rhinitis (Corren 2014). Using foam pillows as opposed to down or feather pillows for patients with a dust mite allergy is also recommended by some experts, although this is unlikely to be relevant with woven encasements placed on the pillows. Regular vacuuming or steam cleaning of carpet, dusting, and floor cleaning may also be helpful. Removing dust-containing fixtures such as stuffed animals is another consideration. If possible for the family, removal of carpeting in favor of hardwood or tiled floors would be preferable to decrease the dust mite burden. High humidity is essential for the growth of the dust mite population, and therefore maintaining the absolute humidity at or below 45–50% in the home is optimal; this may be helpful for mold prevention as well (Ferri 2017). Wearing a mask while cleaning the house may be helpful to prevent exacerbating symptoms due to the movement of dust mite allergen that will be inhaled during the process. Air conditioning may decrease both mold spore and dust mite allergen levels, but the effectiveness depends upon the ambient heat and humidity (Lang 2010).

Cockroach allergy avoidance is potentially difficult depending on the housing situation, as most of the patients with cockroach infestations in their homes reside in apartments. Eliminating suitable environments for the cockroaches is the key to controlling symptoms. Highest allergen levels are found in kitchens and bathrooms due the need for a cockroach to be around food and water. Eating in living or sleeping areas potentially increases the inhalation exposure to cockroach. Insecticides and gel formulations of the insecticides, which are odorless and safe for indoor use, can be placed in the affected rooms, but extensive cleaning after extermination is needed due to the continued presence, even after the living insects have died, of the allergen in cracks and crevices of the home. Behavioral change to reduce the chances of reinfestation is critical to prevent recurrence of symptoms (Ricketti and Cleri 2009).

Avoidance of outdoor molds, and to some extent pollens, can be accomplished by remaining indoors when possible and closing windows and doors to avoid contact with outdoor allergens. Limiting outdoor activity during peak pollen hours, which are late morning to early afternoon, can be helpful in some patients. For those with allergy to outdoor triggers, however, pharmacotherapy or immunotherapy may be the best option.

Avoidance of smoke and secondhand smoke also will help avoid worsening the baseline inflammation present in a patient with allergic rhinitis and help to decrease symptoms. Irritants, such as smoke from burning outdoor vegetation or diesel particles from vehicles, may enhance symptoms and susceptibility to allergic sensitivity. General environmental pollution due to combustion products containing nitrogen and sulfur and particulates is also a concern; thus it is advisable for affected subjects to be aware of outdoor air quality assessments. Outside activities may need to be reduced during peak pollution periods. Indoor combustion products from fireplaces and natural gas appliances are potential sources of indoor pollutants.

5.7.2 Pharmacotherapy

Pharmacotherapy of allergic disease improves quality of life but does not modify the disease itself. There are multiple options for medical therapy with intranasal corticosteroids as the most effective treatment for allergic rhinitis. However, other medications can also improve symptoms.

5.7.2.1 Intranasal Corticosteroids

Intranasal corticosteroids (INCS) are the most effective single therapy for allergic rhinitis with high quality of evidence to indicate efficacy (Wallace and Dykewicz 2017). They treat nasal congestion, rhinorrhea, sneezing, and itching via regulation of the inflammation, edema, and mucus production in the nose. Mechanisms of action of INCS include vasoconstriction, inhibition of mediator release, eosinophil apoptosis, mucosal mast cell reduction, and suppression of cytokine release. INCS have some effect on allergic conjunctivitis usually associated with allergic rhinitis, but significant allergic ocular symptoms often require use of allergy eye drops. There can be an improvement in asthma as well with regular use of INCS, due to the relationship between asthma and allergic rhinitis. Benefit with treatment of allergic rhinitis occurs due to the anatomic connections between the nose and throat, as well as symptomatic improvement leading to less labored breathing and enhanced nasal breathing.

There are multiple types of INCS, such as beclomethasone, fluticasone, and mometasone. These medications have minimal systemic absorption and side effects. INCS can also be used for non-allergic rhinitis due to their general suppression of intranasal inflammation and mucous production. The local activity of the corticosteroid is critical when topically administered, due to affecting cellular activities and inflammation more effectively than systemic corticosteroids, with limited side effects (Ricketti and Cleri 2009). Delayed onset of action of INCS, generally 5–7 days after initiation, is generally expected, although many patients have clinical improvement within the first day of use. For most patients, regular use is needed for optimal effectiveness. Patients with severe congestion may require topical decongestants prior to administering an INCS, or even a course of oral corticosteroids to allow proper delivery of this nasal spray. The use of systemic corticosteroids should be only for severe cases that cannot be controlled by routine measures and not on a chronic basis (Ricketti and Cleri 2009).

Improper technique with INCS can result in local adverse effects. Pointing the nasal spray into the nasal septum may lead to bleeding due to epithelial thinning and decreased integrity of small blood vessels. Rarely, septal perforation is reported, which is why technique demonstration is important prior to prescribing the medication. Proper technique involves directing the nasal spray laterally, away from the septum. Other adverse effects include burning and local irritation as well as sneezing from the spray itself, and these can occur in up to 10% of patients (Marcdante and Kliegman 2015). The taste or smell of the INCS itself can be unpleasant, affecting patient adherence. Occasionally subjects with non-allergic rhinitis or mixed allergic/non-allergic rhinitis will complain of aggravation of symptoms by the odor of certain aqueous sprays, particularly those containing phenylethyl alcohol. Development of aqueous formulations have reduced local irritation and therefore increased the use of these sprays, including in children. Systemic side effects are rare if the INCS is used at the recommended dose, and evaluation of the hypothalamic-pituitary-adrenal axis as well as peripheral eosinophilia and osteocalcin (a marker of bone turnover) showed no effect by a variety of INCS (Ricketti and Cleri 2009). The development of candidiasis due to the use of INCS is rare, but with excessive mucosal drying it has occurred, usually on the septum or anterior inferior turbinate (Henke 2009). Some studies have shown the use of INCS results in increased intraocular pressure with reductions after discontinuation. Monitored use of INCS by a physician or other health professional is recommended, especially if other corticosteroids are being used or prolonged therapy is necessary (Ricketti and Cleri 2009). Long-term use does not result in adverse changes in nasal mucosa.

Intranasal corticosteroid injection is infrequently used since the advent of newer, safer INCS. Previously the injections were used for patients with both allergic and non-allergic conditions, especially nasal polyposis. It was thought that the injections could decrease the need for surgical intervention and associated complications in patients with polyps. Turbinate injections, however, have higher rates of systemic absorption and potential corticosteroid emboli leading to

transient or permanent visual loss; these are not concerns with INCS (Ricketti and Cleri 2009).

5.7.2.2 Oral and Intranasal Antihistamines

Another option for treatment is antihistamine therapy, although their effect on nasal congestion is less helpful than INCS. Antihistamines are a cornerstone of symptomatic therapy, used for over 50 years. Primarily, they help with nasal and ocular pruritus, sneezing, and rhinorrhea. Histamine acts through four receptors, and stimulation of the first receptor leads to most symptoms of allergic rhinitis. Antihistamines are inverse agonists of the H1 receptor, leading to the antihistaminic effects (Marcdante and Kliegman 2015). First-generation antihistamines are lipophilic and cross the blood-brain barrier, and these agents affect other neural receptors. The result is these agents have stronger sedation effects than second-generation antihistamines (Waller et al. 2014). Commonly used first-generation antihistamines are diphenhydramine and hydroxyzine. Their onset of action is within minutes, and they can be taken on an as needed basis. Generally, regular use of first-generation antihistamines is not recommended, especially in children or the elderly, due to effects on cognition and mobility. In children in particular, a deleterious effect on academic performance occurs with regular first-generation antihistamine use. A paradoxical stimulatory reaction also occurs in children. Other side effects are anticholinergic, resulting in blurred vision, urinary retention, dry mouth, tachycardia, and constipation. These effects can be severe, and the sedation effects can be profound as well: therefore the use of heavy machinery or driving a motor vehicle is relatively contraindicated. Large doses of these first-generation antihistamines can lead to cardiac abnormalities such as torsades de pointes. Other populations in addition to the children and the elderly that should use first-generation antihistamines with caution are those taking more than one antihistamine, patients on diuretic medications with history of hypertension, patients with electrolyte abnormalities, or those on antiarrhythmic medications or a history of arrhythmia. There is also a potentiating effect of alcohol and other drugs that affect the central nervous system, such as sedatives (Marcdante and Kliegman 2015). First-generation antihistamines are on the American Geriatrics Society Beers Criteria list of inappropriate medications for older adults (American Geriatrics Society 2015).

Second-generation antihistamines, in contrast, are more hydrophilic and do not as readily cross the blood-brain barrier (Waller et al. 2014). They are less likely to cause a significant sedative effect although this can occur, particularly at higher doses. They do not cause anticholinergic side effects like the first-generation medications and have longer half-lives allowing less frequent dosing. The young and elderly populations, therefore, are able to better tolerate these antihistamines. Cetirizine and loratadine are common over-the-counter second-generation antihistamines used for treatment of allergic rhinitis. Others include desloratadine and levocetirizine, derivatives of loratadine and cetirizine, respectively, which have been referred to as "third-generation antihistamines." Also included in this category is fexofenadine. The description of third-generation antihistamine is used to differentiate these medications, which were designed to have fewer central nervous system effects than second-generation antihistamines. However, this decreased central nervous system effect is not confirmed. Second- and third-generation antihistamines have a rapid onset of action that allows them to be taken on an as needed basis, which is similar to the first-generation antihistamines (Marcdante and Kliegman 2015). It should be noted that combination therapy of oral antihistamine and INCS has not shown additional benefit when compared to INCS use alone (Brozek et al. 2017). For any oral antihistamine, prophylactic administration, 2–5 h before a known allergen exposure, provides the best symptom control (Gentile et al. 2015).

Azelastine and olopatadine are intranasal antihistamine sprays that can be used as needed due to fast onset of action and used regularly for chronic symptoms (Marcdante and Kliegman 2015). Azelastine is a selective histamine receptor antagonist. In addition to histamine blocking, it inhibits inflammation. It does not commonly

cause drowsiness or psychomotor impairment, but these adverse effects can occur. Intranasal azelastine may synergize when combined with an INCS for optimal symptom control. Olopatadine spray is similar to azelastine and also uncommonly causes drowsiness. Both azelastine and olopatadine can have an unpleasant taste, which is commonly noted as a side effect (Ricketti and Cleri 2009). Both antihistamine nasal sprays act within 15–30 min and result in significant reduction of congestion, itching, sneezing, and runny nose (Corren 2014). Azelastine is FDA approved for treatment of non-allergic rhinitis.

5.7.2.3 Oral and Intranasal Decongestants

Oral or intranasal decongestants can be used for nasal congestion treatment, and oral decongestants are frequently combined with antihistamines. Commonly used oral decongestants are pseudoephedrine and phenylephrine, and intranasal are oxymetazoline and phenylephrine; these are sympathomimetic drugs that are vasoconstrictors via alpha adrenergic receptor activation resulting in improved nasal patency (Gentile et al. 2015). The efficacy of pseudoephedrine is confirmed but that of phenylephrine is questioned. Edema is reduced by either topical or systemic use of decongestants; however chronic topical use is associated with rebound congestion or worsening of the condition. Decongestants are aided in their benefits for allergic rhinitis by combining with an antihistamine. Adverse effects with oral decongestants can be significant, including insomnia, irritability, and palpitations. They can also increase intraocular pressure and cause urinary obstruction symptoms; decongestants should be avoided in patients with glaucoma or benign prostatic hypertrophy. The combination of first-generation antihistamine and a decongestant is particularly prone to cause side effects. In large doses, oral decongestants can result in hypertension as well (Ricketti and Cleri 2009). Purchase of decongestants may be limited depending on state laws, due to the use of these medications for illegal methamphetamine manufacturing. There are restrictions in use associated with certain sports teams, which should be considered for older children. Intranasal decongestant sprays can be used for acute relief of nasal congestion, but overuse is associated with rebound congestion and rhinitis medicamentosa. It is therefore recommended to limit daily use of this medication to 3–5 days (Corren 2014). Rhinitis medicamentosa involves the intranasal use of these medications followed by a rebound phenomenon leading to more congestion and edema, which is self-treated by increasing doses of the nasal spray. Discontinuation of the offending spray is the main treatment for rhinitis medicamentosa. Because of the risk of this disorder, especially in patients with allergic rhinitis who may experience significant relief with prolonged use, it is not advised to use intranasal vasoconstrictors except during a period of infectious rhinitis. The rebound effect can be mitigated when intranasal decongestants are combined with INCS. Oral decongestants are not associated with rhinitis medicamentosa (Ricketti and Cleri 2009). It is also important to note that decongestants do not affect other symptoms such as rhinorrhea, pruritus, and sneezing (Gentile et al. 2015).

5.7.2.4 Intranasal Anticholinergics

Intranasal anticholinergic sprays such as ipratropium are used primarily for non-allergic rhinitis; they have a drying effect for improvement of copious nasal drainage. Parasympathetic stimulation leads to a watery secretion mediated by acetylcholine and a vasodilatory effect. Ipratropium's anticholinergic effect leads to a block of the parasympathetic stimulation. It does not penetrate the blood-brain barrier and is poorly absorbed by the nasal mucosa. It does not affect congestion or sneezing symptoms but does control the watery nasal discharge. It is helpful in the common cold, gustatory rhinitis, and rhinorrhea in elderly patients (Ricketti and Cleri 2009). However, adverse effects include overly dry nose leading to irritation and burning (Marcdante and Kliegman 2015). These effects are dose dependent in their severity. Less common side effects include dry mouth, headache, and nasal congestion. It is not used as a first-line agent for treatment of allergic rhinitis due to its lack of effect on

symptoms other than rhinorrhea. In patients with a primary symptom of rhinorrhea, ipratropium combined with an INCS or antihistamine is a consideration (Ricketti and Cleri 2009).

5.7.2.5 Intranasal Cromolyn Sodium

Intranasal cromolyn sodium is another product for use in patients with allergic rhinitis. It stabilizes mast cell membranes and prevents antigen-induced degranulation. Cromolyn is effective in both seasonal and perennial allergic rhinitis for treatment of symptoms of sneezing, rhinorrhea, and nasal pruritus. It has a significant prophylactic effect when used prior to a known allergen exposure, reducing immediate and late symptoms after the exposure. Adverse effects are rare and include an unpleasant taste as well as local irritation. Recommendations for seasonal rhinitis treatment are for use 2–4 weeks prior to the allergen season and continued use throughout the exposure period. Cromolyn has a delayed onset when used for chronic disease treatment, and therefore antihistamine therapy is frequently needed in addition to control symptoms. Regular use leads to maximal benefit. However, studies show that INCS, intranasal antihistamines, and oral antihistamines have a more significant effect than intranasal cromolyn (Ricketti and Cleri 2009).

5.7.2.6 Leukotriene Receptor Antagonists

Montelukast is approved for both seasonal and perennial allergic rhinitis, although it is commonly used in asthma treatment as well (Marcdante and Kliegman 2015). It is a leukotriene receptor antagonist that results in a variety of potential benefits, including reduced eosinophil recruitment and mucous production. However, montelukast does not have a dramatic effect on symptoms but is similar to that of oral antihistamine with the exception of not improving itch and sneeze. Symptom scores and quality of life improvement are statistically significantly improved with montelukast (Lang 2010). Montelukast does relieve nasal symptoms but not to the degree of an INCS. Montelukast is generally an adjunct for patients without adequate response to an antihistamine or nasal corticosteroid, but the reduction in symptoms is not clearly demonstrated with this additional therapy (Ricketti and Cleri 2009).

5.7.2.7 Nasal Lavage

A non-medication treatment option recommended for allergic rhinitis patients with congestion and rhinorrhea symptoms is nasal lavage or saline wash (Fischer 2007). Isotonic and hypertonic saline solutions reduce symptoms (Garcia-Lloret 2011). Mechanisms of action thought to be involved in this process include improvement in mucociliary clearance, washing out of allergens and inflammatory mediators, and a protective effect on nasal mucosa. Side effects are minor, and local burning and irritation are identified as the most common adverse effects. These side effects can be due to improper technique, with nausea occurring if the wash is swallowed. There are no established optimal volumes or dose frequencies for this non-pharmacologic therapy (Gentile et al. 2015).

5.7.3 Allergen Immunotherapy

Environmental control measures and medications are used first to treat allergic rhinitis. If symptoms remain uncontrolled and continue to affect quality of life, allergen immunotherapy should be considered.

Allergen immunotherapy, also known as AIT, is the repeated administration of specific allergens in incremental doses to patients with IgE-mediated conditions therefore preventing the allergic symptoms and inflammatory reactions (Ricketti and Cleri 2009). AIT is the only disease-modifying treatment for allergic rhinitis (Finkas and Katial 2016). Subcutaneous AIT is the traditional and common form of allergen immunotherapy, referred to as "SCIT" or "allergy shots." Recently sublingual immunotherapy, known as SLIT, has been approved for allergy to certain grasses, ragweed, and house dust mite. Although AIT is not recommended for infants and toddlers, it can be initiated in children under the age of 5 years if indicated by severity of disease, risk, and benefit and ability of physician

to correlate the clinical presentation with allergy testing. However, no FDA-approved products are approved for SLIT in children younger than 5 years. There are reports of efficacy of AIT in children as young as 3 years of age. There is also no upper age limit for initiating AIT in the elderly, since clinical benefits have been reported in the older age groups (Cox et al. 2011). Other considerations for starting SCIT should be the transportation available to the patient for regular clinic visits to administer the injections (Gentile et al. 2015).

The mechanism of action for AIT is complex but involves decreased production of specific IgE due to targeted therapy with the triggering allergens. There is also involvement of an immunoglobulin G (IgG)-blocking antibody and alteration of cytokine expression produced in response to allergens (Marcdante and Kliegman 2015). Allergen-specific IgG induced from AIT block degranulation of basophils and mast cells works as an anti-inflammatory process. There is a shift from allergen-specific Th2 cells to T-regulatory cell predominance during the process of immunotherapy, with IL-10 suppressing total and allergen-specific IgE. Tolerance is therefore induced due to this suppression of the IgE response. The pathophysiology of allergen and immune system response is detailed in Sect. 3.2.

Initially, there is an increase in specific IgE followed by a gradual decrease. Clinical improvement may occur before decrease in specific IgE, and some patients do not have a reduction in their IgE level. Efficacy is therefore not entirely dependent on reduction of specific IgE, but AIT does decrease the seasonal elevation in specific IgE level for seasonal allergens. Other benefits of AIT are suppression of late-phase inflammatory responses in the skin and respiratory tract (Ricketti and Cleri 2009). The advantage regarding AIT as opposed to pharmacologic treatment is that the immunotherapy effect is long lasting; studies show at least 2 years of consecutive treatment result in persistent tolerance for pollen allergy, although longer courses, up to 3 years, are needed for perennial allergens (Corren 2014).

SCIT vaccines are prepared based on the patient's specific allergy testing results. It should be administered at a physician's office/clinic with an observation period of 30 min afterward. Due to risk of anaphylaxis, the office/clinic needs to be prepared to treat and manage this risk. It may be advantageous that an epinephrine autoinjector or other form of injectable adrenaline is carried to and from every appointment to ameliorate this anaphylaxis risk, especially in patients with a history of prior reaction (Cox et al. 2011). Conventional recommendations for SCIT involve initial injections given once or twice a week then spaced out according to physician preference to maintenance dosing which is usually every 3–4 weeks. Occasionally, two or three injections may be needed at each visit since mixing compatibility depends on the allergen extracts involved.

Patients should be evaluated every 6–12 months while receiving AIT in order to assess efficacy, discuss any reactions, determine compliance with treatment and establish a timeline for discontinuation or adjustments in dose (Cox et al. 2011). Treatment with SCIT is recommended for a total of 3–5 years for maximal benefit (Ricketti and Cleri 2009). There are other forms of SCIT dosing known as rush or cluster therapy, which involve a quicker dose and concentration escalation to reach maintenance therapy. These may involve incremental injections over a shorter time period of days to weeks in order to reach the maintenance concentration within a period of 1–2 months. The risk of adverse reactions is higher with these protocols, and if a patient is needing quicker escalation than the conventional treatment, it is suggested to have this completed with very close supervision and medication pretreatment (Frew 2013).

A frequent reason for AIT discontinuation by the patient is the unrealistic pretreatment expectation. The magnitude of symptom reduction is variable in patients, although it is usually significant; however, there is no cure for allergic rhinitis. For SCIT, there is persistent improvement after discontinuation of therapy in those who complete the 3–5-year recommended course. The effectiveness of SCIT in allergic rhinitis has been confirmed in many trials specifically with pet allergens, grass, ragweed, and birch pollen (Frew 2013). The benefit of treatment is

significant, especially because it is a cost-effective therapy with long-term improvement and reduced medication costs (Ricketti and Cleri 2009).

Medical therapy will modulate the symptoms of the disease, but immunotherapy alters the natural course of the disease. There is a disease-modifying effect of AIT with reduction of new-onset asthma and the incidence of new sensitizations in children. The mechanisms underlying these processes are not yet fully understood, but these are another positive effect of AIT (Frew 2013).

A major risk of SCIT is systemic reaction and anaphylaxis. There are rare cases of death due to SCIT (Ricketti and Cleri 2009). Children are not at higher risk of reaction to conventional SCIT than adults (Cox et al. 2011). Some adverse events have been due to incorrect dosing, and others occur when patients receive increased concentrations of their dose. This awareness is important when switching vials or escalating dosing, as changes in concentrations or doses affect patients differently. Systemic reactions are also more likely if the patient has an illness or an asthma exacerbation; it is recommended to delay the injection if a patient is experiencing these issues. It is also important to obtain a thorough medication history and review this history at each visit, since use of beta-blocking medications can impact treatment of potential anaphylaxis with reduced responsiveness to epinephrine (Fischer 2007). Pregnancy is a relative contraindication to starting SCIT, but in an established patient on maintenance dosing, this treatment can be continued (Frew 2013). There are no controlled studies on risk or effect of SCIT in patients with immunodeficiency or autoimmune disorders, and concerns about increased risk of SCIT in this group are hypothetical. Therefore, it can be considered in these patient groups if risks and benefits are weighed on an individual basis (Cox et al. 2011).

SLIT, in comparison to SCIT, is an option for patients with a limited number of specific allergies. A ragweed tablet and house dust mite tablet are available, as well as two grass pollen allergy tablets (Greenhawt et al. 2017). Treatment involves a rapid build-up phase or no build-up followed by treatment with rapidly dissolving tablets containing allergens; of note, doses and regiments can vary, especially between Europe and the United States. Oral dosing at home after the first dose given in a medical setting provides the benefit of convenience. Information on these currently available SLIT options as well as their dosing and indications can be found in Table 5. There are statistically significant reductions in rhinitis symptoms and use of allergy medications with SLIT.

Systemic reactions are rare in SLIT, although local reactions such as oral and sublingual itching are common. However, it is an FDA recommendation to provide an epinephrine autoinjector or other form of injectable adrenaline to patients treated with SLIT. The epinephrine would be necessary for outside clinic use in case of a severe allergic reaction following SLIT dosing (Greenhawt et al. 2017). SLIT is safer than subcutaneous therapy, but there continues to be a discussion on its effectiveness when compared to SCIT. More recent studies show equal efficacy, at least with a limited number of allergens (Frew 2013).

5.7.4 Treatments Under Study

Other routes of immunotherapy administration, such as epicutaneous immunotherapy, are undergoing clinical trials to assess their benefit. New technologies for immunotherapy continue to develop. Omalizumab is a recombinant humanized monoclonal antibody which forms complexes with free IgE; it blocks interactions of IgE with mast cells and basophils, as well as lowers free IgE in the circulation (Bousquet et al. 2006). It is approved for treatment of severe allergic asthma and chronic spontaneous urticaria, although it has been studied in treatment of allergic rhinitis. Efficacy has been shown although the cost is prohibitive for routine treatment. In particular, the efficacy of this treatment compared to antihistamines and INCS has not yet been established. Agents that block interleukins are also under consideration, with IL-4 and IL-5 as specific targets. These targeted therapies have some effect in asthmatics and continue to be

Table 5 Commercially available SLIT in the United States

	FDA-approved	Indications	Dosing
House dust mite (Odactra™)	Yes	Patients 18–65 years of age with house dust mite allergy as indicated by positive specific IgE testing or skin prick testing	1 tablet sublingually daily, first dose to be given in office with 30-min observation period
Ragweed (Ragwitek™)	Yes	Patients 18–65 years of age with ragweed allergy as indicated by positive specific IgE testing or skin prick testing	1 tablet sublingually daily, first dose to be given in office with 30-min observation period Begin treatment 12 weeks before ragweed pollen season for best results
Northern grasses (Oralair™)	Yes	Patients 10–65 years of age with allergy to any of the following grasses as indicated by positive specific IgE testing or skin prick testing: sweet vernal, orchard, perennial rye, Timothy, Kentucky blue grass	10–17 yo: 1 tablet (100 IR) day 1, 2 tablet (200 IR) day 2, 1 tablet (300 IR) day 3 and following, once daily sublingually 18–65 yo: 1 tablet (300 IR) once daily sublingually Begin treatment 4 months before grass pollen season for best results First dose to be observed in office with 30-min observation period
Timothy grass (Grastek™)	Yes	Patients 5–65 years of age with Timothy grass or cross-reactive grass allergy as indicated by positive specific IgE testing or skin prick testing	1 tablet sublingually daily, first dose to be given in office with 30 min observation period Begin treatment 12 weeks before grass pollen season, recommend 3-year daily consecutive use for sustained effectiveness

studied for potential benefit in allergic rhinitis treatment. CpG bacterial DNA repeats as adjuvants with vaccines and in immunotherapy, with the goal of altering allergen processing or modifying the immune response, is another treatment under study (Henke 2009).

5.7.4.1 Special Populations

Pregnant women with rhinitis should utilize non-drug therapies initially. Nasal rinses with normal saline are first recommended in order to remove thick mucus, and physical nasal dilators are also available. However, in many women, medications will be needed. Intranasal cromolyn sodium has an excellent safety profile with a an FDA pregnancy category B rating and is appropriate for use in pregnant women. Budesonide is the preferred INCS in pregnancy due to its category B rating. Other INCS are category C in pregnancy. Gestational risk has not been confirmed, and the reported safety data of commercially available products are reassuring. Oral antihistamines can also be considered if this is the patient's preference, and primary symptoms are rhinorrhea, sneezing, and itching. Both diphenhydramine and chlorpheniramine, although older medications, have a long record of use during pregnancy. However, some patients will have significant central nervous system and anticholinergic effects that make these difficult to tolerate. In that case, loratadine and cetirizine are classified as pregnancy category B and can also be used. Olopatadine and azelastine, intranasal antihistamine sprays, are pregnancy category C and are infrequently used in pregnancy (Corren 2014). It would therefore be recommended to avoid them in favor of the abovementioned oral antihistamines, cromolyn nasal spray, or intranasal budesonide spray.

Oral decongestants should also be avoided during the first trimester; there is a questionable association with congenital malformations such as gastroschisis (Corren 2014). Intranasal decongestants can provide temporary relief, but the

recommendations for use of intranasal decongestants for no more than 5 days is to limit the risk of rhinitis medicamentosa (Ellegård 2006). SCIT can be continued during pregnancy if it has not caused systemic reactions and is helpful, but allergen vaccine doses should be maintained and not increased. If pregnancy occurs during a build-up phase and the dose is unlikely to be therapeutic, discontinuation of the immunotherapy should be considered. SCIT should also not be started during pregnancy (Cox et al. 2011). There is insufficient data regarding safety of initiating or continuing SLIT in pregnant or breast-feeding women, and no official recommendations can be made (Greenhawt et al. 2017). There is no evidence of increased risk in prescribing or continuing SCIT during breast-feeding (Cox et al. 2011). It should be noted that the FDA began implementing the Pregnancy Lactation Labeling Rule (PLLR) in 2015, removing categories from drug labeling and instead providing benefit and risk information as a summary. The older category classification is being used in this chapter due to historical familiarity and understanding.

The elderly population also requires special consideration due to the concern for dry nasal mucosal membranes and medication intolerance. Improving moisture content and removing dry secretions are primary concerns for this group. Nasal irrigation should be used by those with chronic rhinitis, especially if non-allergic etiology. An INCS can cause more bleeding than in younger patients due to fragile mucous membranes. First-generation oral antihistamines are not recommended due to the sedation potential and increased risk for anticholinergic side effects, especially in patients with history of glaucoma or benign prostatic hypertrophy. Oral decongestants can cause side effects of hypertension, cardiac arrhythmias, insomnia, agitation, and urinary tract obstruction effects; they are also not recommended in the elderly (Corren 2014).

Children are considered a special consideration in treatment, as there are age recommendations for certain medications. Instruction in proper use of medications, especially intranasal sprays, is essential in this group. A summary of the dosing of medications for allergic rhinitis in children and adults can be found in Table 6.

5.8 Complications of Allergic Rhinitis

The socioeconomic effects from allergic rhinitis are significant. The spectrum of disease ranges from mild to debilitating. Patients on the more severe end of the spectrum have difficulty with quality of life, specifically productivity at work or school and social functioning (Gentile et al. 2015). The indirect costs are remarkable, with impaired productivity or missed work in 52% of patients (Ricketti and Cleri 2009). Decreased productivity rates were approximately 2.3 h per workday with absences of 3–4 days due to the symptoms. Losses for workers total near $600 a year (Ricketti and Cleri 2009). For children, absenteeism from school can also affect a parents' work due to missed work to take care of the child. Children with allergic rhinitis experience significant quality of life disturbance with sleep issues, irritability, and limitation of both physical and social activity that can impact social development and academic performance (Marcdante and Kliegman 2015). In adults, sleep loss is identified as a primary factor for daytime fatigue leading to poor work performance (Corren 2014). A quality of life survey administered to patients with allergic rhinitis and asthma showed similar physical and mental impairment between the two diseases, with lower social functioning in patients with allergic rhinitis when compared to asthma (Ricketti and Cleri 2009).

Other complications of allergic rhinitis are related to comorbidities. Asthma is present in approximately 40% of patients with chronic rhinitis. 80–90% of those with asthma have persistent nasal symptoms of congestion, rhinorrhea, or a combination that can be related to allergic or non-allergic rhinitis (Corren 2014; Scadding et al. 2012). Rhinitis is a risk factor for development of asthma, as allergen exposure can affect the nose and lungs (Scadding et al. 2008). Therefore, patients with severe allergic rhinitis and asthma can experience worsening of their asthma when

Table 6 Common medications for allergic rhinitis

	Generic (common brands)	Over the counter	Adult dose	Pediatric dose	Dose strengths
Intranasal corticosteroids	Fluticasone (Flonase™, Veramyst™)	Flonase: yes Veramyst: no	Both: 1 SEN* qday** (>11 yo***) Can use 2 SEN qday for worsened symptoms for short period of time	Flonase: 4–11 yo 1 SEN qday Veramyst: 2–11 yo 1 SEN qday Both: can use 2 SEN qday for worsened symptoms for short period of time	Flonase 1 spray = 50 mcg Veramyst 1 spray = 27.5 mcg Max- 110 mcg/d Veramyst, 200 mcg/d Flonase
	Budesonide (Rhinocort™)	Yes	1–2 SEN qday (≥12 yo) Can use up to 4 SEN qday for worsened symptoms for short period of time	6–11 yo: 1 SEN qday, can use 2 SEN qday for worsened symptoms for short period of time	1 spray = 32 mcg Max- Peds: 128 mcg/d Adult: 256 mcg/d
	Triamcinolone (Nasacort™)	Yes	1 SEN qday (>12 yo) Can use 2 SEN qday for worsened symptoms for short period of time	2–6 yo: 1 SEN qday 6–12 yo: 1 SEN qday, can use 2 SEN qday for worsened symptoms for short periods of time	1 spray = 55 mcg Max- Peds: 110 mcg/d for 2–6 yo >6 yo and adult: 220 mcg/d
	Ciclesonide (Zetonna™, Omnaris™)	No	Zetonna (≥12 yo): 1 SEN qday Omnaris (≥6 yo): 2 SEN qday	Zetonna not approved for children less than 12 yo Omnaris not approved for children less than 6 yo	Zetonna: 1 spray = 37 mcg Max- 74 mcg/d Omnaris: 1 spray = 50 mcg Max- 200 mcg/d
	Beclomethasone (Qnasl™, Beconase AQ™)	No	Qnasl: 2 SEN qday (≥12 yo) Beconase AQ: 1–2 SEN BID****	Qnasl: 4–11 yo 1 SEN qday Beconase AQ: 6–11 yo 1 SEN BID, can increase to 2 SEN BID for worsened symptoms for short period of time	Qnasl (peds): 1 spray = 40 mcg Max- 80 mcg/d Qnasl (adult): 1 spray = 80 mcg Max- 320 mcg/d Beconase AQ: 1 spray = 42 mcg Max- 336 mcg/d
	Mometasone (Nasonex™)	No	2 SEN qday (≥12 yo)	2–11 yo: 1 SEN qday	1 spray = 50 mcg Max- Peds: 100 mcg/d Adult: 200 mcg/d

(*continued*)

Table 6 (continued)

	Generic (common brands)	Over the counter	Adult dose	Pediatric dose	Dose strengths
Combination intranasal corticosteroid and antihistamine	Azelastine/ fluticasone (Dymista™, Ticalast™)	No	1 SEN BID (≥6 yo)	Not approved for children <6 yo	1 spray = 137 mcg azelastine/50 mcg fluticasone Max- 548 mcg azelastine/ 200 mcg fluticasone
Intranasal antihistamine (second generation)	Azelastine (generic, Astepro™)	No	Generic (≥12 yo): 1–2 SEN BID Astepro 0.15% (≥12 yo): 2 SEN qday or BID	Generic: 5–11 yo 1 SEN BID Astepro 0.1%: 6 mo–5 yo 1 SEN BID Astepro 0.1% or 0.15%: 6–11 yo 1 SEN BID	Generic: 1 spray = 137 mcg Max- Peds: 548 mcg/d Adult: 1096 mcg/d Astepro 0.1%: 1 spray = 137 mcg Peds Max- 548 mcg/d Astepro 0.15%: 1 spray = 205.5 mcg Max- Peds: 822 mcg/d Adult: 1644 mcg/d
	Olopatadine (Patanase™)	No	2 SEN BID (≥12 yo)	6–11 yo: 1 SEN BID	1 spray = 665 mcg Max- Peds: 2660 mcg/d Adult: 5320 mcg/d
First-generation oral antihistamine	Diphenhydramine (Benadryl™)	Yes	50–100 mg q4–6 h (≥12 yo)	6–11 yo: 1 mg/kg q4–6 h or 12.5–25 mg q4–6 h	Max- Peds: 150 mg/d Adult: 300 mg/d
	Chlorpheniramine (Aller-Chlor™)	Yes	Immediate release (≥12 yo): 4 mg q4–6 h Extended release (≥12 yo): 12 mg q12 h	Immediate release: 6–11 yo 2 mg q4–6 h Extended release: not approved for children <12 yo	Max- Peds: 12 mg/d Adult: 24 mg/d
	Hydroxyzine (Vistaril™)	No	25 mg TID***** or QID****** (≥6 yo)	<6 yo: 50 mg/d in divided doses or 2 mg/kg/d in divided doses for patients ≤40 kg	Max- Peds: 50 mg/d Adult: 100 mg/d
Second- and third-generation oral antihistamine	Cetirizine (Zyrtec™)	Yes	10 mg once daily (≥6 yo)	6–<12 mo: 2.5 mg qday 12 mo–<2 yo: can increase to 2.5 mg BID 2–5 yo: can increase to 2.5 mg BID or 5 mg qday	Max- Peds: 5 mg/d Adult: 10 mg/d
	Loratadine (Claritin™)	Yes	10 mg once daily (≥6 yo)	2–5 yo: 5 mg qday	Max- Peds: 5 mg/d Adult: 10 mg/d

(*continued*)

Table 6 (continued)

	Generic (common brands)	Over the counter	Adult dose	Pediatric dose	Dose strengths
	Fexofenadine (Allegra™)	Yes	60 mg q12 or 180 mg qday (≥12 yo)	2–11 yo: 30 mg q12	Max- Peds: 60 mg/d Adult: 120 mg/d of 60 mg formulation, 180 mg/d of 180 mg formulation
	Desloratadine (Clarinex™)	No	5 mg qday (≥12 yo)	6–11 mo: 1 mg qday 12 mo–5 yo: 1.25 mg qday	Max- Peds: 1.25 mg/d Adult: 5 mg/d
	Levocetirizine (Xyxal™)	Yes	2.5–5 mg qday (≥12 yo)	6 mo–5 yo: 1.25 mg qday 6–11 yo: 2.5 mg qday	Max- Peds: 2.5 mg/d Adult: 5 mg/d
Intranasal decongestants	Phenylephrine (4-Way™)	Yes	0.25–1% solution: 2–3 SEN q4, max of 3–5 d (≥12 yo)	2–5 yo: 0.125% solution 2–3 SEN q4, max 3–5 d 6–11 yo: 0.25% solution, 2–3 SEN q4, max 3–5 d	Max dosing as listed for no more than 5 days
	Oxymetazoline (Afrin 0.05%™)	Yes	2–3 SEN BID, max 3–5 d (≥6 yo)	Not recommended in children under 6 yo	Max dosing as listed for no more than 5 days
Oral decongestants	Pseudoephedrine (Sudafed™)	State Dependent, restricted OTC sale	Immediate Release (≥12 yo): 60 mg q4–6 h Extended release (≥12 yo): 120 mg q12 or 240 mg qday	4–5 yo: Immediate Release 15 mg q4–6 h 6–12 yo: Immediate Release 30 mg q4–6 h Extended release not recommended for <12 yo	Max- Peds: 4–5 yo 60 mg/d 6–11 yo 120 mg/d Adult: 240 mg/d
	Phenylephrine (Sudafed PE™)	Yes	10 mg q4 h for max 7 d (≥12 yo)	4–5 yo: 2.5 mg q4 h for max 7 d 6–11 yo: 5 mg q4 h for max 7 d	Max- Peds: 4–5 yo 15 mg/d 6–11 yo 30 mg/d Adult: 60 mg/d
Leukotriene receptor antagonist	Montelukast (Singulair™)	No	10 mg qday (≥15 yo)	6 mo–5 yo: 4 mg qday 6–14 yo: 5 mg qday	Max- Peds: 6 mo–5 yo 4 mg/d 6–14 yo 5 mg/d Adult: 10 mg/d
Miscellaneous intranasals	Cromolyn (NasalCrom™)	Yes	1 SEN TID or QID, can increase up to 6 times daily (≥2 yo)	Not approved for children <2 yo	1 spray = 5.2 mg Max- 62.4 mg/d

(*continued*)

Table 6 (continued)

	Generic (common brands)	Over the counter	Adult dose	Pediatric dose	Dose strengths
	Ipratropium	No	0.03% solution: 2 SEN BID or TID (≥6 yo) 0.06% solution: 2 SEN QID for max 3 weeks (≥5 yo)	0.06% solution 2–4 yo: 1 SEN TID for max 14 days	0.03% solution: 1 spray = 21 mcg Max- 252 mcg/d 0.06% solution: 1 spray = 42 mcg Max- 672 mcg/d

*SEN: spray each nostril, **qday: once daily, ***yo: year old, ****BID: twice daily, *****TID: three times daily, ******QID: four times daily

rhinitis symptoms are at their peak (Corren 2014). Asthma and allergic rhinitis both involve airway inflammation, with asthma affecting the lower airways with bronchial inflammation and allergic rhinitis affecting upper airways with nasal inflammation (Scadding et al. 2008). Patients with allergic rhinitis but without known asthma often have bronchial hyperresponsiveness to inhalation challenges with histamine or methacholine, further indicating the need to assess patients with allergic rhinitis for asthma (Lang 2010). Children with asthma and allergic rhinitis have higher risk of hospitalization than those with asthma alone (Fischer 2007). Appropriate treatment and management of allergic rhinitis can lead to improved asthma in patients with both conditions.

Cross-reactivity between food and inhalant allergens occurs, resulting in pollen-food syndrome, formerly known as oral allergy syndrome. Pollen-food syndrome results in mild localized reactions to certain foods due to sensitization to specific pollens. For example, patients with allergy to birch pollen can develop oral allergy symptoms to raw apples with mouth or throat itching after ingestion of the fruit; patients with oral allergy syndrome do not react to cooked products. Anaphylaxis is extremely uncommon in oral allergy syndrome, as are other systemic symptoms (Ricketti and Cleri 2009; Scadding and Scadding 2016).

There are also side effects due to chronic inflammation leading to dysfunctional eustachian tubes, otitis media, sinusitis, chronic cough, and tonsillar and adenoid hypertrophy. Children with repeated episodes of otitis media have a 35–50% increased risk of having an allergy. The link between allergic rhinitis and nasal polyposis is controversial, but there are documented higher recurrence rates of nasal polyps in patients with allergic rhinitis (Ricketti and Cleri 2009). Rhinosinusitis develops more commonly in those with allergic rhinitis due to impaired sinus drainage.

Sleep issues related to allergic rhinitis occur due to unrelieved nasal obstruction and congestion, which leads to apnea, hypopnea, and frequent arousal from sleep (Corren 2014). These symptoms are most pronounced in the early hours in the morning and worsened when lying down (Scadding et al. 2012).

With treatment adherence to an appropriate regimen for allergic rhinitis, the prognosis is good, and complicating factors can be avoided. However, adherence is difficult as medication doses can be missed, and regular visits for SCIT can be problematic to maintain.

5.9 Conclusion

Allergic rhinitis is a chronic disorder that can cause significant impairment if not diagnosed and treated appropriately. Skin prick testing is a standard for diagnosis, but serum testing can also

be used. Empiric treatment in mild cases is reasonable. Avoidance of the inciting allergen is key when possible, but pharmacotherapy and immunotherapy may also be necessary. The development of advanced treatments and potential cures for allergic rhinitis is desirable; newer therapies in the United States include SLIT. The goal for treatment is to manage the condition and decrease the impact on quality of life, which may be more significant than in patients with asthma. Managing comorbid conditions is critical for preventing disease progression and improving control. It is also important to differentiate allergic rhinitis from non-allergic medical conditions since the symptoms are nonspecific and both conditions may occur simultaneously, but the treatments differ. With a thorough understanding of allergic rhinitis, the goal is to identify this condition early in the symptom progression in order to improve the patient's quality of life and prevent complications.

References

American Geriatrics Society. Updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2015;63(11):2227–46.

Borish L. Allergic rhinitis and chronic sinusitis. In: Goldman L, Schafer AI, editors. Goldman-Cecil medicine. 25th ed. Philadelphia: Elsevier Saunders; 2016. p. 1687–93.

Bousquet J, van Cauwenberge P, Ait Khaled N, Bachert C, Baena-Cagnani CE, Bouchard J, et al. Pharmacologic and anti-IgE treatment of allergic rhinitis ARIA update (in collaboration with GA2LEN). Allergy. 2006;61:1086–96. https://doi.org/10.1111/j.1398-9995.2006.01 144.x.

Brozek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. J Allergy Clin Immunol. 2017;140:950–8. https://doi.org/10.1016/j.jaci.2017.03.050.

Corren J. Allergic rhinitis and conjunctivitis. In: Adkinson Jr N, Bochner B, Burks A, et al., editors. Middleton's allergy principles and practice, vol. 1. 8th ed. Philadelphia: Elsevier Saunders; 2014. p. 640–85.

Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol. 2011;127:S1–55. https://doi.org/10.1016/j.jaci.2010.09.034.

Ellegård EK. Pregnancy rhinitis. Immunol Allergy Clin North Am. 2006;26:119–35. https://doi.org/10.1016/j.iac.2005.10.007.

Ferri FF. Allergic rhinitis. In: Ferri's clinical advisor. 1st ed. Philadelphia: Elsevier; 2017. p. 63.

Finkas LK, Katial RK. Rhinitis. In: Scholes MA, Ramakrishnan VR, editors. ENT secrets. 4th ed. Philadelphia: Elsevier; 2016. p. 167–72.

Fischer TJ. Allergic rhinitis. In: Christy C, Garfunkel LC, Kaczorowski JM, editors. Pediatric clinical advisor: instant diagnosis and treatment. 2nd ed. Philadelphia: Mosby Elsevier; 2007. p. 16–7.

Frew AJ. Immunotherapy of allergic disease. In: Rich R, Fleisher T, Shearer W, et al., editors. Clinical immunology. 4th ed. London: Saunders; 2013. p. 1122–30.

Garcia-Lloret M. Chap 192, Allergic rhinitis and conjunctivitis. In: Rudolph CD, Rudolph AM, Lister GE, et al., editors. Rudolph's pediatrics. 22nd ed. New York: The McGraw-Hill Companies; 2011.

Gentile DA, Pleskovic N, Bartholow A, Skoner DP. Allergic rhinitis. In: Leung D, Szefler S, Bonilla F, et al., editors. Pediatric allergy: principles and practice, vol. 2015. 3rd ed. Edinburgh: Elsevier; 2015. p. 210–8.

Greenhawt M, Oppenheimer J, Nelson M, Nelson H, Lockey R, Lieberman P, et al. Sublingual immunotherapy: a focused allergen immunotherapy practice parameter update. Ann Allergy Asthma Immunol. 2017;118:276–82.e272. https://doi.org/10.1016/j.anai.2016.12.009.

Henke DC. Rhinitis: allergic and idiopathic. In: Runge MS, Greganti MA, editors. Netter's internal medicine. 2nd ed. Philadelphia: Elsevier Saunders; 2009. p. 56–60.

Joe SA, Liu JZ. Nonallergic rhinitis. In: Flint P, Haughey B, Lund V, et al., editors. Cummings otolaryngology. 6th ed. London: Elsevier Saunders; 2015. p. 691–701.

Lang DM. Allergic rhinitis. In: Carey WD, editor. Current clinical medicine. 2nd ed. Philadelphia: Elsevier Saunders; 2010. p. 19–23.

Marcdante KJ, Kliegman RM. Allergic rhinitis. In: Kliegman RM, Stanton B, St. Geme J, et al., editors. Nelson essentials of pediatrics. Philadelphia: Elsevier Saunders; 2015. p. 282–5.

O'Connell TX. Rhinitis. In: O'Connell TX, editor. Instant work-ups: a clinical guide to medicine. 2nd ed. Philadelphia: Elsevier; 2017. p. 348–52.

Quillen DM, Feller DB. Diagnosing rhinitis: allergic vs. nonallergic. American Family Physician. 2006. https://www.aafp.org/afp/2006/0501/p1583.html. Accessed 21 Dec 2017.

Ricketti AJ, Cleri DJ. Allergic rhinitis. In: Grammar LC, Greenberger PA, editors. Patterson's allergic diseases. 7th ed. Baltimore: Lippincott Williams & Wilkins; 2009. p. 466–80.

Scadding GK, Kariyawasam HH. Upper airway disease: rhinitis and rhinosinusitis. In: Spiro SG, Silvestri GA,

Agusti A, editors. Clinical respiratory medicine. 4th ed. Philadelphia: Saunders; 2012. p. 471–86.

Scadding GK, Scadding GW. Diagnosing allergic rhinitis. Immunol Allergy Clin North Am. 2016;36:249–60. https://doi.org/10.1016/j.iac.2015.12.003.

Scadding GK, Durham SR, Mirakian R, Jones NS, Leech SC, Farooque S, et al. BSACI guidelines for the management of allergic and non-allergic rhinitis. Clin Exp Allergy. 2008;38:19–42. https://doi.org/10.1111/j.1365-2222.2007.02888.x.

Scadding GK, Church MK, Borish L. Allergic rhinitis and rhinosinusitis. In: Holgate S, Churc M, Broide D, et al., editors. Allergy. 4th ed. Edinburgh: Elsevier Saunders; 2012. p. 203–26.

Standring S. Nose, nasal cavity and paranasal sinuses. In: Gray's anatomy; 2016. p. 556–70.e551. Philadelphia: Elsevier. https://doi.org/10.1016/B978-0-7020-5230-9.00033-9.

Wallace DV, Dykewicz MS. Seasonal Allergic Rhinitis: a focused systematic review and practice parameter update. Curr Opin Allergy Clin Immunol. 2017;17:286–94. https://doi.org/10.1097/ACI.0000000000000375.

Waller DG, Sampson AP, Renwick AG, Hillier K. Antihistamines and allergic disease. In: Medical pharmacology and therapeutics. 4th ed. Philadelphia: Elsevier; 2014. p. 449–54.