Rhinitis 2020: A Practice Parameter Update

Authors: Dykewicz MS, Wallace DV, Amrol D, Baroody F, Bernstein J, Craig T, Dinakar C, Ellis A, Finegold I, Golden DBK, Greenhawt M, Hagan J, Horner C, Khan DA, Lang D, Larenas-Linnemann D, Lieberman J, Meltzer E, Oppenheimer J, Rank M, Shaker M, Shaw J, Steven G, Stukus D, Wang J

Chief Editor(s): Dykewicz MS and Wallace DV
Workgroup Contributors: Dykewicz MS, Wallace DV, Amrol D, Baroody F, Bernstein J, Craig T, Finegold I, Hagan J, Larenas-Linnemann D, Meltzer E, Shaw J, Steven G
Joint Task Force on Practice Parameters Reviewers: Wallace DV, Golden DBK, Bernstein JA, Dinakar C, Ellis A, Greenhawt M, Horner C, Khan DA, Lang D, Lieberman J, Oppenheimer J, Rank M, Shaker M, Stukus D, Wang J

Reprints: Joint Task Force on Practice Parameters (JTFPP) liaison: Peris Flagg (American Academy of Allergy, Asthma, and Immunology, 555 E. Wells Street, Suite 1100, Milwaukee, WI 53202, pflagg@aaaai.org); JTFPP.allergy@gmail.com

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Abbreviations:

AAAAI	American Academy of Allergy, Asthma, and Immunology
ACAAI	American College of Allergy, Asthma, and Immunology
ACE	Angiotensin-converting enzyme
AR	Allergic rhinitis
ARCT	Allergic rhinitis control test
AUC	Area under the curve
BENARS	Blood eosinophilic non-allergic rhinitis
CBS	Consensus based statements
CHM	Chinese herbal medicine
CNS	Central nervous system
CRSsNP	Chronic rhinosinusitis without nasal polyps
CRSwNP	Chronic rhinosinusitis with nasal polyps
CysLTs	Cysteinyl leukotrienes
DP	*Dermatophagoides pteronyssinus*
DSCG	Disodium cromoglycate
FDA	Federal Drug Administration
GINA	Global Initiative for Asthma
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HPA	Hypothalamic–pituitary–adrenal
ICRs	Individual Case Safety Reports
IgE	Immunoglobulin E
INAH	Intranasal antihistamine
INS	Intranasal corticosteroids
IR	Irritant rhinitis
JTFPP	Joint Task Force on Practice Parameters
kDa	Kilodalton
LAR	Local allergic rhinitis
LTRA(s)	Leukotriene receptor antagonist(s)
MASK	Mobile Airways Sentinel network
NAPT	Nasal allergen provocation test

NAR	Non-allergic rhinitis
NARES	Non-allergic rhinitis with eosinophilia syndrome
OAS	Oral allergy syndrome
PA	Pyrrolizidine alkaloids
PAR	Perennial allergic rhinitis
PGA	Physician's global assessment
PSE	Pseudoephedrine
QALY	Quality-adjusted life-year
QOL	Quality of life
RCAT	Rhinitis control assessment test
RCT	Randomized controlled trial
REM	Rapid eye movement
RQLQ	Rhinitis Quality of Life Questionnaire
RUDS	Reactive upper airways dysfunction syndrome
SAR	Seasonal allergic rhinitis
SCIT	Subcutaneous allergy immunotherapy
sIgE	Specific IgE
SLIT	Sublingual immunotherapy
TNSS	Total nasal symptom score
TRPV1	Transient receptor potential vanilloid 1
TSDDs	Total standardized daily doses
TVRSS	Total vasomotor rhinitis symptom score
VMR	Vasomotor rhinitis
WER	Work exacerbated rhinitis

Corresponding Author:
Mark S. Dykewicz, MD
Raymond and Alberta Slavin Endowed Professor in Allergy & Immunology
Chief, Section of Allergy & Immunology;
Division of Infectious Diseases, Allergy and Immunology; Department of Internal Medicine
Director, Allergy & Immunology Fellowship Program
School of Medicine
1402 S. Grand Blvd, M157
St. Louis, MO 63104
Email: mark.dykewicz@health.slu.edu

Introduction

The diagnosis of rhinitis is suggested by the presence of 1 or more of the following symptoms: nasal congestion, rhinorrhea (anterior and posterior), sneezing, and itching. (1) Rhinitis can be classified by etiology, as allergic or non-allergic and differentiated from conditions that have overlapping symptoms of rhinitis.

Although the term rhinitis connotes inflammation, and allergic rhinitis (AR) and some types of non-allergic rhinitis (NAR) are associated with inflammation, (e.g., non-allergic rhinitis with eosinophilia syndrome (NARES), infectious rhinitis) some forms of NAR such as vasomotor rhinitis or atrophic rhinitis may not be associated with inflammation of the nasal mucosa. Rhinitis frequently is accompanied by symptoms involving the eyes, ears, and throat. Conditions that have overlapping symptoms with rhinitis include rhinosinusitis w/wo nasal polyps, cerebrospinal fluid rhinorrhea, ciliary dyskinesia syndrome, and structural/mechanical factors,

such as congenital anomalies, deviated septum and pharyngonasal reflux. Recognition of whether a patient has AR or NAR, or another mimicking condition is important because management will differ.

AR affects up to 60 million people in the U.S. annually, can have a major impact on quality of life, and poses a substantial economic burden on society. It also is often associated with and can potentially impact allergic conjunctivitis, rhinosinusitis, asthma and sleep disturbances.

Prevalence

Self-reported rates of AR are 10% to 30% of adults and as many as 40% of children in the United States. (2) In recent surveys that required a physician confirmed diagnosis of AR the prevalence rates were 14% of US adults and 13% US children. (3, 4) Canadian data supports an even higher prevalence of up to 20% of the population having physician diagnosed AR. (5) Chronic NAR has been estimated to affect 17-52% of adults while up to 34% of rhinitis patients in the US may have a combination of AR and NAR, often referred to as “mixed rhinitis”. (6-10)

Quality of life in rhinitis

Issues of quality of life associated with rhinitis include disturbed sleep, daytime somnolence and fatigue, irritability, depression, impairment of physical and social functioning, and attention, learning, and memory deficits. 35%-50% of adults reported that nasal allergies have at least a moderate effect on their daily life. (3) Sleep disturbances associated with rhinitis include difficulty falling asleep, staying asleep, and awakening refreshed. Nearly one in four of adult US respondents report they are unable to sleep or are awakened most days or every day and up to 45% of children experience sleep disruption because of nasal allergy symptoms. (3, 11) Most studies indicate associations between nasal allergies and anxiety/mood syndromes, with several mechanisms proposed to mediate this relationship. (12) Up to 10% of workers reported absenteeism because of their nasal allergies, and up to 25% reported work interference (presenteeism), with an estimated 23-33% decrease in productivity on days when allergies were at their worst compared with days when the respondent experienced no symptoms. (3) Compromised health due to increased symptom severity, decreased sleep quality and quantity, adverse effects on mental function, and antihistamines that are soporific are significantly related to work productivity. (13) AR can, by itself, introduce significant inattention, impairment of cognition and decreased daytime school performance. (14)

Limited available data report that health-related quality of life is reduced in patients with NAR, with greatest reductions in patients with NARES. (15) A decreased sense of smell, present in both AR and NAR, can lead to a significant decrease in quality of life, including disturbing a patient’s ability to appreciate flavors, losing the pleasures of eating, and increasing health risks such as not appreciating spoiled food or leaking gas and adding larger quantities of sugar and salt to highlight flavors, thus worsening general health. (16)

Economic and societal burden of rhinitis

The total direct medical cost of rhinitis is approximately $US 3.4 billion, with almost half

attributable to prescription medications. (17, 18) Rhinitis is a significant cause of lost work and school days, and decreased work productivity/presenteeism and school performance. Appropriate therapy can substantially reduce both societal and employer costs. Very few of the economic evaluations have formal cost assessments that compare the incremental costs and benefits of alternative treatment strategies. Lack of treatment, under treatment, or nonadherence to treatment have been seen to increase direct and indirect costs. (19)

Classification of Allergic Rhinitis: Severity, frequency, and environmental exposure

Assessment of rhinitis by severity, frequency, and exposure can assist the clinician in developing the most appropriate treatment strategies for an individual patient. (See Figures 2 and 3). *Mild rhinitis* severity is present when symptoms are not interfering with quality of life such as impairment of daily activities, work or school performance, leisure activities and sleep. *Moderate/severe rhinitis* is present when symptoms are troublesome or there is negative impact on any of these quality of life parameters. (1, 20) Other groups have proposed a division into mild, moderate and severe, (21) but as this division does not clearly translate into a change in therapy, the most accepted division is still the dual one, which is also used in the majority of clinical trials.

Symptom frequency has been divided by some into *intermittent* (< 4 days/week or < 4 consecutive weeks /year) and *persistent* (> 4 days/week and > 4 consecutive weeks/year). (22) This strict definition has some limitations, e.g. a patient who has symptoms three days/week year-round would be classified as “intermittent” although they might more closely resemble a “persistent” patient.

The preceding definitions of severity and frequency may be applied to AR, NAR or mixed rhinitis (when both allergic and non-allergic components contribute to rhinitis symptoms). AR may also be classified by the temporal pattern of environmental exposure to a triggering allergen: *seasonal* (ICD-10 J30.2, e.g. from pollens, J30.1), *perennial* (year round, e.g. dust mites, J30.89 “other allergic rhinitis” and J30.9 “allergic rhinitis, unspecified”), or *episodic environmental* from exposures not normally encountered in the patient’s environment, such as visiting a home with pets. (1) AR from animals (J30.81) may be perennial with ongoing exposure, or episodic environmental.

In the U.S., AR has traditionally been viewed as either seasonal (SAR) or perennial (PAR) and it is this classification system that the Federal Drug Administration (FDA) uses when approving new medications for AR. The reality is that a patient may have both SAR and PAR, SAR or PAR with non-allergic rhinitis (ICD10: J30 Vasomotor and allergic rhinitis), intermittent symptoms with perennial AR, or persistent symptoms with seasonal AR. It is also recognized that the distinction between SAR and PAR has limitations; in different climatic regions, the same aeroallergen can be either seasonal or perennial. Nonetheless, the recognition that an individual has SAR and is allergic to particular pollen allergens of known seasonality in a region may help guide administration of medications concurrent with (or in anticipation of) that defined seasonal exposure. That said, one must be mindful that nasal inflammation and thereby need for treatment may persist for weeks after a

pollen season is over. The majority of patients are polysensitized to both pollens and perennial allergens. In a population of 6000 AR patients, it was shown that 55% of patients with seasonal symptoms and 45% of those with perennial symptoms had intermittent AR; thus, the SAR-PAR classification is independent from the intermittent-persistent one. (23) Since then, numerous studies have duplicated these findings in other regions.(24) (25)

Local Allergic Rhinitis

In Local Allergic Rhinitis (LAR), also referred to as entopy, there is: a) a clinical history of perennial and/or seasonal symptoms following allergen exposure, with b) negative skin prick tests (and intradermal tests, when performed) and absence of serum specific IgE [sIgE] antibodies but c) a positive nasal allergen provocation test (NAPT) to aeroallergens. (26-29) While one major study center in Europe has contributed the bulk of the research on LAR as discussed above, additional small studies from Australia (30), Sweden (31), Egypt (32), and China (33, 34) have supported their findings. There have been limited US studies, not all confirming these findings. (35, 36)

A dual (immediate and late) response to NAPT had been noted in 37-70% of LAR. (37, 38) Although it would be expected that local sIgE would be detected in all patients with NAPT challenge-diagnosed LAR, some studies of LAR from pollens detect local sIgE in as few as 30%. (38, 39) When present in patients with SAR, an increase in nasal sIgE is noted both during NAPT challenge and during pollen season. (39) Likewise, in one dust mite LAR study, of patients who had a positive NAPT-dust mite challenge, only 22% had nasal sIgE to dust mites. (37) A recent method of detecting nasal sIgE by the direct application of the solid phase of a commercial ImmunoCAP test showed a sensitivity of 43% and high specificity, and offers promise for future clinical use. (40) However, given the current low sensitivity of assays for the local sIgE and the time-consuming and technically difficult NAPT procedure (41, 42), an in vitro test would be preferred. Studies have suggested that the basophil activation test might serve as a surrogate marker of LAR. It has been shown that using the basophil activation test with *D. pteronyssinus* extract and olive tree identifies 50% to 66%, respectively, of NAPT established LAR patients with a specificity of 93%, and showing identical specificity for both LAR and AR. (43)
In some studies, using NAPT, up to 26% of all rhinitis patients and up to 100% of NAR patients have LAR. (30, 31, 34, 35, 44-47) In one population-based observational study which categorized all rhinitis patients, over 25% and 63% were diagnosed to have LAR and AR, respectively, indicating that less than 12% had other types of non-allergic rhinitis. (48) The coexistence of dual perennial LAR and seasonal AR (prick test positive) has also been described. (49, 50) However, prevalence rates of LAR in China have been reported to be much lower, e.g., 7.7%. (51) LAR is reported to be more prevalent in women, to be associated with a family history of atopy equal to or greater than that of AR, and to have a mean onset of 21 years; however, LAR may start in childhood 36% of the time. (48, 52, 53) Local occupational rhinitis, diagnosed by nasal provocation studies, should be considered in workers with a convincing history but with negative immunological tests. (54)

The most frequently reported symptoms in LAR are watery rhinorrhea, sneezing and itching, compared to congestion and mucoid rhinorrhea for NAR patients. (48, 55) While most LAR

patients are monosensitized, most commonly to dust mite, up to 37% are polysensitized to seasonal and/or perennial allergens. (45, 48, 56) Of particular interest is a significantly lower incidence (2.7%) of animal dander sensitization in LAR patients compared to AR patients (31%). (48) The majority of adult LAR patients have moderate to severe, persistent, and perennial symptoms, with common comorbidities of conjunctivitis (50-65%), and asthma (18 %-47%). These studies show that the severity of LAR and associated comorbidities increase with disease duration. (38, 48, 57-59)

The mainstay of current LAR treatment has consisted of avoidance and pharmacotherapy. However, recent well-controlled trials suggest that if the specific triggering allergen can be accurately identified, subcutaneous allergy immunotherapy (SCIT) or sublingual immunotherapy (SLIT) might be considered. SCIT has been successfully used to treat dust mite, grass, and birch induced LAR, in two different European centers. (39, 59-61) A randomized, double blind placebo controlled (DBPC) parallel group study demonstrated that SCIT with *Dermatophagoides pteronyssinus* (DP) in LAR DP-sensitized patients produced significant improvement with reduction in total symptom score (47%), reduction in total medication scores (51%), and reduced responses to NAPT-DP (with total suppression in 50% of patients) over a 24-month treatment period. (61) Significant symptom improvement and nasal tolerance to NAPT-DP was noted as early as six months into treatment. (59) A small randomized DBPC 24-month trial of birch SCIT to patients with seasonal AR produced a significant reduction in symptom medication score, a decrease in local sIgE, and an increase in IgG4 levels. (39) In this study, local sIgE levels significantly increased during birch season in all patients, but a blunted seasonal increase was noted at 24 months in the active treatment group. (39) An observational study using pre-seasonal grass SCIT demonstrated significant clinical improvement and increased NAPT nasal tolerance in all patients. (60) However, in this early study, 40% of the SCIT group developed positive skin prick tests after six months of treatment followed by serum sIgE and sIgG antibodies to grass after 12 months of treatment. (60) The same group completed a randomized DBPC study involving 56 AR patients with LAR to grass, established by either a positive NAPT or nasal sIgE $\geq$ 0.35 kU/L. (62) There was significant improvement in combined symptoms medication score and RQLQ after 6 months of preseasonal treatment. The effect was sustained during the 2nd year when year-round SCIT was used. There was a significant increase in serum IgG4 levels and allergen tolerance with 83% of patients completing at least 6 months of treatment tolerating over 50 times higher concentration of grass pollen during NAPT challenge, with 56% having a negative challenge. (62) In this controlled study, only 7.4% of the active vs. 3% of the control group developed serum sIgE to grass at the end of year one, showing that active SCIT treatment is unlikely to be creating systemic atopy. (62) A larger, prospective ten-year cohort study (2005-2016) of untreated patients with LAR showed a progressive worsening of the rhinitis, increased development of asthma, reduced quality of life, and loss of allergen tolerance. (63) While a significant change was noted after 5 years, (52) this becomes progressively worse throughout the entire 10 years. The development of systemic atopy was not found to be significantly greater in LAR patients (9.7%) vs. matched healthy controls (7.8%). (63)

While the literature supports LAR as a real entity, further large, multi-center, long-term,

well-controlled studies with children and adults are needed to better define the prevalence, evolution, diagnosis, and treatment of LAR.

Non-allergic rhinitis (NAR)

By definition NAR is defined as rhinitis that is independent of an IgE mediated mechanism that includes vasomotor rhinitis (VMR) (64) (sometimes referred to as non-allergic rhinopathy or idiopathic rhinitis), infectious rhinitis, food induced rhinitis (65), hormonal rhinitis (66), drug induced rhinitis (67), non-allergic occupational rhinitis (68), atrophic rhinitis (69), Non-allergic rhinitis with eosinophilia syndrome (NARES) (25), rhinitis of the elderly and idiopathic rhinitis (70). For this reason, Non-allergic Noninfectious Rhinitis (NANIR) is often the term used to describe this group of patients. (71) In reality, NAR can be acute of chronic, is often present in conjunction with allergic rhinitis ("mixed rhinitis") (72) and is frequently associated with hyper-reactivity of the nasal mucosa. (73) In a study by Rondon, compared to those with AR, patients with NAR were more likely to be older and to have severe congestion and rhinorrhea but less likely to have asthma. (48) The exact prevalence of NAR is unknown, but some estimates suggest that worldwide up to 200 million people have NAR. (71)

Vasomotor rhinitis

Vasomotor rhinitis (VMR), a subtype of NAR, can be acute or chronic and is often activated by temperature and humidity changes, especially cold dry air, airborne irritants, strong odors, including tobacco smoke, and/or exercise.(74) VMR, often a diagnosis of exclusion, is frequently referred to as idiopathic rhinitis. (75) The symptoms of VMR are variable, consisting mainly of nasal obstruction and increased clear secretion. Sneezing and pruritus are less common. Cough is also a common component of VMR. (76)

"Idiopathic rhinitis", is sometimes used as an alternative term to VMR, and usually excludes NARES. (77)However, the term is confusing as some studies have found high levels of eosinophils and mast cells in some patients categorized as having "idiopathic rhinitis". (78) In this practice parameter we do not use the term.

The diagnosis of VMR is based on exclusion of other forms of rhinitis, especially allergic rhinitis, infectious rhinitis, and anatomic/surgical structural changes of the nose and sinuses. The history is the most important determinant leading to diagnosis. The physical exam findings can vary widely and laboratory tests, skin prick tests and sIgE are helpful only to exclude allergic rhinitis. Nasal challenge for VMR, to determine nasal hyperresponsiveness, e.g., using cold dry air or hypertonic saline in a challenge chamber, may be used in research to assess drug efficacy but is rarely used for clinical diagnosis. (76, 79) More recently, optical rhinometry with intranasal capsaicin challenge has been demonstrated to assist in the diagnosis of a subset of VMR patients with non-allergic irritant rhinitis. (80)

While the pathophysiology of VMR is not fully understood, there is evidence that it involves a neurogenic pathway with an increase in neural efferent traffic to the nasal mucosa with

an imbalance between parasympathetic and sympathetic nasal innervation. (81) Support for this is partially based upon the beneficial effects of ipratropium bromide and vidian neurectomy (the vidian nerve contains both the parasympathetic and the sympathetic innervation to the nasal mucosa). (81, 82) Subjects with predominant rhinorrhea (sometimes referred to as *cholinergic rhinitis*) appear to have enhanced cholinergic glandular secretory activity which can be effectively reduced with the use of atropine and ipratropium bromide. (83, 84) Patients with predominant symptoms of nasal congestion appear to have nociceptive neurons that have heightened sensitivity to stimuli such as temperature change, airborne irritants, foods (especially hot and spicy foods), alcoholic beverages, cold dry air, and exercise. (85-88) Measurement of neuropeptides such as substance P in models of hypertonic saline and cold dry air induced rhinitis further support a neurogenic mechanism for VMR. (79)

However, somewhat conflicting research based upon the response to intranasal capsaicin, a selective transient receptor potential vanilloid 1 (TRPV1) receptor agonist, suggests that nociceptive C fibers in the trigeminal nerve lead to hypersensitivity of the TRP ion channels on sensory afferent neurons innervating the nasal mucosa and that this can induce the symptoms of VMR. (89) In clinical studies patients with irritant rhinitis (IR) have higher TRPV1 expression in the nasal mucosa and higher concentrations of substance P in nasal secretions when compared to controls. (90) From these data, the term “neurogenic rhinitis” has been proposed to replace VMR and IR to describe this type of NAR.

Infectious Rhinitis

Infectious rhinitis and rhinosinusitis may be acute or chronic. Infectious rhinitis may range from self-limited rhinitis secondary to common viral upper respiratory infections to more severe disease caused by other pathogens, such as fungal infections in an immunocompromised patient (74) Acute infectious rhinitis is usually a result of 1 of many viruses, but secondary bacterial infection with sinus involvement (bacterial rhinosinusitis) may be a complication. (1, 91) Viral infections account for as many as 98% of acute infectious rhinitis and the majority of rhinitis symptoms in the young child. (1) Symptoms of acute infectious bacterial rhinosinusitis include nasal congestion, mucopurulent nasal discharge, pain and pressure, headache, olfactory disturbance, postnasal drainage, and cough. While these symptoms may overlap and mimic those of allergic rhinitis (AR), the presence of a recurrent seasonal pattern of symptoms, the presence of an obvious allergic trigger, and symptoms of nasal or ocular pruritus strongly suggest the diagnosis of AR. This diagnostic distinction is important to avoid inappropriate treatment of AR. (92)

Inappropriate prescribing of antibiotics is often secondary to misinterpretation of the symptoms and signs of infectious viral rhinitis/rhinosinusitis with bacterial rhinosinusitis. This has led to over prescribing antibiotics and with this increasing bacterial antibiotic resistance. Recent research demonstrates antibiotic prescribing rates as high as 69% to 79% for acute infectious rhinitis, which may account for up to 60% of all antibiotic prescriptions written by a practice, despite often a lack of benefit and increase risk of adverse effects, including resistance. (93-104)

Symptoms distinguishing viral versus bacterial infectious rhinitis/rhinosinusitis are minimal and recent evidence suggests that separating viral from bacterial infections based on clinical presentation is often not possible. (98, 105-107) In addition, since viral induced infectious rhinitis/rhinosinusitis can cause sinus CT changes that mimic acute bacterial rhinosinusitis, a CT scan should be deferred unless complications are a concern. (108-110) Up to 70% of children with viral infectious (111) and as many as 87% of adults will have abnormalities on CT scan during the common cold. (112) Similarly, nasal culture and cytology of nasal secretions provide minimal assistance in distinguishing non-bacterial infectious from bacterial rhinosinusitis and often positive bacterial cultures from the nose or sinus may represent colonization and not a pathogen. (92, 113-115) The transition from viral infectious rhinitis to bacterial rhinosinusitis and appropriate treatment for the rhinosinusitis has been a focus of treatment guidelines due to the resistance of bacteria that are known to cause acute bacterial rhinosinusitis. (92, 113, 116-123) Most guidelines suggest deferring antibiotic treatment for 7 to 10 days after onset of symptoms of infectious rhinosinusitis to avoid overuse of antibiotics. Controversies in the management of chronic rhinosinusitis are addressed in the most recent Joint Task Force publication on rhinosinusitis. (91)

Unique populations susceptible to frequent or persistent and refractory infectious rhinitis include patients with anatomic abnormalities of the nares and sinuses, chronic rhinosinusitis with nasal polyps (124), ciliary dysfunction, cystic fibrosis, primary immunodeficiency, acquired immunodeficiency and children. The differential diagnosis of infectious rhinitis in children includes not only AR but foreign bodies, acute *S. aureus* bacterial infection of the nares and enlarged or infected adenoids. (125)

Food induced rhinitis: Gustatory Rhinitis

The main symptom is clear rhinorrhea after ingestion of food, especially hot and spicy foods. (126) The mechanism is thought to be a neurologic reflex of the non-cholinergic, non-adrenergic system.

Food induced rhinitis: IgE-mediated food allergy and allergic rhinitis

Outside of the oral allergy syndrome (OAS) discussed below, there is no evidence of IgE-mediated food-induced rhinitis symptoms without the presence of anaphylaxis with whole-body symptoms, e.g., hives, difficulty breathing, or diarrhea; therefore, there is no indication to test for food allergens when evaluating patients presenting with symptoms of rhinitis. Furthermore, there have been no published studies of oral food challenges producing isolated rhinitis symptoms. With the specificity of both skin prick testing and sIgE testing to foods being less than 50% (127) and recognizing that sensitization does not equate to clinical allergy, unnecessary food testing can lead to unwarranted food avoidance resulting in a reduced quality of life, uncalled-for financial expenditure, and possible nutritional deficiency.(128, 129) Testing with a “panel” of foods without attention to the medical history and epidemiology of allergic rhinitis, can result in mismanagement.(130)

While a high rate of sensitization to certain food (fruits, nuts, and vegetables), as demonstrated by prick skin tests or sIgE, is reported in patients with pollen-induced AR, e.g., birch, mugwort,

ragweed, and grass, most of these patients will not experience symptoms when ingesting cross-reacting foods. (131) AR patient-reported prevalence of the OAS varies between 6 to 93%, generally being higher in adults vs. children; females; patients having severe rhinoconjunctivitis symptoms, multiple pollen allergies, and longer duration of AR; and in geographical locations with high pollen levels. (131-135) While there have been limited studies utilizing oral food challenges to diagnose OAS in patients with AR, these have reported a much lower prevalence rate of 0.1% to 4.3%. (136) There have been, unfortunately, no studies in the United States that have adequately studied the prevalence of OAS including the development of rhinitis symptoms upon ingestion of pollen-related foods. In patients with OAS, symptoms of itching and swelling are usually mild and limited to the oropharyngeal area, but systemic reactions, including AR symptoms, have been reported. One large review reported that 9% of patients with OAS had systemic reactions beyond the gastrointestinal tract which, at times, included nasal congestion, rhinorrhea, and sneezing. (137) In fact, patients with plant food reactions are at much lower risk of having systemic reactions if they have concurrent AR pollinosis compared to those without pollen-induced AR. (138)

Food induced rhinitis: Alcohol-induced rhinitis symptoms

Alcohol-induced upper airway symptoms are felt to be due to alcohol hyperresponsiveness (including vasodilator effects) and not due to “alcohol allergy”. Nasal congestion is the most common alcohol-induced upper airway symptom, followed by rhinorrhea. Alcohol-induced upper respiratory symptoms have been reported in up to 14% of healthy individuals, 33% of asthmatics and 75% of patients with aspirin-exacerbated respiratory disease (AERD).(139) Alcohol hyperresponsiveness correlates with the severity of the nasal inflammatory response, being greater in patients who have NSAID exacerbated respiratory disease or chronic rhinosinusitis with nasal polyps [CRSwNP](with or without asthma) compared to patients with AR or chronic rhinosinusitis without nasal polyps [CRSsNP]. (139, 140) In asthmatics, a corresponding increase in lower respiratory symptoms is also noted. While the triggering mechanism for alcohol-induced respiratory symptoms is unknown, the elevation of systemic cysteinyl leukotrienes observed following alcohol consumption may be at least one major contributing factor. (139) In some patients with AR, alcohol-induced symptoms may be intermittent, e.g., only present during seasonal exacerbations, may appear one hour or later following ingestion, have a duration of more than one hour but less than one day, and may require between 1-3 drinks for symptom provocation. (140) For most affected patients, any alcoholic beverage can provoke symptoms, however, chronic rhinosinusitis patients without asthma have reported that wine may be worse than other alcoholic beverages. (140) Alcohol-induced symptoms in patients with NSAID exacerbated upper respiratory disease have been reported to diminish following aspirin desensitization. (141) With the above noted association of alcohol-induced rhinitis symptoms with CRSwNP, CRSsNP, asthma, and NSAID-exacerbated respiratory disease, the clinical history of alcohol as a trigger for rhinitis symptoms should prompt the health care provider to consider these diagnoses and to pursue further diagnostic testing, e.g., rhinoscopy or spirometry, if indicated.

Hormonal rhinitis

Estrogen and progesterone-induced changes occurring with pregnancy, menstrual cycle, menopause and puberty can all affect nasal congestion. Increase of estrogen can cause nasal vascular engorgement leading to congestion. In addition, progesterone and estrogen can increase eosinophil migration into the nasal mucosa in contrast to testosterone which decreases eosinophils in the nasal mucosa. This association of hormones to eosinophils may account for the greater prevalence and severity of rhinitis in females following puberty. (142) Rhinitis associated with pregnancy presents with congestion and while this may be and secondary to increases in estrogens and progesterone, the exact mechanism is not known. (143, 144) Other endocrine disease such as hypothyroidism and acromegaly also have been associated with nasal congestion. (71)

Drug induced rhinitis

Drug-induced rhinitis can be classified based upon proposed mechanism of action as local inflammatory, neurogenic, and idiopathic. (145) An acute inflammation response may be induced following the ingestion of ASA or other NSAIDS with isolated nasal symptoms or nasal symptoms as part of the NSAID-exacerbated respiratory disease with acute asthma symptoms and associated chronic rhinosinusitis with nasal polyposis. Disruption of the sympathetic and parasympathetic tone by alpha and beta-adrenergic blockers produce rhinorrhea and nasal congestion through a neurogenic mechanism. The responsible pharmacological agents may be 1) centrally-acting sympatholytic, e.g., clonidine, reserpine, and methyldopa; 2) peripherally-acting sympatholytic, e.g., guanethidine and phentolamine; 3) ganglion-blocking, e.g., trimethaphan, or 4) vasodilators (phosphodiesterase type-5 inhibitors), e.g., sildenafil. (145) No mechanism has been clearly identified for many drugs that can produce nasal symptoms, e.g., calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, gabapentin, and psychotropics, e.g., risperidone and chlorpromazine. (145, 146) The effect of exogenous estrogens and oral contraceptives on nasal physiology is uncertain although it has been suggested that oral contraceptives may reduce allergen-provoked nasal congestion during ovulation but increase sneezing at the end of the menstrual cycle. (147-149) Overuse of topical decongestants can result in rhinitis medicamentosa, a form of “drug-induced rhinitis”, which is further discussed under the “Intranasal Decongestants” section.

Work related rhinitis

Work related rhinitis is comprised of 1) *de novo* occupational rhinitis (due to exposures from a particular occupational environment, not usually encountered outside the work environment) and 2) work exacerbated rhinitis (WER) (pre-existing or concurrent - allergic or non-allergic - rhinitis that is worsened by workplace exposures). Most occupational rhinitis primarily is due to high molecular weight agents (>10 kDa) is IgE and Th2 cell driven and is associated with exposure to an allergen at work. Low molecular weight (<10 kDa) occupational sensitizers may also induce occupational rhinitis symptoms through mechanisms without associated IgE. (71, 150) Following specific inhalational challenge, high molecular weight agents produced a significantly higher level of acute-phase reactant proteins, cell adhesion molecules, endothelial growth factors and vitamin D binding-proteins when compared to low molecular weight agents. (151). In WER, aggravation of

rhinitis symptoms is often caused by non-allergic irritant triggers, such as from cold dry air, dust particles, smoke, chemicals or strong odors. Rarely, when a single high-level exposure or multiple low-dose exposures to an irritant gas, vapor, dust or smoke results in chronic rhinitis, this is referred to as reactive upper airways dysfunction syndrome (RUDS). In nasal mucosa biopsies of individuals exposed to chlorine dioxide, pathological changes found include lymphocytic inflammation of the lamina propria, epithelial desquamation, and increased number of nerve fibers. (152) Analogous to irritant-induced asthma/reactive airways dysfunction syndrome (153), the predominant basis for making the diagnosis of RUDS is based upon occupational history.

Atrophic rhinitis

Atrophic rhinitis is a chronic nasal condition associated with atrophy of the nasal mucosa and paradoxically presenting as nasal congestion due to a sensation of decreased airflow, likely a result of decreased airflow resistance. Atrophic rhinitis can be categorized as primary or secondary. While the pathophysiology of primary atrophic rhinitis is unknown, it is associated with mucosal colonization, predominantly with *Klebsiella ozaenae*, although other organisms have also been described. Primary atrophic rhinitis is more commonly seen in young to middle-aged adults in developing countries with dry climates, e.g., Saudi Arabia, China, Africa, and India and is uncommon in the United States and Europe. (154). One United States study of atrophic rhinitis patients, categorized approximately 19% as primary atrophic rhinitis with a mean age of 52 years (154). It is characterized by progressive atrophy of the nasal mucosa, resorption of underlying bone and turbinates, nasal dryness, and foul-smelling nasal crusts associated with a constant awareness of a bad smell. Biopsy findings consist of squamous metaplasia, glandular cell atrophy, and loss of pseudostratified epithelium. By definition, there is no history of nasal surgery or trauma in primary atrophic rhinitis as is often the case in secondary atrophic rhinitis.

Secondary atrophic rhinitis is more common in the United States and less severe than primary atrophic rhinitis. Secondary atrophic rhinitis often develops as a result of excessive nasal surgery, trauma, irradiation, or chronic granulomatous nasal infections. Therefore, patients with secondary atrophic rhinitis for which an iatrogenic cause has not been determined should be evaluated for an underlying inflammatory systemic disease, e.g., leprosy, sarcoidosis, or syphilis. Repeated, and often radical, sinonasal surgeries for chronic rhinosinusitis, allergic fungal rhinosinusitis, and/or nasal sarcoidosis produce a widening of the nasal vault, referred to as an “empty nose syndrome” (155). The empty nose syndrome, as may occur after aggressive resection of the inferior and sometimes middle turbinates, is associated with the perception of severe nasal obstruction and inability to sense airflow through the nose. It is “paradoxical” because examination typically finds widely patent nasal cavities and nasal resistance as assessed by rhinomanometry is normal or low. Some patients sense profound dyspnea even though there is no pulmonary disease. (156) (157)

Treatment has traditionally focused on reduction of crusting.(154, 158) Conservative treatment can consist of nasal saline irrigation, glycerin containing nose drops, nasal emollients, antibiotics, and vasodilators. (155) Surgical interventions attempt to decrease

the size of the nasal cavities thereby promoting regeneration and increasing lubrication of the nasal mucosa and improving nasal vascularity. This can be achieved by surgically closing the nasal cavities (Modified Young's procedure) or implanting prostheses submucosally to decrease nasal cavity size (155, 159). There are no recent randomized controlled studies that compare these treatment options(108).

Non-allergic rhinitis with eosinophilia syndrome

NARES (Non-allergic Rhinitis with Eosinophilia Syndrome) was first was used in 1981 as a term to describe a case series of nonasthmatic patients who reported perennial, intermittent symptoms of profuse clear rhinorrhea and paroxysms of sneezing as well as nasal or ocular pruritus, lacrimation and nasal congestion without complete obstruction. Patients were characterized by elevated nasal eosinophils greater than 20% but with the absence of specific IgE by skin and blood testing in all but 3 of 52 subjects. The original cohort included no patients with clinical evidence of chronic rhinosinusitis with nasal polyps. Oral aspirin and inhaled methacholine challenges performed on limited numbers of subjects were negative. (160) Onset of symptoms ranged from the first to fifth decades.

However, other systematic evaluations of non-allergic subjects with eosinophilic non-allergic rhinitis showed significant associations with rhinosinusitis with nasal polyps, sinus mucosal thickening and asthma leading to speculation that NARES may be a prelude to the onset of chronic rhinosinusitis, asthma or perhaps NSAID-exacerbated respiratory disease. (161, 162).

Blood eosinophilia is occasionally present in patients with NARES and the term blood eosinophilic non-allergic rhinitis (BENARS) had been proposed but not routinely used to represent this possible condition. (163) The prevalence of NARES is unknown but is suspected to represent 1-5% of children and from 5-15% of adults with rhinitis. (162, 164, 165) One cluster analysis from a single center in Beijing characterized NARES in 23.6 % of predominately adult subjects with chronic rhinitis. (166) Nasal eosinophilia persisted in non-allergic children who were followed throughout the year including the winter season when not exposed to allergens. (165) Total nasal resistance and mucociliary transport time is increased in patients with NARES when compared to healthy controls.(167).

The differential diagnosis of persistent nasal eosinophilia includes perennial allergic rhinitis with positive allergy skin or IgE blood tests, local allergic rhinitis, rhinosinusitis with nasal polyps, chronic rhinosinusitis without polyps, eosinophilic granuloma, allergic fungal rhinosinusitis and NSAID-exacerbated respiratory disease.(168)

NARES is particularly responsive to corticosteroids. (162) In one uncontrolled study, montelukast 10 mg daily reduced nasal obstruction, rhinorrhea, sneezing and nasal pruritus in subjects with NARES and asthma. (169) Intranasal cromolyn was studied and found to have no benefit in NARES. (170)

To date there has not been consensus regarding the specific clinical criteria for diagnosis of NARES. The lower limits of nasal eosinophilia required for diagnosis has been variable ranging from 5 to 25% and the percentage may vary depending on specimen type. (171,

172) Current clinical guidelines have not recommended routine assessments of nasal eosinophils. (1) The diagnosis of NARES should be considered in non-allergic patients presenting with prominent symptoms of perennial rhinorrhea and sneezing in the absence of facial pain, nasal obstruction, rhinosinusitis with nasal polyps on rhinoscopy and sinus mucosal thickening in individuals with notable response to nasal steroids or with eosinophilia in blood or if assessed in nasal secretions.

Elderly patients and rhinitis

Rhinitis in the elderly may be caused by the same types and subtypes of rhinitis common in other age groups. It occurs in up to 30% of the elderly, and >40% of these patients rate their rhinitis as moderate to severe, and almost 70% of these can be expected to have an ocular component. (69) Allergic rhinitis is the most common type of rhinitis in the elderly but is less frequent than its incidence in younger age groups. In addition to allergic rhinitis, because of the concomitant use of multiple medications in the elderly, drug induced rhinitis is not infrequent. Alpha-1 adrenergic antagonists used for benign prostatic hyperplasia (173), ACE-inhibitors (146, 174-176), possibly beta-adrenergic inhibitors (177) and phosphodiesterase inhibitors (178), can induce symptoms of rhinitis. (See earlier section on Drug induced rhinitis.)

Physiologic changes due to aging result in alterations in neural, histologic, mucosal, and olfactory status which have direct impact on the functioning of the nose (179). While the mechanism for the clear rhinorrhea reported to be the major rhinitis symptom in over 70% of this older population is not fully understood, there appears to be an imbalance of the sympathetic and parasympathetic tone, resulting in cholinergic hyperreactivity and excessive rhinorrhea. (180, 181). On the other hand, aging is also associated with reduced body water content and less effective nasal mucociliary clearance, leading, at times, to thicker mucous secretions, increased postnasal drip, and potentially, to increased respiratory infections. (182-185) Structural changes due to aging can also reduce nasal cartilage elasticity and tip support which can further interfere with nasal airflow. (185) Age related reduced blood flow to the nasal mucosa, basement membrane thickening, and epithelial atrophy have also been described. (186) (187) Through a combination of these structural and physiological changes, the elderly are more susceptible to nasal dryness, intranasal crusting, epistaxis, ulceration and atrophy of the nasal mucosa.(185)

Therapy for the elderly presenting with hyperactive cholinergic symptoms has not been well studied; however, because of the mechanism of action, intranasal ipratropium seems to be a logical intervention. (188) Second generation oral antihistamines, intranasal antihistamines, leukotriene inhibitors, and intranasal corticosteroids are effective and well tolerated in the elderly when used for an appropriate indication, but controlled data comparing efficacy in this population are lacking. (183) Sedating antihistamines, secondary to their systemic anticholinergic effects, should be avoided in the elderly due to the risk of urinary retention, constipation, delirium and ocular pressure changes. (189) As noted below under the “Oral Antihistamines” section, a 2015 U.S. prospective population-based cohort study suggested a link between higher cumulative use of agents with stronger anticholinergic effects (including sedating oral antihistamines) and the risk of developing dementia.

Diagnosis and Management of Rhinitis

Methods and Overview of the Practice Parameter Guideline Development Process

This guideline contains systematically developed recommendations intended to optimize patient care and to assist physicians and/or other health care practitioners and patients to make decisions regarding diagnosis and therapy for rhinitis. This guideline updates "**The diagnosis and management of rhinitis: an updated practice parameter"** published in 2008. (190) The strength of the consensus based statements is determined to be either **strong** or **conditional** as defined below. The certainty of evidence for each recommendation is determined to be **high, moderate, low**, or **very low** as defined below. When the JTFPP did not have adequate published evidence with which to determine the certainty of evidence but recognized, nonetheless, the need to provide guidance to the clinician, the consensus based statements were based upon the collective expert opinion and experience of the workgroup and JTFPP. We have provided the tabulated vote for and against each such statement.

The guideline development process involves several stages. The workgroup begins the process by developing a list of key clinical questions and topics to be addressed. At least two workgroup members are assigned to write and review each section. A PubMed literature search is completed to determine the most updated information for each consensus based statement and discussion. The draft sections are reviewed by the workgroup chair and co-chair with subsequent revision by the authors. Subsequently, all sections are reviewed and revised by the entire workgroup through several rounds of electronic and teleconference reviews. The guideline is reviewed in detail by the JTFPP and revisions, when needed, are made in conjunction with the workgroup. The external review follows as described above under "Resolving conflict of interest" in the preface.

Table 1. Grading the Strength of the Consensus Based Statements

Strong Consensus Based Statement (CBS)
The workgroup and JTFPP are confident that the desirable effects of adherence to the statement outweigh the undesirable effects. This CBS may be appropriate to be used as a practice standard indicator. When making a strong CBS the wording is "We recommend" implying that the clinician "should" follow the recommendation. The implications of a **strong CBS** are: • For patients—most people in your situation would want the recommended course of action and only a small proportion would not; request discussion if the intervention is not offered. • For clinicians—most patients should receive the recommended course of action. • For policy makers—the recommendation can be adopted as a policy in most situations.
Conditional CBS
The workgroup and JTFPP reach a decision that the desirable effects of adherence to a CBS probably outweigh the undesirable effect. When making a conditional CBS, the wording is "We suggest" implying that the clinician "may" follow the recommendation. The implications of a **conditional CBS** are: • For patients—most people in your situation would want the recommended course of action, but many would not.

- For clinicians—you should recognize that different choices will be appropriate for different patients and that you must help each patient to arrive at a management decision consistent with her or his values and preferences. It is likely that shared-decision making will plan a major role in arriving at the management decision.
- For policy makers—policy making will require substantial debate and involvement of many stakeholders.

Table 2. Grading the Certainty of Evidence for each Consensus Based Statement

High = Further research is very unlikely to change our confidence in the estimate of effect. The recommendation is based on high quality evidence, e.g., multiple highly rated randomized controlled trials, systematic reviews and metanalyses.
Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. The recommendation would likely be based upon somewhat limited evidence, e.g., reduced number or quality of randomized controlled trials, controlled trials without randomization.
Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. The recommendation would likely be based upon very weak evidence, e.g., non-experimental studies, registries, comparative studies.
Very low = Any estimate of effect is very uncertain. The recommendation is based largely very low quality studies and/or on expert opinion.

Consensus Based Statement without determination of certainty:
When there are either no published studies, or very limited and/or very weak evidence, a consensus statement without any category of certainty of evidence was developed. The degree of agreement by all JTFPP and workgroup members is indicated, with voting details provided if there were dissenting votes.

Table 3: JTFPP Practice Parameter Consensus Based Statements on the Diagnosis and Management of Rhinitis

#	Consensus Based Statement (CBS) or Grading of Recommendations, Assessment, Development and Evaluation (GRADE) recommendation	Strength of Recommendation	Certainty of Evidence
1	**CBS: We recommend that the clinician complete a detailed history and a physical examination in a patient presenting with symptoms of rhinitis.**	**Strong**	**Low**
2	**CBS: We recommend that for patients presenting with rhinitis symptoms, a review of all current medications should be completed to assess if drug-induced rhinitis may be present.**	**Strong**	**Ungraded**
3	**CBS: We recommend that aeroallergen skin prick testing or sIgE testing be completed to confirm the diagnosis of AR in a patient with a history consistent with AR.**	**Strong**	**High**
4	**CBS: We recommend that the clinician not perform food skin prick testing or sIgE for foods in their routine evaluation of a patient presenting with the signs and symptoms compatible with the diagnosis of allergic rhinitis**	**Strong**	**Ungraded**

5	**CBS: We suggest that the use of a validated instrument, e.g. scoring system, scale, or questionnaire be considered to help determine the severity of rhinitis and to monitor the degree of disease control.**	**Conditional**	**Low**
6	**CBS: We recommend against prescribing a 1st generation antihistamine and in favor of a 2nd generation antihistamine when prescribing an oral antihistamine for the treatment of allergic rhinitis.**	**Strong**	**High**
7	**CBS: We suggest that the clinician not select an oral leukotriene receptor antagonist for the initial treatment of allergic rhinitis due to reduced efficacy when compared to other agents.**	**Conditional**	**Very Low**
8	**CBS: We recommend that the clinician not select an oral leukotriene receptor antagonist for the treatment of non-allergic rhinitis.**	**Conditional**	**Ungraded**
9	**CBS: We recommend that the clinician offer intranasal antihistamines as an initial treatment option for patients with seasonal allergic rhinitis.**	**Strong**	**High**
10	**CBS: We recommend that the clinician offer intranasal antihistamines as a first-line monotherapy option for patients with non-allergic rhinitis.**	**Strong**	**High**
11	**CBS: We recommend that the clinician offer intranasal antihistamines as a first-line option for patients with episodic allergic rhinitis.**	**Conditional**	**Ungraded**
12	**CBS: We recommend that when choosing monotherapy for persistent allergic rhinitis, intranasal corticosteroids be the preferred medication**	**Strong**	**High**
13	**CBS: We suggest that the clinician offer intranasal corticosteroids as an initial monotherapy option for non-allergic rhinitis.**	**Conditional**	**Low**
14	**GRADE: We recommend that for the initial treatment of moderate to severe seasonal allergic rhinitis in patients 15 years of age and older, the clinician use an intranasal corticosteroid over an LTRA.**	**Strong**	**High**
15	**CBS: We suggest that the use of intranasal decongestants be short-term and used for intermittent or episodic therapy of nasal congestion.**	**Conditional**	**Low**
16	**CBS: We suggest that in patients having severe mucosal edema which impairs the delivery of other intranasal agents, an intranasal decongestant be considered for up to 5 days of use.**	**Conditional**	**Ungraded**

17	**CBS: We suggest that oral decongestant agents be used with caution in older adults and children younger than 4 years old, and in patients of any age who have a history of cardiac arrhythmia, angina pectoris, cerebrovascular disease, uncontrolled hypertension, bladder outlet obstruction, glaucoma, hyperthyroidism, or Tourette syndrome.**	**Conditional**	**Low**
18	**CBS: We recommend that oral decongestants be avoided during the first trimester of pregnancy.**	**Strong**	**Low**
19	**CBS: We suggest that in patients with perennial allergic rhinitis and non-allergic rhinitis who have rhinorrhea as their main nasal symptom be offered intranasal ipratropium.**	**Conditional**	**Low for PAR; moderate for NAR**
20	**CBS: We suggest that intranasal cromolyn be offered as an option to be taken just prior to acute allergen exposure to reduce symptoms of episodic environmental allergic rhinitis.**	**Conditional**	**Very Low**
21	**GRADE: We suggest that the clinician consider the combination of an intranasal corticosteroid and an intranasal antihistamine for the initial treatment of moderate to severe nasal symptoms of seasonal allergic rhinitis in patients age ≥12.**	**Conditional**	**High**
22	**CBS: We suggest that the clinician consider the combination of an intranasal corticosteroid and an intranasal antihistamine for treatment resistant moderate to severe seasonal allergic rhinitis and perennial allergic rhinitis.**	**Conditional**	**Moderate**
23	**CBS: We suggest that the clinician consider the combination of an intranasal corticosteroid and an intranasal antihistamine for treatment resistant moderate to severe non-allergic rhinitis.**	**Conditional**	**Low**
24	**CBS: We suggest that for patients taking an intranasal corticosteroid who have persistent rhinorrhea, the clinician may consider the addition of intranasal ipratropium.**	**Conditional**	**Moderate**
25	**CBS: We suggest that patients with persistent nasal congestion unresponsive to a intranasal corticosteroid or to a intranasal corticosteroid/intranasal antihistamine combination be offered combination therapy with addition of an intranasal decongestant for up to 4 weeks.**	**Conditional**	**Low**
26	**CBS: We suggest that for allergic rhinitis patients with nasal congestion uncontrolled with an oral antihistamine, the clinician consider the addition of pseudoephedrine, when tolerated.**	**Conditional**	**Moderate**
27	**CBS: We suggest that for management of seasonal allergic rhinitis when a patient prefers not to use nasal sprays, the clinician may consider the use of an oral leukotriene receptor antagonist in combination with an oral**	**Conditional**	**Moderate**

	antihistamine for symptoms not controlled with an oral antihistamine.		
28	**GRADE: We recommend that the clinician not prescribe, as initial treatment, a combination of an oral antihistamine and an intranasal steroid in preference to monotherapy with an intranasal steroid in patients 12 years of age and older with symptoms of seasonal allergic rhinitis.**	**Strong**	**Moderate**
29	**CBS: We suggest that the clinician not prescribe the combination of an oral antihistamine and an intranasal corticosteroid in preference to monotherapy with an intranasal steroid in all patients with seasonal allergic rhinitis and perennial allergic rhinitis.**	**Conditional**	**Very Low**
30	**CBS: We cannot make a specific recommendation for or against the combined use of oral leukotriene receptor antagonist and intranasal corticosteroid for allergic rhinitis, due to the lack of adequate evidence.**	**N/A**	**Very Low**
31	**CBS: We suggest that the clinician offer an intranasal corticosteroid as one first line therapy for non-allergic rhinitis.**	**Conditional**	**Low**
32	**CBS: We suggest that the clinician offer an intranasal antihistamine as one first line therapy for non-allergic rhinitis.**	**Conditional**	**Very Low**
33	**CBS: We suggest that allergen immunotherapy (subcutaneous or sublingual) be offered through shared decision-making to patients with moderate to severe allergic rhinitis who 1) are not controlled with allergen avoidance and/or pharmacotherapy or 2) choose immunotherapy as the preferred method of treatment, e.g., due to the desire to avoid the adverse effects, costs, or long-term use of pharmacotherapy, and/or 3) desire the potential benefit of immunotherapy to prevent or reduce the severity of co-morbid conditions, such as asthma.**	**Conditional**	**Moderate**
34	**CBS: We suggest that allergen immunotherapy (subcutaneous or sublingual) be considered for patients with controlled mild and moderate asthma with coexisting allergic rhinitis.**	**Conditional**	**Moderate**
35	**CBS: We cannot make a recommendation for or against the use of acupuncture for the treatment of allergic rhinitis.**	**N/A**	**Very Low**
36	**CBS: We cannot make a recommendation for or against the use of specific herbal products for the treatment of allergic rhinitis.**	**N/A**	**Very Low**

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Clinical history and physical examination

Consensus Based Statement # 1: We recommend that the clinician complete a detailed history and a physical examination in a patient presenting with symptoms of rhinitis.
Strength of Recommendation: Strong
Certainty of Evidence: Low

Consensus Based Statement # 2: We recommend that for patients presenting with rhinitis symptoms, a review of all current medications should be completed to assess if drug-induced rhinitis may be present.
Strength of Recommendation: Strong
Certainty of Evidence: Ungraded due to lack of studies addressing this specific issue
Note: Unanimous vote in favor by workgroup and JTFPP

Clinical history in rhinitis patients

The most important single element for establishing the diagnosis of rhinitis, allergic or non-allergic, and differentiating it from other conditions with overlapping symptoms, is the clinical history. (1, 191) (20) The age of onset, duration, frequency, severity, timing during the year, suspected triggers, pattern of presentation, and progression of each patient-specific symptom should be obtained and recorded. The history should include the success or failure of past therapeutic interventions, including self-prescribed over-the-counter medications, homeopathic agents, or physician-prescribed treatments. The family history and personal history of comorbid allergic conditions, e.g., asthma and chronic rhinitis with or without chronic rhinosinusitis should be discussed. The overall medical, social, and psychiatric history, medication history (current and past), environmental exposures in the home or workplace, and family views on disease state and healthcare should be included in the patient history. As the final therapeutic decisions will involve shared decision-making, the history should explore the wishes and desires of both the patient and family in selecting diagnostic procedures and therapeutic interventions, including their willingness to adhere to these therapies.

In clinical practice, especially in primary care, the diagnosis of AR is often made solely by history (192). The use of validated questionnaires is more beneficial for excluding allergic rhinitis than for confirming allergic rhinitis. The use of one validated 4-question screening tool has been shown to have a high negative predictive value for positive skin prick tests to common aeroallergens (193). Furthermore, if a patient has a late onset of symptoms (> age 45), no family history of allergies, no seasonality of symptoms or symptoms around cats, dogs or other furry pets and has trouble with non-allergic triggers such as deodorants/fragrances, the likelihood of having a component of non-allergic rhinitis before diagnostic skin or serologic testing is 98% predictive (194). While the history has greater reliability and predictive value than solely relying upon the physical exam, the combination of history and physical exam is still advised(195).

Table 4. Patient reported symptoms and likely diagnosis:

Note: This table is developed based predominantly on expert opinion

Symptom	Allergic rhinitis	Non-allergic rhinitis	Acute URI	Chronic rhinosinusitis without nasal polyps	Chronic rhinosinusitis with nasal polyps
Rhinorrhea, sniffing	Intermittent/persistent, most common symptom, clear watery	Common but less than AR overall, but some subtypes have rhinorrhea as a major symptom	Acute, clear to purulent, watery to mucoid, associated with crust formation	Clear to mucoid	Clear to mucoid
Sneezing	Intermittent/persistent, almost universal	Intermittent, less common than in AR, rarely persistent	Acute	Rare	Rare
Hyposmia/anosmia	Occasional	Occasional	Acute, may be present	Common	Very common
Nasal congestion/blocked nose, mouth breathing	Persistent>intermittent, very common	Most common symptom, usually persistent	Acute onset, common	Chronic, very common	Chronic, almost universal
Mouth breathing	Common	Common	Common	At times	Common
Ocular pruritus, watery discharge, red eyes	Very common	Not common	Not common	Rare	Rare
Post-nasal drip	Not common, persistent> intermittent	Very common	Acute, not uncommon	Common	May be present
Nasal/palate/ear itching	Intermittent/persistent	Rare	Minor	Rare	Rare
Sore throat	Not common, persistent> intermittent	Not common	Common	At times	Not common
Constant clearing of throat	Not common	Common	Not uncommon	Common	Not common
Chronic cough	Not common, persistent>intermittent	Common unless post nasal drip treated (persistent > intermittent)	Acute, common	Not uncommon	Not common
Bleeding of nose	Rare	Not common	Rare	Rare	Rare
Facial or sinus pain/pressure	Rare, persistent> intermittent	Common	Common, acute	Common, chronic	Not common
Eustachian tube dysfunction	Occasional	Occasional	Common	Not common	Not common

Snoring	Not common, persistent>intermittent	Common	Acute, common	Common	Common
Sleep disturbance/sleep apnea	Common, persistent>intermittent	Common	Common	Common	Common
Headache as part of symptomology	Occasional	Common	Common	Common	Common

Physical Examination:

For a patient with rhinitis symptoms, a physical exam should be completed that encompasses not only the upper airway but also the lower airway, eyes, ears, and skin, to identify findings that may suggest the presence of a co-morbid allergic or non-allergic condition.(1, 20, 195) (see Table V for more details). These co-morbid conditions may include accompanying allergic conjunctivitis, otitis, eustachian tube dysfunction, chronic rhinosinusitis with and without nasal polyps, asthma, and/or atopic dermatitis (1) (196-198). Documentation of normal findings, e.g., no septal perforation, is important to establish baseline exam findings prior to the prescribing of medications that might lead to adverse events. While specific nasal and oropharyngeal physical exam findings, e.g., pale, boggy nasal mucosa, allergic shiners, and pharyngeal hyperplasia, may support the diagnosis of allergic rhinitis, there are no pathognomonic findings that distinguish allergic vs. non-allergic vs. infections rhinitis. (1, 195, 199, 200). Furthermore, a patient with a history of rhinitis who is asymptomatic or minimally symptomatic at the time of the physical exam, may have minimal or no abnormal findings. (201) While conducting a physical exam is recommended by all major rhinitis guidelines in order to make the diagnosis of allergic rhinitis, (1, 20, 191), the very limited, low-quality research evidence that is available demonstrates a much lower sensitivity and specificity and high interpreter variability for the physical exam when compared to the patient's history for making a diagnosis of allergic rhinitis, suggesting that both are essential to increase diagnostic accuracy. (195, 201, 202) Considering both the high prevalence of allergic and non-allergic rhinitis and the large number differential diagnoses for rhinitis, perhaps the greatest benefit of completing the physical exam is to exclude one of the rare, but potentially life-threating diagnosis, e.g., intranasal tumor, which may even co-exist with allergic rhinitis.

The nasal pharyngeal exam can usually be accomplished with the use of a nasal speculum with appropriate lighting or an otoscope with a nasal adapter(1), although these provide a more limited view of the nasal cavity than a nasopharyngolaryngoscope. For mucosal edema that prohibits an adequate exam, the use of a topic nasal decongestant may reduce turbinate mucosal edema, allowing for better visibility and delineation of abnormal findings, e.g., distinguishing nasal polyps from polypoidal mucosal hypertrophy. A pneumatic otoscope allows for the assessment of tympanic membrane mobility and presence of transudative fluid. At times, an impedance tympanometer may also be of benefit to assess tympanic membrane mobility and the presence/absence of middle ear fluid. A nasopharyngolaryngoscope exam should be completed when a more extensive nasal/pharyngeal/laryngeal exam is required due to suspected structural or functional abnormalities, inadequate therapeutic response or a

suspected complication, e.g., deviated septum, rhinosinusitis with or without nasal polyps, foreign body, nasal septal perforation, or vocal cord dysfunction.

Table 5. Physical examination of patient presenting with symptoms compatible with rhinitis (modified from Table V in 2008 Rhinitis Practice Parameter) (1)

Vital signs (including weight and height): Record on all patients.
General observations: facial pallor, elongated facies, preferred mouth breathing, and any evidence of systemic disease.
Eyes: Excessive lacrimation, erythema and swelling of the bulbar and/or palpebral conjunctiva, cobblestoning of the tarsal conjunctiva, swelling or dermatitis of outer eyelids, Dennie-Morgan lines, or venous stasis below the lower eyelids (''allergic shiners'' which may occur in allergic or non-allergic rhinitis).
Nose: Reduced patency of nasal valve; alar collapse; transverse external crease; external deformity such as saddle nose (loss of nasal bridge that may occur from nasal trauma or systemic disorders such as relapsing polychondritis, granulomatosis with polyangiitis, cocaine abuse, or some systemic infections); septal deviation or perforation, spurs, ulcers, perforation, prominent vessels, or excoriation; nasal turbinate hypertrophy, edema, pallor or erythema, and crusting; discharge (amount, color, consistency), and nasal polyps. The presence of tumors or foreign bodies should be noted.
Ears: Tympanic membrane dullness, erythema, retraction, perforation, reduced or increased mobility, and air-fluid levels.
Oropharynx: Halitosis, dental malocclusion or high arched palate associated with chronic mouth breathing, tonsillar or adenoidal hypertrophy, cobblestoning of the oropharyngeal wall, pharyngeal postnasal discharge, temporomandibular joint pain or clicking with occlusion, furrowing, coating, or ulceration of tongue or buccal mucosa.
Neck: Lymphadenopathy, or tenderness, thyroid enlargement or nodule
Chest: Signs of asthma such as wheezing, or other abnormal or diminished sounds by auscultation.
Skin: Rashes, especially eczematous or urticarial (distribution and description), or dermatographism.
Other organ systems: When history or general observation indicate these should be included.

Note: This list is not intended to be totally inclusive. Elements of the examination that will assist in the differential diagnosis of rhinitis or that may indicate complications of treatment are included. Documentation of presence or absence of these elements should be considered.

Differential Diagnosis of Rhinitis:

The differential diagnosis of chronic rhinitis symptoms includes allergic rhinitis, non-allergic rhinitis, mixed rhinitis, including the rhinitis specific subtypes discussed in previous sections; common conditions that mimic rhinitis such as rhinosinusitis with or without nasal polyps and nasal septal deviation; and more uncommon conditions. (Table 4) A comprehensive history, physical examination, and appropriate testing is important to ascertain the correct diagnosis as this will help direct the therapeutic approach recognizing that some diseases mimicking rhinitis can lead to substantial morbidity and even mortality. Furthermore, more than one cause of nasal symptoms can be present concurrently and contribute to the rhinitis-induced morbidity.

Selected conditions that may mimic rhinitis:

Nasal Septal Deviation (NSD) (203): NSD is a common cause of fixed nasal obstruction leading to nasal congestion. It appears to be as common an anatomical cause of congestion as nasal valve collapse and turbinate hypertrophy (204). It may cause bilateral or unilateral congestion

and is often associated with nasal valve collapse and compensatory turbinate hypertrophy (204-206). The importance and effectiveness of septoplasty for NSD does not appear to be universally accepted (207) (208).

Nasal Valve Collapse: The internal nasal valve is the narrowest portion of the nasal cavity and is the anatomical area bounded medially by the nasal septum, and laterally by the inferior edge of the upper lateral cartilage and the anterior aspect of the inferior turbinate. As such the nasal valve is the area most commonly associated with the subjective perception of obstruction and is responsible for more than 2/3 of the airflow resistance produced by the nose (209). Nasal valve collapse refers to any weakness or further narrowing of the nasal valve and can result in change of airflow that is perceived as nasal congestion. The nasal examination should note the patency of the nasal valve and any alar collapse. If there is improvement in breathing when performing the Cottle maneuver—pulling the patient's cheek laterally to open the nasal valve angle—this may suggest nasal valve pathology.

Turbinate Hypertrophy: Hypertrophy, with or without concha bullosa, can account for severe unilateral or bilateral obstruction and accounts for severe congestion equally as commonly as nasal valve collapse and septal deviation (204). Hypertrophy can be primary, e.g., from allergic and non-allergic rhinitis or compensatory, often being associated with congenital or traumatic septal deviation (205). While medical treatment for some causes of turbinate hypertrophy, e.g., allergic rhinitis, can be very effective, not infrequently a surgical approach will be required for other causes. The consensus for treatment in refractory cases can include turbinate reduction (210, 211) (212) When performing septoplasty for unilateral nasal septal deviation, it is often necessary to also perform turbinate reduction surgery due to compensatory hypertrophy of the contralateral inferior turbinate. (213).

Cerebral Spinal Fluid Leak usually presents as a unilateral clear rhinorrhea, without congestion, often worsened in the upright position, and with increased in frequency following head trauma or surgery; however, some cases may be spontaneous (214). Suggested diagnostic testing in the past included glucose determination, normally found in CSF, but not in nasal secretions. A determination of beta-2 transferrin levels in nasal drainage is now the preferred test. Nasal drainage can be collected and remain stable at room temperature for a week or more (214). For diagnostic confirmation and preparation for surgery, high resolution CT and magnetic resonance cisternography are accurate, non-invasive and complementary (215). Treatment is often surgical in the form of endoscopic or open repair to prevent complications which include meningitis (216, 217) (214) 2018) (218).

Adenoidal Hypertrophy (AH) is one of the most common anatomic causes of nasal obstruction in children. Lateral X-ray of the nasopharynx is an effective tool to assess for AH in children and findings correlate well with symptoms (219). The combination of clinical assessment (good specificity) with lateral X-ray (good sensitivity) is one good method for assessment of the degree of AH (220). In addition, when feasible, the severity of AH can usually be adequately assessed by the nasopharyngolaryngoscope exam(221). Complications include acute and recurrent otitis, otitis media with effusion, hypoacusia, altered speech development, and sleep

disordered breathing. Prolonged mouth breathing may lead to defective dental growth and facial bone development (222, 223). Medical therapy includes topical nasal corticosteroids, found to be effective with high quality evidence, montelukast or a combination of both; however, data suggest that single drug therapy may be just as effective as the combination(224-226). When medical therapy fails, surgical removal should be considered. Young age and apnea hypopnea index greater than 1 increase the likelihood that surgery will be necessary (227).

Nasal Foreign Body is common among young children (228-230). Most cases present with unilateral congestion and foul-smelling purulent rhinorrhea. Foreign bodies are estimated to account for 30% of ENT emergencies of which 19% are intranasal (228). Complications of nasal foreign bodies include infection, nasal perforation and epistaxis (229). Of particular importance is the increase of nasal impaction with button batteries that can be corrosive and lead to septal perforation(231). Removal may require general anesthesia, especially in cases of prolonged impaction because of associated inflammation (232).

Ciliary Dyskinesia can be primary or secondary. Secondary ciliary dysfunction can result from chronic infections, irritants or multiple nasal surgeries and might be transient and reversible. Primary ciliary dyskinesia is a rare genetic disorder, referred to as immotile-cilia syndrome (IMCS), that may present with cough, nasal congestion and symptoms of asthma, chronic rhinosinusitis with nasal polyps (in children and adults), bronchiectasis, recurrent otitis, rhinitis and rhinosinusitis. In addition, infertility and situs inversus may complicate IMCS. In the past, screening tests include saccharine transit time or nasal challenge with tagged particles; however, nasal nitric oxide (nNO) is a simple and commonly available test to screen for IMCS as extremely low levels of nNO are produced by the nasal epithelium in IMCS. (233). Genetic testing for primary ciliary dyskinesia should also be considered. Unless there is a confirmed positive result on genetic testing, a biopsy and electron microscopy will be needed for a definitive diagnosis.

Pharyngonasal reflux secondary to prematurity or neuromuscular diseases may present as congestion in early life. In addition, esophageal reflux can cause nasal symptoms in adults and children and may even predispose to obstructive sleep apnea (234). The most common symptom of eosinophilic esophagitis is reflux and EOE is frequently associated with rhinitis and especially symptoms of allergic rhinitis (235). Testing for and treatment of reflux in sinonasal disease lacks consensus and most available data refer to reflux causing pharyngeal and laryngeal disease without focus on isolated nasal symptoms (236, 237).

Nasal/Sinus Tumor: Two recent documents from the World Health Organization (WHO) address ENT tumors. A 2018 document discusses the classification of ENT tumors (238). An earlier WHO document from 2017 addresses clinical characteristics and imaging findings of benign masses of the nose and sinuses (239).

Vasculitis, sarcoidosis and other systemic diseases: The differential diagnosis of systemic diseases that can cause nasal symptoms is not included in this section; however, questioning

for constitutional symptoms in all patients with rhinitis can be justified as a way to help exclude a systemic disease manifesting with rhinitis type symptoms.

Table 6. Differential diagnosis of allergic/non-allergic rhinitis (including conditions that can mimic rhinitis):

Note: Table developed largely based upon expert opinion and intended to offer considerations for the clinician

Condition	History that may differentiate from rhinitis	Physical Exam findings	Diagnostic studies	Treatment
Chronic rhinosinusitis with nasal polyps (CRSwNP)	May have reduced sense of smell/taste; chronic congestion, nocturnal mouth breathing, NSAIDS induced respiratory symptoms	Mucosal polypoidal changes that will not shrink with topical decongestant, non-painful growths	Fiberoptic nasopharyngoscopy, sinus CT	Saline irrigation, consider short course oral corticosteroids, Intranasal corticosteroids (INCS), leukotriene receptor antagonists, surgery, Anti IL4/13 (dupilumab). Aspirin desensitization in Aspirin/NSAID Exacerbated Respiratory Disease --- Research ongoing: Anti-IL5, IL-5 receptor antagonist, Anti-IgE.
Chronic rhinosinusitis without nasal polyps (CRSsNP)	Facial pain/pressure, headache, mucopurulent discharge, decreased sense of smell, post-nasal drip,	Mucopurulent discharge, facial tenderness, cobblestoning posterior pharyngeal wall	Fiberoptic nasopharyngoscopy, sinus CT, consider immune system evaluation	Evidence for treatment effectiveness may differ between CRSwNP and CRSsNP. Options include INCS, saline irrigation, ,

	fatigue, poor sleep quality, depression			chronic macrolide antibiotics (conflicting evidence), acute antibiotics for superimposed infection, surgery
Septal wall abnormalities, e.g., deviated septum, septal erosion, nasal septal perforation	Severity worse unilateral side, previous surgery, trauma, history of abuse of cocaine (perforation)	Septal deviation noted, septal erosion and/or perforations, septal spurs, asymmetrical nasal vault openings	Fiberoptic nasopharyngoscopy, sinus CT	Surgery, e.g., septoplasty or surgical correction of perforations, septal button (for septal perforation)
Nasal valve collapse	Nasal congestion as main symptom, poor response to medication	Improvement in breathing when performing the Cottle maneuver, i.e. pulling the patient's cheek laterally to open the nasal valve angle	Fiberoptic nasopharyngoscopy and anterior rhinoscopy	Adhesive spring-like externally applied nasal strips, nasal cones, surgery
Turbinate Hypertrophy: with or without concha bullosa	Severe unilateral or bilateral obstruction. Hypertrophy can be primary or compensatory and often associated with congenital or traumatic septal deviation	Turbinate hypertrophy	Fiberoptic nasopharyngoscopy, Sinus CT	INCS, Surgery
Adenoidal hypertrophy	Child with recurrent ear infections	Posterior nasal, pharyngeal	Tympanogram, fiberoptic nasopharyngoscopy,	INCS, leukotriene receptor antagonists,

	and/or snoring, congestion as main or only symptom, possible sleep disturbance	fullness may be noted, adenoids may not be visualized on regular exam	lateral neck radiological studies, CT scan	Consider short course oral steroids, surgery
Foreign body	History of possible foreign body placement by child or impaired adult (with or without direct observation), mucopurulent discharge	Unilateral halitosis, mucopurulent discharge, use topical decongestant during exam for visualization and possible dislodgment	May require otolaryngologist referral for rigid rhinoscopy for both diagnosis and treatment (possibly under sedation for child)	Removal of foreign body
Nasal tumors (benign or malignant)	Progressive unilateral congestion, bloody discharge, nasal or ear pain	Unilateral mass incompatible with normal mucosal edema or polyps	Consider fiberoptic nasopharyngoscopy, CT scan, and/or referral to Otolaryngologist for examination, possible biopsy, and treatment	Surgery usually required, variable depending on diagnosis
Cerebral spinal fluid leak	Unilateral clear discharge, intermittent, increased with dependent head position, recent surgery or trauma	Clear discharge unilateral – may or may not be noted on exam	Test nasal discharge for beta-2 transferrin and if positive refer to Otolaryngologist	Otolaryngologist to evaluate if there is need for surgical leak closure
Primary ciliary dyskinesia syndrome	Recurrent rhinosinusitis, otitis, sinus surgeries, dx of rhinosinusitis with nasal polyps, atypical asthma, bronchiectasis	Findings compatible with chronic rhinosinusitis w/without nasal polyps	Nasal NO; nasal brush biopsy and electron microscopic exam are definitive tests; consider genetic testing; consider chest x-ray	No effective medical treatment other than infection intervention with antibiotics, surgery frequently required for chronic

				rhinosinusitis or chronic otitis

Consensus Based Statement # 3: We recommend that aeroallergen skin prick testing or sIgE testing be completed to confirm the diagnosis of AR in a patient with a history consistent with AR.
Strength of Recommendation: Strong
Certainty of Evidence: High

Consensus Based Statement #4: We recommend that the clinician not perform food skin prick testing or sIgE for foods in their routine evaluation of a patient presenting with the signs and symptoms compatible with the diagnosis of allergic rhinitis.
Strength of Recommendation: Strong
Certainty of Evidence: Ungraded due to lack of studies addressing this specific issue
Note: Unanimous vote in favor by workgroup and JTFPP

Diagnostic testing

Diagnosing rhinitis may be possible combining the patient's history and physical findings. However, in most cases laboratory and/or skin tests will confirm the diagnosis. Classically this was done by conjunctival challenge to grass pollen by Noon as he pioneered immunotherapy. (240) Throughout the early part of the 20th century, skin tests both puncture and intradermal were the rule. Once IgE was discovered, in vitro laboratory tests could identify antibodies to specific allergens.

The 2008 Practice Parameters Allergy Diagnostic Tests (75) stated: "Prick/puncture tests or intracutaneous tests are the preferred techniques for IgE-mediated hypersensitivity. It is advisable to use prick/puncture devices, which are relatively nontraumatic and elicit reproducible results when placed on specific areas of the body (i.e., arms or back). Optimal results depend on use of potent test extracts and proficiency of the skin tester (i.e., demonstration of coefficient of variation 30% at different periods). Intracutaneous tests are generally used for specific allergens (i.e., Hymenoptera venoms and penicillin), but they may also be applied if prick/puncture test results are negative and there is a strong historical likelihood of clinical allergy to specific allergens. A 2016 (241) meta-analyses of 7 studies with 430 patients found that skin prick testing sensitivity was 85% and specificity 77%. Intradermal studies were too few to give significant results. (242) A large study from Turkey compared intradermal with skin prick tests. Among 4223 patients with allergic rhinitis and or asthma, prick tests were positive in 57% of subjects. Intradermal tests were applied to 344 patients with marked allergic symptoms; 44% were positive, 33% to dust mites, 22% to fungal spores. These were not compared to nasal challenge results. (242-244) In some cases of rhinitis, especially where local allergic rhinitis is suspected, a nasal allergen challenge can be helpful. (16) (245)

Severity assessment including QOL by survey instruments and questionnaires

Consensus Based Statement # 5: We suggest that the use of a validated instrument, e.g. scoring system, scale, or questionnaire be considered to help determine the severity of rhinitis and to monitor the degree of disease control.
Strength of recommendation: Conditional
Certainty of evidence: Low

Assessment of AR severity as defined narratively under "Classification of AR" can guide treatment (See Figures 2 and 3). Some investigators have tried to translate the patient's assessment of severity using a visual analogue scale VAS scale (i.e. 0 to 10 where 0 is no symptoms and 10 is worst possible symptoms). The VAS is sensitive to detect changes in quality of life for patients with AR,(246) but the cut-off value for mild versus moderate-severe varies per study between 4-6.(247, 248) Bousquet et al identified 3052 patients with allergic rhinitis (1895 confirmed with testing) and classified their rhinitis severity based on ARIA guidelines. Patients were asked to answer the question "Overall, how much are your allergic symptoms bothering you today?" by making an "X" on a single 10 cm line which has no markings. The verbal anchors are "Not at all bothersome" (starting at 0) and "Very bothersome" (ending at 10 cm). (249) Receiver operating curves found that this simple one question VAS score correlated well with ARIA severity; a VAS score < 5 cm was classified as having "mild" AR, while a score > 6 cm was "moderate severity"(247). Subsequently a score of ≥ 5 has been used to represent moderate/severe.

A variety of quality of life (QOL) questionnaires, some specific to rhinitis and others being generic QOL instruments, have been used to assess AR severity. (250) Generic QOL scales offer comparison between different disorders and patient populations(251) ; for example, adults with moderate to severe perennial rhinitis and moderate to severe asthma have equal functional impairment(252, 253) . In contrast, disease-specific QOL questionnaires, including those specific for rhinitis, describe disease-associated problems more accurately and seem to be reflective of changes associated with therapeutic interventions (251, 254).Visual analog scales may also correlate well with rhinitis symptom scores and quality of life measures, leading to improved symptom control. (246) There is also a highly significant correlation between a VAS and the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). A subsequent study further validated the VAS and determined that changes in the VAS of 23mm were found to be clinically significant. (246) A large European study found a smart phone app using the MASK (Mobile Airways Sentinel network)-Rhinitis VAS to be a reliable indicator of AR control and this control correlated well to work productivity.(255, 256)

Control of Allergic Rhinitis

In addition to assessing AR *severity* and the impact on quality of life, assessing *control* is an important goal. As has shown to be helpful with asthma, AR severity can be measured in patients before treatment while measures of disease control are more applicable to optimize therapy in treated patients.(257) . The Rhinitis Control Assessment Test (RCAT), is a simple, reliable, self-administered 6 item questionnaire utilizing a 5-point Likert scale (258) (259-261). (See Appendix, Figure 1) Developed to assist physicians in the assessment of patient rhinitis control in clinical practice, it also helps patients appreciate what rhinitis control is. The RCAT

was developed and validated against total nasal symptom scores (TNSS) and the physician's global assessment (PGA). Subsequent work identified a cut-off score of 21 as representing good control, with a Minimal Important Difference of 3. Downloadable forms for administering the RCAT are readily available online. (258)

The Allergic Rhinitis Control Test (ARCT) is a validated 5-item self-assessment using a 5-point frequency scale with similarities to the Asthma Control Test (102) (262, 263). The Control of Allergic Rhinitis and Asthma Test (24) is a validated 10-item questionnaire that was tested in patients consulting an allergist. (264-266). Limitations exist for control-based classifications as it is not clear whether AR control varies as a function of the disease-inducing allergen, and these questionnaires have not been validated in children (257)).(31)

Figure 1. Rhinitis Control Assessment test. (258, 261)

1. During the past week, how often did you have nasal congestion?

Never	Rarely	Sometimes	Often	Extremely often
☐5	☐4	☐3	☐2	☐1

2. During the past week, how often did you sneeze?

Never	Rarely	Sometimes	Often	Extremely often
☐5	☐4	☐3	☐2	☐1

3. During the past week, how often did you have watery eyes?

Never	Rarely	Sometimes	Often	Extremely often
☐5	☐4	☐3	☐2	☐1

4. During the past week, to what extent did your nasal or other allergy symptoms interfere with your sleep?

Never	Rarely	Sometimes	Often	Extremely often
☐5	☐4	☐3	☐2	☐1

5. During the past week, how often did you avoid any activities (for example, visiting a house with a dog or cat, gardening) because of your nasal or other allergy symptoms?

Never	Rarely	Sometimes	Often	Extremely often
☐5	☐4	☐3	☐2	☐1

6. During the past week, how well were your nasal or other allergy symptoms controlled?

Completely	Very	Somewhat	A little	Not at all
☐5	☐4	☐3	☐2	☐1

PHARMACOTHERAPY

Review of monotherapy and then combination pharmacologic therapeutic options for rhinitis (with an emphasis on treatment of allergic rhinitis) is presented first. Thereafter a stepwise pharmacologic treatment of allergic rhinitis will be presented, using algorithms for intermittent (Figure 2) and persistent (Figure 3) allergic rhinitis. Similarly, pharmacologic treatment algorithms have been developed for the management of intermittent (Figure 3) and persistent (Figure 4) non-allergic rhinitis.

Review of pharmacotherapy classes for rhinitis

Oral Antihistamines

Consensus Based Statement #6: We recommend against prescribing a 1st generation antihistamine and in favor of a 2nd generation antihistamine when prescribing an oral antihistamine for the treatment of allergic rhinitis.
Strength of Recommendation: Strong
Certainty of Evidence: High

Oral antihistamines are of established benefit in allergic rhinitis. The overall efficacy of first-generation antihistamines (e.g. diphenhydramine, hydroxyzine, chlorpheniramine) compared with less/non-sedating 2ndgeneration antihistamines (e.g. cetirizine and levocetirizine, fexofenadine, loratadine and desloratadine) for the management of allergic rhinitis symptoms has not been adequately studied. However, selecting a second-generation antihistamine reduces the potential side effects including sedation, performance impairment, poor sleep quality and anticholinergic-mediated symptoms (e.g. dry eyes, dry mouth, constipation, urinary hesitancy and retention) that have been associated with the first-generation antihistamines. (1)

First-generation antihistamines may produce performance impairment in school (267-269) and driving (270) (271-274) that can exist without subjective awareness of sedation (275); and the use of first-generation antihistamines has been associated with increased automobile and occupational accidents.(270-274) (276) Individual variation exists with respect to development of sedative effects with first-generation antihistamines.(269, 277, 278) One systematic review of first-generation antihistamines concluded that they induced non-amnestic deficits in attention and information processing. (279) One early study compared chlorpheniramine vs. placebo and found that drowsiness and dry mouth were greater than placebo for the first two weeks but after this time point doses of chlorpheniramine less than 24 mg a day resulted in no significant difference in subjective drowsiness, dizziness, irritability or dry mouth compared to placebo over the remaining 6 weeks of the study.(280) Other studies using chlorpheniramine as a comparator have reported similar increased symptoms of drowsiness, dry mouth and dizziness for the first few days but tolerance to these subjective side effects of this medication occurred over time.(281-283) Tolerance to adverse central nervous system (CNS) effects in an individual may or may not occur with regular daily use.(284) Although bedtime dosing of 1st generation oral antihistamines has been suggested as a strategy to avoid daytime sedation, there can be residual CNS effects the next day because some agents have a very long terminal elimination half-life (>24 hours for chlorpheniramine).(285) Bedtime administration of first-generation antihistamines undesirably increased the latency to onset of restful rapid eye movement (REM) sleep and reduces the duration of REM sleep. (284, 286)

Beyond concerns about subjectively perceived side effects, one of the anticholinergic side effects more recently reported in association with 1st generation antihistamines is an associated higher risk of dementia. A 2015 U.S. prospective population-based cohort study suggested a link between higher cumulative use of strong anticholinergics and the risk of developing dementia, with over70% being Alzheimer's Disease. (287) For dementia, adjusted hazard ratios for 10

years of cumulative anticholinergic use (including first-generation antihistamines, tricyclic antidepressants, and bladder antimuscarinics) compared with nonuse were 0.92 (95% CI, 0.74-1.16) for total standardized daily doses (TSDDs) for 1-90 days, with a proportional increased risk for longer daily use, with a cumulative 3 years of daily use being 1.54 (95% CI, 1.21-1.96). (287) A longitudinal study showed that the use of anticholinergics in the elderly was associated both with reduced immediate recall and executive functioning was associated in conjunction with increased brain atrophy manifest as reduced total cortical volume and temporal lobe cortical thickness and greater lateral ventricle and inferior lateral ventricle volumes. (288) These findings further support use of second-generation antihistamines over first-generation antihistamines for allergic rhinitis.

Use of first-generation antihistamines in the treatment of non-allergic rhinitis

Patients with non-allergic and allergic rhinitis experience similar symptoms including nasal congestion, post-nasal drainage and rhinorrhea although through different mechanistic pathways.(289) Responses to various treatments in NAR and AR may vary.(290) A major symptom of patients with NAR that is frequently not well controlled despite combination topical nose sprays with anti-cholinergic activity is post-nasal drainage. (289) There are no double-blind placebo-controlled trials evaluating the therapeutic efficacy and safety of 1st generation oral antihistamines like chlorpheniramine maleate for the treatment of NAR/VMR. In a risk/benefit assessment, mindful of a) the considerable concerns about safety of first generation antihistamines as reviewed under discussion for Consensus Based Statement #6, and b) recognition that it is not possible in a standard office setting to accurately assess development of some clinical adverse effects from these agents (e.g. development of subtle changes in cognition or other potential CNS side effects such as decreased reaction time), some clinicians suggest that monitored use of first generation oral antihistamines as an adjunctive anti-cholinergic agent may be considered in patients with nonallergic rhinitis who have bothersome post-nasal drainage refractory to other therapies. The decision to use first generation antihistamines for NAR remains controversial, should be individualized and should involve a physician and patient shared-decision making discussion, reviewing the potential risks and benefits, and patient preferences. If first generation oral antihistamines are used to treat post nasal drip in VMR/NAR, patients should be carefully monitored for any clinically observable side effects, the lowest effective dose should be used and these agents should be discontinued when side effects are identified. Special consideration/caution should be taken into account using these agents in frail elderly patients, (291) individuals with existing known chronic disorders (dementia, Alzheimers, BPH) that would be complicated by their use or those working in occupations involving heavy machinery, driving or flying.

Oral Leukotriene Receptor Antagonists

Consensus Based Statement # 7: We suggest that the clinician not select an oral leukotriene receptor antagonist for the initial treatment of allergic rhinitis due to reduced efficacy when compared to other agents.

Strength of Recommendation: Conditional

Certainty of evidence: Very Low

Consensus Based Statement # 8: We recommend that the clinician not select an oral leukotriene receptor antagonist for the treatment of non-allergic rhinitis.
Strength of Recommendation: Conditional
Certainty of evidence: Ungraded as no studies
Note: Unanimous vote in favor by workgroup and JTFPP

Leukotriene receptor antagonists (LTRAs) are modestly effective in the treatment of seasonal and perennial allergic rhinitis (292-294) (295). Multiple systematic reviews have concluded that LTRAs have effectiveness similar to oral antihistamines with loratadine as the usual comparator, (294, 296-299) but others find that LTRAs are less effective than antihistamines. (299) (300) LTRAs are less effective than intranasal corticosteroids (INCS). (294, 297-299) Considering that the LTRA montelukast is equally or less effective than oral antihistamines for AR, and is less effective than INCS, clinicians should not routinely offer a LTRA as preferred therapy for patients with AR. Nonetheless, in shared decision-making considering preference by some patients for oral agents, LTRA is a treatment option that may be offered in less severe rhinitis. Intranasal corticosteroids would be preferred therapy for more severe allergic rhinitis because of their greater effectiveness. The use of an oral LTRA in combination with an oral antihistamine may be more effective than monotherapy with an LTRA (montelukast) for allergic rhinitis, although not all studies are consistent with this finding (301) (297, 302). The combination of an oral LTRA and an oral antihistamine is similarly effective as monotherapy with an INCS for allergic rhinitis though it is likely more costly and burdensome to maintain (303) (304).

There is no evidence to support the use of LTRAs in non-allergic rhinitis. There is no mechanistic rationale or expert opinion that supports the use of a LTRA in NAR.

Montelukast has been approved down to 6 months of age. It is not associated with somnolence and side effects are uncommon and generally minimal. (305, 306) There are post-marketing reports of rare drug-induced neuropsychiatric events including sleep disturbances, depression, anxiety, aggression, psychotic reactions, and suicidal thinking and behavior. Infants are more prone to drug-associated sleep disturbances, children present most often with symptoms of depression and anxiety, and adolescents are more prone to symptoms of depression, anxiety and suicidal behavior (307) (308-310). Unexpectedly, a worldwide review of Individual Case Safety Reports (ICSRs) associated with montelukast determined that completed suicides were reported more frequently for children than adolescents or the total population. (309) Most studies are low quality evidence, e.g., case reports or observational studies, mainly in children and adolescents; high-quality epidemiological studies are needed to evaluate the association and quantify the risk of neuropsychiatric adverse events, not only in children and adolescents, but also in adults. (310) It is advised that clinicians monitor patients who may be at elevated risk for suicidal ideation or psychiatric symptoms.

In patients with AR comorbid with asthma, montelukast could result in significant improvements in both conditions compared to placebo and therefore can be considered an

option for patients with both conditions.(311) (303) However, due to the only modest efficacy and also the potential increased risks of montelukast compared to oral antihistamines, for the management of AR and comorbid asthma, the clinician should weigh the benefits of montelukast monotherapy versus an inhaled corticosteroid for asthma and an antihistamine or intranasal corticosteroid for AR.

Intranasal agents

Intranasal antihistamines

Consensus Based Statement #9: We recommend that the clinician offer intranasal antihistamines as an initial treatment option for patients with seasonal allergic rhinitis.
Strength of recommendation: Strong
Certainty of Evidence: High

Consensus Based Statement # 10: We recommend that the clinician offer intranasal antihistamines as a first-line monotherapy option for patients with non-allergic rhinitis.
Strength of recommendation: Strong
Certainty of evidence: High

Consensus Based Statement #11: We recommend that the clinician offer intranasal antihistamines as a first-line option for patients with episodic allergic rhinitis.
Strength of recommendation: Conditional
Certainty of Evidence: Ungraded due to lack of studies addressing this specific issue
Note: There was a unanimous vote in favor by workgroup and JTFPP

For relief of nasal symptoms of SAR, intranasal antihistamines are equal to or superior to oral antihistamines, (312-314) and may benefit patients who fail oral antihistamine treatment. (314, 315) Intranasal antihistamines (INAH) have a more rapid onset of action compared to intranasal corticosteroids (INCS) and oral antihistamines, (312-318) are more effective than oral antihistamines in the control of nasal congestion, (313, 316, 317) and provide a favorable safety profile. Comparisons of INCS to INAH for reduction of nasal symptoms are conflicting, with some showing equality (319-321) and some showing superiority of INCS. (322) In a systematic review of INCS and INAH, INAH provide comparable relief of allergic eye symptoms. (323) Two intranasal antihistamines, azelastine and olopatadine are approved by the FDA for the treatment of seasonal allergic rhinitis. Azelastine is also approved for the treatment of perennial allergic rhinitis and vasomotor rhinitis.

Azelastine has high binding affinity to H1 receptors and can also inhibit H2 antihistamine receptors, as well as the synthesis or expression of mediators of allergic inflammation and neuropeptides. (324-326) Azelastine may also work in part by desensitizing TRPV1 ion channels which are triggered by hot stimuli, such as capsaicin, and are important in the pathophysiology of NAR. (89) In contrast to azelastine, intranasal olopatadine is a selective H1 receptor

antagonist but has also been shown to have some mast cell inhibitory properties, described with the olopatadine eye drop preparation. (327)

Intranasal antihistamines have a rapid onset of action in allergic rhinitis ranging from 15-30 minutes, compared to an average of 150 minutes for oral antihistamines. (312-318, 324) They have been shown to improve nasal as well as non-nasal allergic rhinitis symptoms and quality of life. (316, 317, 328) Azelastine has also been shown to be clinically effective in controlling symptoms of non-allergic rhinitis (NAR). (329) Although olopatadine has been demonstrated to significantly reduce nasal symptoms induced by a hyperosmolar mannitol challenge in patients with vasomotor NAR, there are no placebo controlled trials to support its efficacy in relief of NAR symptoms. (330)

Nineteen percent of patients treated with azelastine in the initial clinical trials reported bitter taste lasting around 30 mins (329) Subsequent studies using azelastine as 1 puff each nostril twice daily reduced total nasal symptoms scores and was associated with less somnolence and bitter taste (0.4% and 8.3%, respectively) compared to what was reported in the pivotal trials (11.5% and 19.7% respectively). (331) Reformulating azelastine nasal spray with sucralose to mask the bitter taste demonstrated similar safety and tolerance profile to the original formulation and a reduction in bitter taste (from 8% to 7%). (64, 332) In contrast to the pivotal SAR studies, somnolence was not an issue for NAR patients compared to placebo (3.2% vs 1.0%). (324, 326, 329) While the initial clinical trials using a larger dose reported somnolence in around 11%, (333) more recent studies have found rates of 0.4% to 3%, which were equal or only slightly greater than in placebo groups. (332, 334-337) Intranasal olopatadine was well tolerated with the most common adverse events reported being bitter taste, headache, epistaxis, and pharyngolaryngeal pain with a relatively low incidence of somnolence (<1%). (338-341)

Intranasal olopatadine and azelastine have been compared in a placebo controlled multicenter trial in patients with SAR and were shown to be equally effective in controlling symptoms. (342) Moreover, their side effect profiles were comparable except for bitter taste which was more pronounced for azelastine. (342) A randomized, double-blind, parallel-group, multicenter non-inferiority study showed no significant difference between intranasal olopatadine and intranasal azelastine in controlling nasal symptoms in patients with non-allergic vasomotor rhinitis. (343) No significant differences were observed for adverse events, including taste, or treatment satisfaction between treatment groups. (343) While taste aversion has been demonstrated to all intranasal antihistamines, taste varies between formulations. Therefore, a trial of a second formulation may identify a preferred alternative formulation in patients who have had symptomatic benefit from an intranasal antihistamine.

Intranasal corticosteroids (INCS)

Consensus Based Statement # 12: We recommend that when choosing monotherapy for persistent allergic rhinitis, intranasal corticosteroids be the preferred medication.
Strength of Recommendation: Strong

Certainty of evidence: High

Consensus Based Statement # 13: We suggest that the clinician offer intranasal corticosteroids as an initial monotherapy option for non-allergic rhinitis.
Strength of the recommendation: Conditional
Certainty of evidence: Low

GRADE Recommendation (2017)(344)# 14: We recommend that for the initial treatment of moderate to severe seasonal allergic rhinitis in patients 15 years of age and older, the clinician use an intranasal corticosteroid over an LTRA.
Strength of the Recommendation: Strong
Certainty of evidence: High

Intranasal corticosteroids (INCS) remain the most effective monotherapy for allergic rhinitis and are therefore recommended as preferred monotherapy for moderate to severe allergic rhinitis that have negative impact on quality of life. (1, 303, 304, 345, 346) More recent guidelines continue to support this recommendation. (191, 347) Not only are these agents effective in controlling nasal symptoms in patients with AR, but they have also been shown to be effective in the control of allergic ocular symptoms. (1, 348, 349)

The effectiveness of INCS has been reported in studies that have involved a large number of patients with NAR (190), especially those with NARES.(350-352) Intranasal corticosteroids have also been reported to be effective in the treatment of VMR.(190, 350, 353) However, a 2019 Cochrane review concluded that it is unclear whether intranasal corticosteroids reduce patient-reported disease severity in non-allergic rhinitis patients compared with placebo.(354)

The sensory attributes of INCS (aftertaste, nose runout, throat rundown, and smell) play an important role in patient preference and adherence to therapy. (355) To address some of these concerns, nonaqueous intranasal preparations with hydrofluoroalkane aerosol are now available for the treatment of allergic rhinitis in the United States. (356-358)

When given in recommended doses INCSs are not generally associated with clinically significant systemic side effects. (1) They have not been shown to affect the hypothalamic–pituitary–adrenal (HPA) axis. (1) A meta-analysis of relevant trials relating to growth in children suggests that short term use of INCS may decrease short-term growth velocity (using knemometry), but there was no such effect on longer term growth velocity (using stadiometry). (359) The heterogeneity of the studies was high in the stadiometry trials. Therefore, when using INCS in children, it is prudent to use the lowest effective dose and monitor growth carefully.

There have been reports of a possible association between the development of posterior subcapsular cataracts and the use of intranasal or inhaled corticosteroids in older patients Case reports of increased ocular pressure from intranasal corticosteroids have been published (360); however, blinded studies have not confirmed this adverse effect. (1) (361) A meta-analysis of 10 clinical trials with 2226 patients did not show a significant risk of elevating intraocular

pressure or developing a posterior subcapsular cataract in patients with allergic rhinitis using INCS. (362)

The most common side effects of INCS are local and include dryness, burning, stinging, blood tinged secretions, and epistaxis. The incidence of epistaxis ranges from 4% to 8% over short treatment periods (2 to 12 weeks) and can reach 20% in studies carried over a year. (1, 191) Nasal bleeding with long term use of topical nasal corticosteroids may approach 28%. (361) The epistaxis reported from intranasal corticosteroids can be worsened by the use of anticoagulant agents. (363) (364-367)

Septal perforations, although rare, have been reported. (1, 191) Biopsy specimens from the nasal mucosa of patients with perennial rhinitis who have been treated with INS continuously for 1 to 5 years showed no evidence of atrophy. (1, 191)

Intranasal capsaicin

Capsaicin, a pungent compound found in hot red peppers, topically applied to the nasal mucosa has been shown to reduce nasal hyperreactivity. While capsaicin has not been approved by the FDA for the treatment of rhinitis, it has been used for the treatment of non-allergic or mixed rhinitis to reduce nasal congestion, rhinorrhea, postnasal drainage, sinus pressure, sinus pain, and headache. Capsaicin is a selective TRPV1 ion channel agonist that reduces nerve conduction of nociceptive C fibers, thereby reducing parasympathetic hyperactivity and neuropeptide release, resulting in attenuation of nasal congestion, rhinorrhea, and postnasal drainage symptoms. (89, 90, 289, 368-373) Clinical trials investigating the therapeutic benefit of capsaicin on patients with AR did not find a significant effect in reducing nasal hyper-reactivity or in improving rhinorrhea (374). Cochrane analysis for AR found only one small trial where intranasal capsaicin had a therapeutic benefit. (375) For the treatment of idiopathic NAR, a recent Cochrane analysis found that capsaicin appears to improve nasal symptoms which can last 36 weeks after treatment but this assessment is based on only a few small studies of low scientific evidence quality. (376) When used to treat NAR and VMR compared to placebo therapies, some studies have described significant therapeutic efficacy and safety of chronic usage of local capsaicin formulations. (377-382) Because all of these trials used different study designs and dosing regimens, the ability to compare primary endpoints is significantly limited. (377, 379, 380, 383, 384) Recent data comparing idiopathic and mixed rhinitis treated with capsaicin demonstrated a slightly increased symptom reduction in the idiopathic treatment group than in the mixed rhinitis group, 79% and 68% respectively. (385) Future well-conducted, large, randomized controlled trials are required to further assess the effectiveness of capsaicin using different concentrations and in NAR patients with mild, moderate, and severe symptoms.

Intranasal decongestants

Consensus Based Statement # 15: We suggest that the use of intranasal decongestants be short-term and used for intermittent or episodic therapy of nasal congestion.
Strength of the recommendation: Conditional
Certainty of Evidence: Low

Consensus based statement #16: We suggest that in patients having severe mucosal edema which impairs the delivery of other intranasal agents, an intranasal decongestant be considered for up to 5 days of use.
Strength of Recommendation: Conditional
Certainty of Evidence: Ungraded due to lack of studies addressing this specific issue
Note: There was a unanimous vote in favor by workgroup and JTFPP

Intranasal decongestants, e.g., oxymetazoline and xylometazoline, are alpha adrenergic agonists. They cause improvement in nasal conductance for up to 10 hours resulting in nasal vasoconstriction and decreased nasal edema but they do not block allergen -provoked mediator release. (386, 387) Oxymetazoline and xylometazoline cause similar decongestive effects with statistically significant beneficial changes in nasal resistance, nasal airflow and nasal cross-sectional areas which provide clinically meaningful improvement in nasal congestion. (388) On average, the effect of oxymetazoline begins within 30 seconds (389). Xylometazoline was found to have superior efficacy for nasal decongestion compared with intranasal corticosteroids in a 28-day AR study. (390) Similarly, oxymetazoline has been shown to be clearly more effective than oral pseudoephedrine in reducing nasal congestion. (391) However, intranasal decongestants are not routinely recommended for continuous use because of the potential development of alpha receptor tachyphylaxis and subsequent rhinitis medicamentosa. (392) The development of rhinitis medicamentosa is highly variable; it may develop within 3 days of use or fail to develop after 6 weeks of daily use. (392-397) Intranasal decongestants have no effect on itching, sneezing, or nasal secretion and can be associated with local stinging or burning, sneezing, and dryness of the nose and throat.

Recent placebo-controlled studies of perennial and seasonal allergic rhinitis demonstrated that concurrent administration of intranasal corticosteroids and intranasal decongestants provided additional efficacy both subjectively in rapidity of onset compared to the corticosteroid alone and in magnitude of nasal congestion symptom score improvement compared to oxymetazoline alone, and objectively as measured by acoustic rhinometry increases in volume. Furthermore, when the decongestant was given along with the intranasal steroid once a day for up to 4 weeks, the development of rhinitis medicamentosa did not occur. (398, 399) Safety concerns about use of intranasal decongestants in pregnancy are discussed in the later section on “Rhinitis in pregnancy”.

Oral decongestants

Consensus Based Statement # 17: We suggest that oral decongestant agents be used with caution in older adults and children younger than 4 years old, and in patients of any age who have a history of cardiac arrhythmia, angina pectoris, cerebrovascular disease, uncontrolled hypertension, bladder outlet obstruction, glaucoma, hyperthyroidism, or Tourette syndrome.
Strength of recommendation: Conditional
Certainty of Evidence: Low

<u>Consensus Based Statement # 18:</u> We recommend that oral decongestants be avoided during the first trimester of pregnancy
<u>Strength of recommendation:</u> Strong
<u>Certainty of Evidence:</u> Low

The oral decongestant pseudoephedrine, an alpha-adrenergic agonist, is effective at relieving nasal congestion. It is indicated for nasal congestion due to AR, rhinosinusitis, and the common cold. (400) For the management of concomitant seasonal allergic rhinitis and mild to moderate asthma, the combination of an oral decongestant and a second-generation oral antihistamine significantly reduced both rhinitis and asthma symptoms compared to placebo. (401) Pseudoephedrine is a key ingredient used in making methamphetamine. In an effort to reduce illicit production of methamphetamine, restrictions have been placed on the sale of pseudoephedrine in the United States. (402) This has promoted substitution of oral phenylephrine for pseudoephedrine in many allergy and cold and cough remedies. However, oral phenylephrine has been demonstrated to be ineffective at reducing nasal congestion at doses up to 40mg. (403-405)

Pseudoephedrine can result in adverse effects such as insomnia, loss of appetite, irritability, and palpitations. (406) Elevation of blood pressure after taking an oral decongestant is very rarely noted in normotensive patients and only occasionally in patients with controlled hypertension. A meta-analysis of 24 trials showed a statistically significant elevation of systolic blood pressure in both normotensive and in patients with controlled hypertension, but these small values, 0.99 mm Hg and 1.2 mm hg respectively, are unlikely to be clinically significant in most patients. (407) However, because of the variation in patient response, patients receiving oral decongestants should be followed for changes in blood pressure. Concomitant use of caffeine and stimulants, such as medications used for management of attention-deficit/hyperactivity disorder, may be associated with an increase in adverse events. (408) Oral decongestants should be used with caution in patients with rhinitis with certain conditions, such as cerebrovascular or cardiovascular disease, hyperthyroidism, closed-angle glaucoma, bladder outlet obstruction, and Tourette syndrome. The problem of rebound congestion is not a factor with the use of orally administered nasal decongestants. (400)

Oral decongestants, when used in appropriate doses, are usually well tolerated in children over the age of 6 years of age. However, use in infants and young children has been associated with agitated psychosis, ataxia, hallucinations, and even death. (409-411) At times, even at recommended doses these agents may cause increased stimulatory effects resulting in tachyarrhythmias, insomnia, and hyperactivity, especially when combined with other stimulants. (412) Therefore, the risks and benefits should be carefully considered before using oral decongestants in both adults and children.

Safety concerns about use of oral decongestants in pregnancy are discussed in the later section on Rhinitis in pregnancy.

Intranasal ipratropium

Consensus Based Statement # 19: We suggest that in patients with perennial allergic rhinitis and non-allergic rhinitis who have rhinorrhea as their main nasal symptom be offered intranasal ipratropium
Certainty of evidence: Low for PAR, moderate for NAR

Ipratropium bromide at either 0.03% or 0.06% concentrations is safe, well tolerated, and is effective for the treatment of rhinorrhea related to perennial allergic (0.03%), and non-allergic rhinitis (0.03%) as well as for the common cold (0.06%)(413-415). While ipratropium bromide 0.06% is FDA approved for the treatment of SAR in both children and adults, no randomized controlled trials have been completed to study its effectiveness. (416) Rhinorrhea is significantly reduced in chronic perennial rhinitis, vasomotor rhinitis, gustatory rhinorrhea, and cold-induced rhinorrhea, e.g., skiers nose, but with no significant effect on congestion or sneezing.(413, 417) (418, 419) (420, 421) When ipratropium bromide was administered prior to nasal methacholine challenge in patients with allergic and non-allergic rhinitis there was reduced rhinorrhea and sneezing but there was no significant effect on airway resistance.(415, 422) Rhinorrhea was significantly reduced not only in cold air exposure but also following ingestion of hot soup, leading the authors to suggest that the nasal discharge is reflex-mediated.(423) In PAR, ipratropium bromide was effective in reducing rhinorrhea for one year when used on a continuous basis. (420) The efficacy of ipratropium appears to especially benefit anterior rhinorrhea. It has not been shown to be of significant value when postnasal drainage is the dominant complaint. The most common adverse effects reported are nasal dryness and epistaxis, although these are usually mild and rarely lead to discontinuation of treatment. (421) (420) As discussed under the section on “Combination therapy”, when ipratropium bromide is combined with an INCS or an oral second-generation antihistamine, an additive benefit has been demonstrated.

Intranasal cromolyn

Consensus Based Statement # 20: We suggest that intranasal cromolyn be offered as an option to be taken just prior to acute allergen exposure to reduce symptoms of episodic environmental allergic rhinitis.
Strength of Recommendation: Conditional
Certainty of evidence: Very low

The primary benefit of cromolyn sodium is to stabilize mast cells and thus inhibit the release of mast cell mediators that promote IgE mediated allergic rhinitis. (424, 425) Intranasal administration of cromolyn sodium improves symptoms of SAR when compared to placebo. (426-428). In PAR, with marked skin test responses (429), benefit has been found in some but not all studies of patients with PAR. (430) Intranasal cromolyn may reduce nasal eosinophils in patients with AR. (431) Ten milligrams of intranasal cromolyn inhibited allergen induced nasal airway resistance in 80% and 50% of subjects at four and eight hours respectively after the administration of cromolyn, suggesting efficacy for around six hours.(432) A large 2 week multicenter, randomized, double-blind, placebo-controlled, parallel-group design study of the

over-the-counter use of intranasal cromolyn sodium demonstrated efficacy (reduction in overall symptoms, sneezing and nasal congestion) and concluded intranasal cromolyn was safe and effective for over-the-counter use. (424, 428)

Nasal cromolyn administered just before acute allergen exposure can reduce development of symptoms of AR.(433-435) Therefore, nasal cromolyn can be useful in short term prevention of development of episodic environmental AR symptoms if administered just prior to anticipated acute exposure to an allergen not normally present in a patient's home or work environment. However, there have been no direct comparative trials between intranasal cromolyn and other treatments for such use.

Cromolyn is reported to have an excellent safety record and has been studied and also reported to be safe in pregnancy. (424, 428, 436) There are a very limited number of cases suggesting the possibility of acute and suspected IgE mediated reactions to disodium cromoglycate (DSCG). (437, 438)

The treatment effect of intranasal cromolyn in SAR is not robust and some have advocated temporary use of a nasal decongestant while initiating intranasal cromolyn in subjects with near total nasal obstruction. (1) Intranasal cromolyn was studied and found to have no benefit in NARES.(170) A placebo controlled trial of intranasal cromolyn showed no benefit in VMR, although some anecdotal cases suggest benefit in isolated individuals with VMR. (439) Intranasal cromolyn was found to have no benefit on nasal polyps. (440)

Intranasal cromolyn has similar efficacy to oral antihistamines in the treatment of AR. However, intranasal cromolyn reduced nasal eosinophils in comparison to oral antihistamine. (431) Intranasal cromolyn may be less efficacious than levocabastine nasal spray in SAR. (441) Intranasal cromolyn is less efficacious than intranasal steroid sprays in SAR. (442)

Combination therapy

Combination therapy is often used in clinical practice either as directed by the physician or by patient self-treatment. Only a few rhinitis therapeutic combinations have been subjected to rigorous study. The scientific evidence will be presented, when available, but the AR and NAR treatment algorithms are based upon both scientific evidence and expert opinion. The algorithms were developed to assist the clinician in selecting both the preferred monotherapy and when to consider specific agents for combination therapy.

Intranasal corticosteroid and intranasal antihistamines combined

GRADE Recommendation (2017)(344) # 21: We suggest that the clinician consider the combination of an intranasal corticosteroid and an intranasal antihistamine for the initial treatment of moderate to severe nasal symptoms of seasonal allergic rhinitis in patients age ≥12.

Strength of the recommendation: Conditional

Certainty of evidence: High

Consensus Based Statement # 22: We suggest that the clinician consider the combination of an intranasal corticosteroid and an intranasal antihistamine for treatment resistant moderate to severe seasonal allergic rhinitis and perennial allergic rhinitis.
Strength of recommendation: Conditional
Certainty of evidence: Moderate

Consensus Based Statement # 23: We suggest that the clinician consider the combination of an intranasal corticosteroid and an intranasal antihistamine for treatment resistant moderate to severe non-allergic rhinitis.
Strength of recommendation: Conditional
Certainty of evidence: Low

Double blind, placebo controlled (DBPC) trials in AR have demonstrated that the combination of an intranasal corticosteroid and intranasal antihistamine is more effective at reducing symptoms of AR and has a faster onset of action than the individual components. (344) This has been demonstrated in five DBPC trials with a *fixed* combination of intranasal azelastine and fluticasone propionate in a single device (MP29-02, Dymista), in patients with moderate to severe SAR, ages 12 and above (443-445) and one DBPC trial showed its superiority over placebo in children 6-11 years. (446) Its superior efficacy in reducing the PM 12h-reflective total nasal symptom score over IN fluticasone was also demonstrated over the whole range of a 12-months' randomized, open-label trial in patients with chronic rhinitis (perennial AR and non-allergic AR), although no NAR-subgroup analysis was presented. (447) A 6-week randomized trial of 162 NAR patients demonstrated significantly greater ($p<0.01$) reduction in nasal obstruction score with the combination of an INCS and an INAH compared to monotherapy with an INCS. (448)

However, as reviewed in the 2017 Rhinitis GRADE document, all these studies were designed to compare the use of combination therapy vs. monotherapy as initial treatment of SAR and not as add-on therapy.(344) The JTFPP recognizes that in clinical practice, in most cases, the combination will be used when monotherapy has failed to relieve symptoms in patients with SAR, PAR, and NAR in all ages for which the product has been approved. However, for PAR and NAR, the recommendations are based predominantly on expert opinion.
MP29-02 contains a combination of two active substances, fluticasone propionate and azelastine, in an intranasal device that delivers enhanced spraying compared to some other nasal spray devices. As such, slightly higher fluticasone $AUC_{0\text{-}tlast}$ and C_{max} have been reported compared to those of commercially available intranasal fluticasone propionate. (449) Of note, are the safety data reported from the above mentioned 12-months' trial, with MP29-02 1 spray per nostril bid, in which 8/404 patients were discontinued at six months, because of an adverse event (3 decreased serum cortisol, 3 cataract, 2 acne) versus 1/207 in the commercially available fluticasone group (cataract). (447, 450) Two additional combination devices, currently not FDA approved, have been studied. The combination of intranasal olopatadine hydrochloride and intranasal fluticasone propionate compared to intranasal azelastine and fluticasone provided similar efficacy. (451) Solubilized intranasal azelastine and budesonide provided

significantly faster onset of action for nasal pruritus and sneezing compared to solubilized budesonide alone. (452)

Intranasal corticosteroid with intranasal ipratropium for control of rhinorrhea

Consensus Based Statement # 24: We suggest that for patients taking an intranasal corticosteroid who have persistent rhinorrhea, the clinician may consider the addition of intranasal ipratropium
Strength of the recommendation: Conditional
Certainty of evidence: Moderate

In patients with rhinorrhea not fully responsive to INCS therapy, the addition of ipratropium bromide is beneficial. Intranasal ipratropium bromide plus intranasal beclomethasone was more effective than either active agent alone, in reducing the average severity and duration of rhinorrhea in allergic and non-allergic rhinitis. (352)

Intranasal corticosteroid with intranasal decongestant

Consensus Based Statement # 25: We suggest that patients with persistent nasal congestion unresponsive to an intranasal corticosteroid or to an intranasal corticosteroid/intranasal antihistamine combination be offered combination therapy with addition of an intranasal decongestant for up to 4 weeks.
Strength of the recommendation: Conditional
Certainty of evidence: Low

In PAR and SAR, concurrent administration of intranasal corticosteroids and intranasal decongestants provides greater reduction in nasal congestion symptoms and greater improvement in nasal volume than that of an intranasal decongestant alone. (398, 399) Further, the combination tended to reduce nasal congestion faster than the intranasal corticosteroid alone. When intranasal decongestant was given along with the intranasal steroid once a day for up to 2 weeks, the development of rhinitis medicamentosa, a concern with intranasal decongestant use as monotherapy, did not occur. (398, 399) In addition, in a small study where 19 healthy subjects received intranasal decongestant for 2 weeks followed by the addition of intranasal corticosteroid for 3 days, oxymetazoline-induced tachyphylaxis and rebound congestion were reversed by intranasal fluticasone. (453). In a 4-week, DBPC trial involving 50 patients with chronic rhinitis taking INCS and cetirizine with persistent nasal congestion, the addition of oxymetazoline provided significant reduction in nasal congestion scores compared to placebo without the development of rhinitis medicamentosa. (454) A post-hoc analysis demonstrated that the addition of oxymetazoline afforded significantly greater nasal congestion reduction in the AR compared to the NAR subgroup. (454) Whereas the combination of an intranasal corticosteroid and an intranasal antihistamine remains the preferred and most supported option in patients with AR with persistent symptoms after monotherapy (see above), it might be reasonable to consider adding an intranasal decongestant to an intranasal steroid for the first few days of therapy in patients with allergic

rhinitis and significant nasal congestion. At this time, existing evidence is scant and is not sufficient to support the prolonged use of the above combination.

Oral antihistamine with oral decongestant

Consensus Based Statement #26: We suggest that for allergic rhinitis patients with nasal congestion uncontrolled with an oral antihistamine, the clinician consider the addition of pseudoephedrine, when tolerated.
Strength of Recommendation: Conditional
Certainty of evidence: Moderate

Controlled studies demonstrate that combination of oral antihistamine and oral decongestant is more effective in reducing symptoms of AR, including nasal congestion, than the individual components (455-457), but adverse effects of oral decongestants are a concern. Given the evidence that this combination is effective, if this regimen is prescribed, the clinician should take into account the dose response relationship of the side effect profile for oral decongestants and titrate to the lowest effective dose. As presented in the Rhinitis 2008 PP, pseudoephedrine is far superior to other decongestants (402), however there are limited antihistamine-pseudoephedrine combinations, e.g., fexofenadine/pseudoephedrine. If a fixed combination is chosen, side effects such as insomnia should be taken into account. If side effects with the fixed combination are an issue for the patient, the dose should be adjusted, if possible, or the fixed combination stopped and either separate monotherapy products selected to allow for dose titration, or a different therapeutic class of rhinitis agents chosen, e.g., intranasal corticosteroids.

Intranasal decongestant with intranasal ipratropium

There is no published literature on the effect of combination intranasal decongestant with intranasal ipratropium for the treatment of AR and therefore no recommendation for or against this combination can be made. In one short-term study (<10 days), there was no rhinitis medicamentosa or rebound congestion noted with the combination; however, there was no clinically important differences in ciliary motility and mucociliary clearance observed. (458)

Oral antihistamines with oral leukotriene receptor antagonists

Consensus Based Statement # 27*:* We suggest that for management of seasonal allergic rhinitis when a patient prefers not to use nasal sprays, the clinician may consider the use of an oral leukotriene receptor antagonist in combination with an oral antihistamine for symptoms not controlled with an oral antihistamine.
Strength of recommendation: Conditional
Certainty of evidence: Moderate

Some studies find the concomitant use of leukotriene receptor antagonist with various oral antihistamines provide additive benefit in reducing symptoms and improving quality of life in patients with SAR, (294, 459-463), while others have shown inconclusive or conflicting results,

or no benefit over individual medications. (464, 465) One study showed prophylactic treatment with the combination of montelukast and cetirizine together to be more effective than cetirizine alone in preventing symptoms and reducing allergic inflammation. (466) Although some studies find that the concomitant administration of an oral leukotriene receptor antagonist and an oral antihistamine can have an additive effect, this approach is usually less efficacious than administering intranasal corticosteroids as monotherapy. (297, 298, 302, 303) The decision to use this combination rather than an intranasal agent should be made following a shared-decision making discussion.

As many as 40% of patients with allergic rhinitis have coexisting asthma. (294) The combination of montelukast and a second-generation antihistamine may protect against seasonal decrease in some measures of lung function, e.g., FEF 25-75, in patients with allergic rhinitis. (467) However, the combined mediator antagonism of montelukast with cetirizine is less effective than combined intranasal and inhaled corticosteroids in attenuating nasal and bronchial inflammatory markers. (468)

Combination Therapies that have NOT been shown to be convincingly superior to Monotherapy

Oral antihistamine with intranasal corticosteroid

GRADE Recommendation (2017)(344) # 28*:* We recommend that the clinician not prescribe, as initial treatment, a combination of an oral antihistamine and an intranasal steroid in preference to monotherapy with an intranasal steroid in patients 12 years of age and older with symptoms of seasonal allergic rhinitis.
Strength of the recommendation: Strong
Certainty of evidence: Moderate

Consensus Statement #29: We suggest that the clinician not prescribe the combination of an oral antihistamine and an intranasal corticosteroid in preference to monotherapy with an intranasal steroid in all patients with seasonal allergic rhinitis and perennial allergic rhinitis.
Strength of recommendation: Conditional
Certainty of evidence: Very Low

The evidence, as reviewed in the JTFPP 2017 Rhinitis GRADE guideline, looks at the initial use of monotherapy with an intranasal corticosteroid or combination therapy of an intranasal corticosteroid and an oral antihistamine for SAR in patients 12 years of age and older. (1)That review did not find significant increased symptom relief from the combination, compared to intranasal corticosteroid monotherapy. There was insufficient evidence that looked at add-on therapy. Therefore, the certainty of evidence is very low for the approach normally taken by clinicians, e.g., to add combination therapy when monotherapy fails. Furthermore, there is a very low certainty of evidence that children with SAR and patients with PAR should likewise be prescribed intranasal corticosteroid monotherapy rather than combination therapy.

Oral leukotriene receptor antagonists with intranasal corticosteroids

Consensus Based Statement # 30: We cannot make a specific recommendation for or against the combined use of oral leukotriene receptor antagonist and intranasal corticosteroid for allergic rhinitis, due to the lack of adequate evidence.

Strength of Recommendation: N/A
Certainty of Evidence: Very low

There is no strong evidence to support use of oral LTRA in addition to an intranasal corticosteroid. One study found no further benefit when an oral LTRA was added to an intranasal corticosteroid for the treatment of allergic rhinitis. (469) One study found that montelukast add-on therapy to fluticasone nasal spray is more efficacious in controlling nighttime symptoms but similar in efficacy in controlling total symptom score. (470) With very weak evidence, suggesting on one hand a possible benefit and on the other no benefit, the JTFPP was not able to offer any recommendation. This suggests that future studies, were they to occur, might provide additional information on the value of using such a combination for the treatment for rhinitis.

Allergic rhinitis pharmacologic treatment algorithms

In making decisions about selection of therapies for AR, we recommend that a clinician use guidance from an algorithm (See Figures 2 and 3) that is based upon multiple considerations including relative effectiveness, onset of action, potential for adverse effects, patient preference, symptom severity, and whether a patient has intermittent or persistent allergic rhinitis**.** The step-wise progression and decision tree is based largely on expert opinion. This algorithm was developed for clinical guidance and should be viewed as suggested, conditional recommendations. The certainty of the evidence for the various decision steps in the algorithm varies from being very low to high, based upon the evidence for each drug or combination of drugs. The algorithm also considers onset of action of the various agents. The following section reviews data about onset of action of agents used for the treatment of allergic rhinitis. See discussion for each drug class or combination of drug classes for detailed review of data considered.

Figure 2: Algorithm Intermittent Allergic Rhinitis

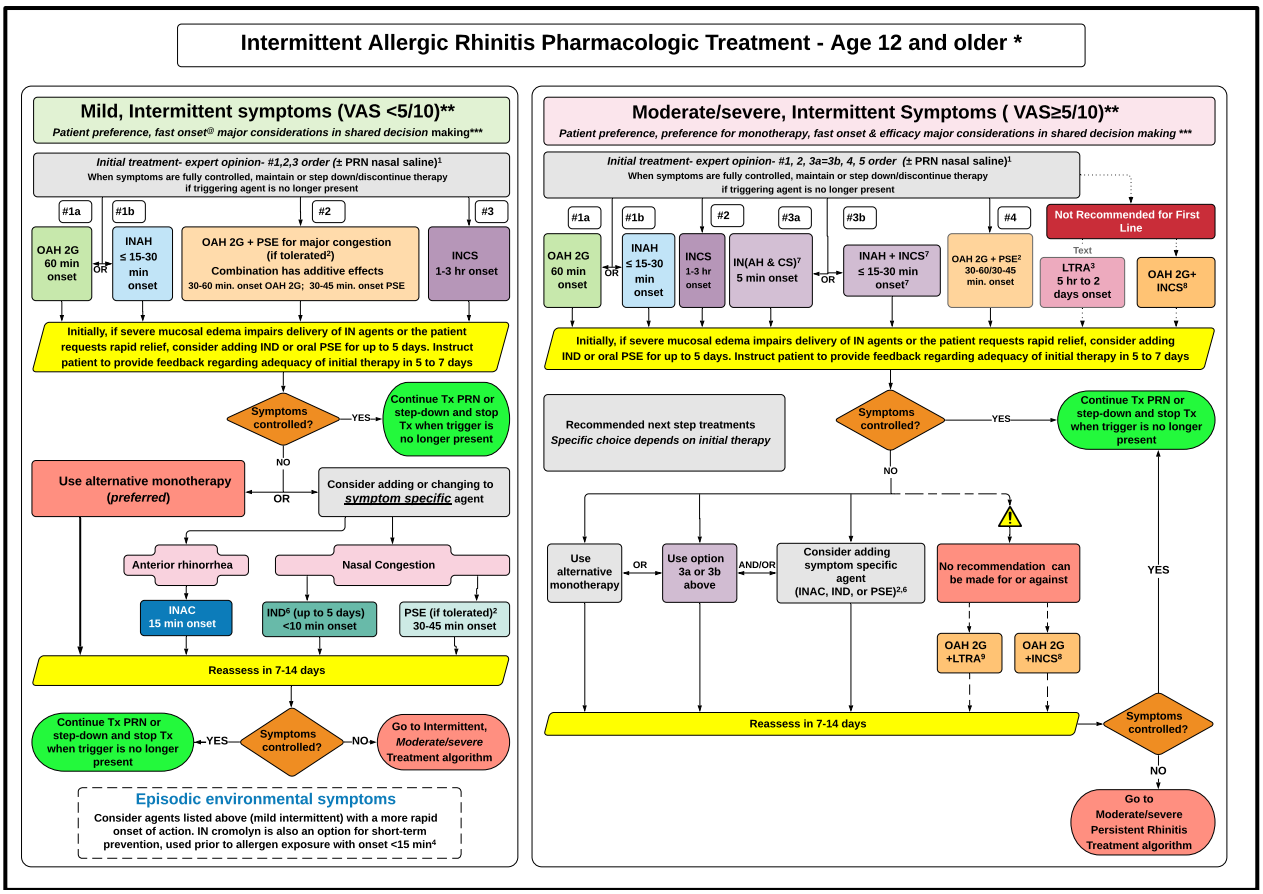
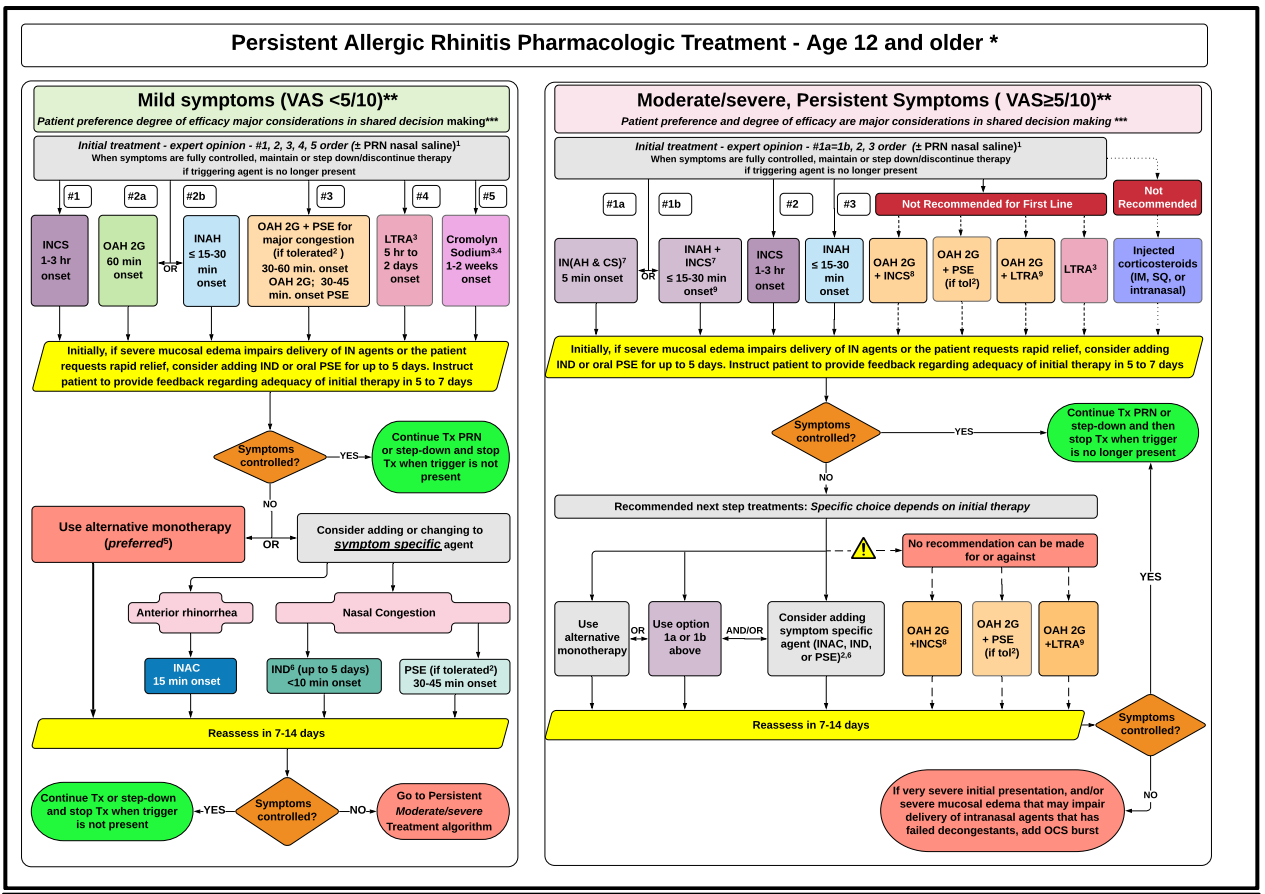


Figure 3: Algorithm Persistent Allergic Rhinitis



LEGEND FOR ABBREVIATIONS

- INAC Intranasal anticholinergic
- INAH Intranasal antihistamine
- IN cromolyn Intranasal cromolyn
- INCS Intranasal corticosteroid
- IN(AH & CS) Intranasal antihistamine and corticosteroid administered by a single device
- INAH+INCS These two preparations administered by separate devices
- IND Intranasal decongestant
- LTRA Leukotriene receptor antagonist
- OAH 2G Oral antihistamine,2nd generation
- OCS Oral corticosteroid
- PSE Pseudoephedrine
- VAS Visual analogue scale

* While most of the meds listed in the algorithm are approved for use in children < age 12, comparative trials have, for the most part, been limited to those equal to or greater than 12 yrs of age. The principles of treatment of children are the same as for adults, but special care must be given to dosage adjustment, adverse effects, and long-term safety.

** Severity of rhinitis, based upon symptoms and degree of overall control can be assessed by the patient using a visual analogue scale (VAS) of 1-10/10, with 10 being the most severe. Alternatively, the patient and provider can define "mild" as normal daily activities, sport, leisure, work, school, and sleep and no troublesome symptoms. "Moderate-severe" would indicate that one or more of these items are abnormal or impaired.

*** Meds in JTFPP expert opinion suggested order, based upon major considerations noted .

@See Onset of Action Table for more details

FOOTNOTES FOR INTERMITTENT AND PERSISTENT ALLERGIC RHINITIS

1. Order considers relative efficacy, but INCS monotherapy may be preferred when monotherapy and/or avoidance of adverse taste from INAH are desired. INCS may be preferred over INAH monotherapy when dosed over several days as INCS may become more effective with longer use.
2. PSE, if tolerated without significant adverse effects e.g. insomnia, irritability, aggravation of hypertension and cardiac arrhythmias
3. Unlikely to adequately control symptoms
4. IN cromolyn is recommended for qid dosing for persistent symptoms, has a slow onset of action of 1-2 weeks, has limited efficacy, but is very safe and may be preferred by some pts. However, may be used just prior to episodic allergen exposure to blunt acute allergic response, with protective effect within 15 min.
5. If 1st line is 2a, 2b, 3, 4 or 5, suggest going with #1 (INCS) as monotherapy
6. IND, caution advised when used > 5 days due to risk for rhinitis medicamentosa (rebound congestion), although some evidence that concomitant INCS use can minimize risk of rebound. Consider INCS + IND if IND is to be used > 5 days
7. No studies compare INCS/INAH administered in a single device as 1 spray each nostril twice daily versus individual medications administered consecutively, each dosed as 1 spray each nostril twice daily. Preference for using a single device is based primarily on convenience. Using the two individual medications would be preferred primarily due to affordability.
8. OAH 2G + INCS have not been shown to have any additive benefit over using just the INCS
9. For OAH 2G + LTRA, there is lack of adequate evidence to make a specific recommendation for or against this combination vs. monotherapy

Allergic Rhinitis pharmacotherapy: Onset of action

Onset of action for symptom relief may be an important consideration in selection of treatment (See Table 7). There are relatively few head to head trials that directly compare time to onset of symptom relief from different agents. Typically, data from studies using environmental exposure units (471) find quicker onset of action than outdoor park challenges, and traditional

field studies do not measure symptom relief until 12 hours or more after commencing treatment (472, 473) One cannot rely upon one clinical trial to give firm estimates of action onset of a specific pharmacological class or product. For patients with mild intermittent symptoms and minimal congestion, oral antihistamines provide symptom relief in 1-2 hours. When combined with oral pseudoephedrine, nasal congestion can be improved within 30 minutes. Topical decongestants such as oxymetazoline improve nasal airflow in under 10 minutes but possible rebound congestion limits long term use of these medications (this may be mitigated with concomitant use of a nasal steroid). Intranasal antihistamines (INAH) offer a quicker onset of action within 15 minutes along with greater overall efficacy, and intranasal ipratropium provides relief of rhinorrhea within 15 minutes. Intranasal corticosteroids give the greatest long-term relief for persistent symptoms with peak results taking up to 2 weeks, but significant improvement can be seen within 2-4 hours When an INAH is added to an INCS, the onset of action is reduced to only 5 minutes offering almost immediate symptom relief along with long term control. Montelukast offers similar symptom relief to some oral antihistamines, but with a much slower onset of action making as needed use unhelpful. While cromolyn may be helpful for pre-exposure prophylaxis, treatment of current symptoms requires 1-2 weeks of 3-4 times daily treatment to see a benefit.

The time to peak symptom relief is even more difficult to discern from the literature. No studies are designed to look at time to maximal symptom relief and few studies even note when maximal relief is achieved. In addition, the studies reviewed for maximal efficacy are a mix of seasonal and perennial studies with different allergens and pollen counts and thus cannot be compared. The only conclusions that can be drawn are that INCS take at least 2 weeks of regular use to achieve maximal benefit, while oral antihistamines are maximally effective within 1-8 days. INAH achieve maximal results in 1 day in one study, but incremental gains were seen up to 4 weeks in another. Montelukast probably achieves peak effectiveness by the second week.

The time for onset of action and maximum effect as described in Table 5 are based on representative studies in SAR with pollen as the allergen, using symptom scores except for ipratropium, which used methacholine and the amount of nasal secretions, and oxymetazoline which used maximal nasal airflow in patients with pre-existing turbinate hypertrophy.

Table 7: Onset of action of pharmacological agents for allergic rhinitis.

Agent	Study Design	Onset of Action	Maximal Effect	First Measure of Onset	References for onset	References for peak action
Intranasal steroid/antihistamine	EEU*	5 minutes (azelastine/fluticasone propionate)	2 weeks or greater	5 min	(474)	(319)
Intranasal decongestant-oxymetazoline	Peak nasal airflow	<10 minutes	? within an hour	10min	(475)	
Intranasal antihistamine	EEU	15min (azelastine)	1 day to 4 weeks	15 min	(476) (477)	(317, 340)
	EEU	30min (olopatadine)	1 day to 4 weeks	30 minutes	(318) (477, 478)	(340)
Intranasal anticholinergic	Methacholine challenge	15 minutes (ipratropium)	1 hour	15 min	(479)	(479)
Oral antihistamine	EEU	30-90 min (desloratadine)		30 minutes	(480)	
	EEU	45 min (levocetirizine)		15 minutes	(481)	
	EEU	60min (cetirizine)	1-8 days	15 min	(476)	(482)
	EEU	60-75 min (loratadine)	1-8 days	15 min	(476) (483) (481)	(484)
Oral antihistamine with decongestant	Single Dose Park Setting	30 min (loratadine/pse)	unknown	15 min	(485)	
Intranasal corticosteroids	EEU	1-6 hours (ciclesonide)	2-4 weeks	1 hour	(486) (487)	(488)

Agent	Study Design	Onset of Action	Maximal Effect	First Measure of Onset	References for onset	References for peak action
	EEU	2.5 hours (mometasone)	4 weeks	30 minutes	(478)	(489)
	EEU	3-8 hours (budesonide)	2-4 weeks	1 hour	(452, 490)	(491, 492)
	2-week seasonal study	8 hours (fluticasone furoate)	2 weeks	30 min	(493)	(488, 489, 492)
	Not EEU, Park study or other	2-12 hours (fluticasone propionate)	2-4 weeks	2,4,12 hours (meta-analysis)	(494)	(491)
Leukotriene Receptor Antagonist	EEU	within 5 hours (montelukast)	By week 2	5 hours	(495, 496)	(497)
Intranasal mast cell stabilizer	2 Week Seasonal Study	2 weeks (cromolyn)	At least 2 weeks	1 week	(498)	(498, 499)
Intranasal mast cell stabilizer before allergen exposure	EEU, nasal allergen challenge	Application 1-7 minutes *before* allergen exposure	NA	≥ 10 min	(435)	NA

* EEU Environmental Exposure Unit

PSE: pseudoephedrine

Pharmacotherapy for non-allergic rhinitis (NAR)

Consensus Based Statement # 31: We suggest that the clinician offer an intranasal corticosteroid as one first line therapy for non-allergic rhinitis.
Strength of the recommendation: Conditional
Certainty of evidence: Low to Moderate

Consensus Based Statement # 32: We suggest that the clinician offer an intranasal antihistamine as one first line therapy for non-allergic rhinitis.
Strength of the recommendation: Conditional
Certainty of evidence: Very low

While INCS are generally recommended for treatment of NAR, their efficacy for some subsets of NAR is uncertain, and is less than that which is achieved for AR. (500) There is conflicting clinical research on whether inflammatory NAR responds better to INCS than does non-inflammatory NAR. (501, 502) As noted earlier, a 2019 Cochrane review concluded that it is unclear whether intranasal corticosteroids reduce patient-reported disease severity in non-allergic rhinitis patients compared with placebo.(354)

Topical intranasal antihistamines, azelastine and olopatadine, have been shown to reduce symptoms of NAR. (503) Two 3 week multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trials (n=223 study 1; n=203 study 2) conducted in patients with VMR revealed numerical improvements in total vasomotor rhinitis symptom score (TVRSS) for azelastine compared to placebo from baseline (mean numerical change 1.54 vs. 84, p= .002 in study 1; mean numerical change 1.54 vs. .88, p=.005 in study 2). There were no statistical differences in study dropout rate for azelastine versus placebo in either study and the only difference in adverse events between azelastine versus placebo was bitter taste (19% vs.2%). (329) In a randomized, double-blind, parallel-group, multicenter comparison study of olopatadine versus azelastine administered over 14 days in subjects ≥12 years of age with chronic VMR, both medications were found to equally reduce symptoms. The main adverse event was taste disturbance in approximately 10% with azelastine and 5% with olopatadine. (343) In this study the authors acknowledge a limitation of this study was that subjects could have previously been on either study drug and enrolled after a washout period of seven days. (343) In a study that measured substance P after administering nasal lavage hypertonic saline before and after treatment with azelastine versus placebo, azelastine was able to reduce substance P secretion to a statistically significant degree (p<.05). (79) Another short-term non-placebo controlled study compared intranasal azelastine to intranasal triamcinolone in NAR and AR and found both to be equally effective in both groups at improving nasal symptom scores, nasal peak inspiratory flow rate, Epworth sleepiness scale and quality of life. (504)

Less used and non-FDA approved treatments include topically applied capsaicin [see separate section], botulinum toxin A (505) injected or topically applied, and vidian neurectomy for severe refractory cases of VMR. (1) Botulinum toxin A (505) applied on the nasal mucosa or injected submucosally has been demonstrated to be effective in reducing hypersecretions and nasal congestion in VMR (506) (507) (508) (509) but to a lesser degree than ipratropium bromide. (506) In severe, refractory cases of VMR, vidian neurectomy has been used, although there has been concern regarding potential adverse events. In a recent systemic review, endoscopic vidian neurectomy compared with the traditional transantral approach was not associated with any long-term sequelae and provided improvement in rhinorrhea and nasal obstruction for several years following surgery. (510)

Non-allergic rhinitis pharmacologic treatment algorithm

As with AR, we recommend that a clinician use guidance from an algorithm (See Figures 4 and 5) that is based upon multiple considerations including relative effectiveness, onset of action, potential for adverse effects, patient preference, symptom severity, and whether a patient has intermittent or persistent rhinitis. The step-wise progression and decision tree is based largely

on expert opinion. Compared to the evidence for making treatment decisions in AR, the evidence for making recommendations for treatment of NAR is generally more limited, and there are fewer treatment options.

Figure 4: Algorithm Intermittent Nonallergic Rhinitis

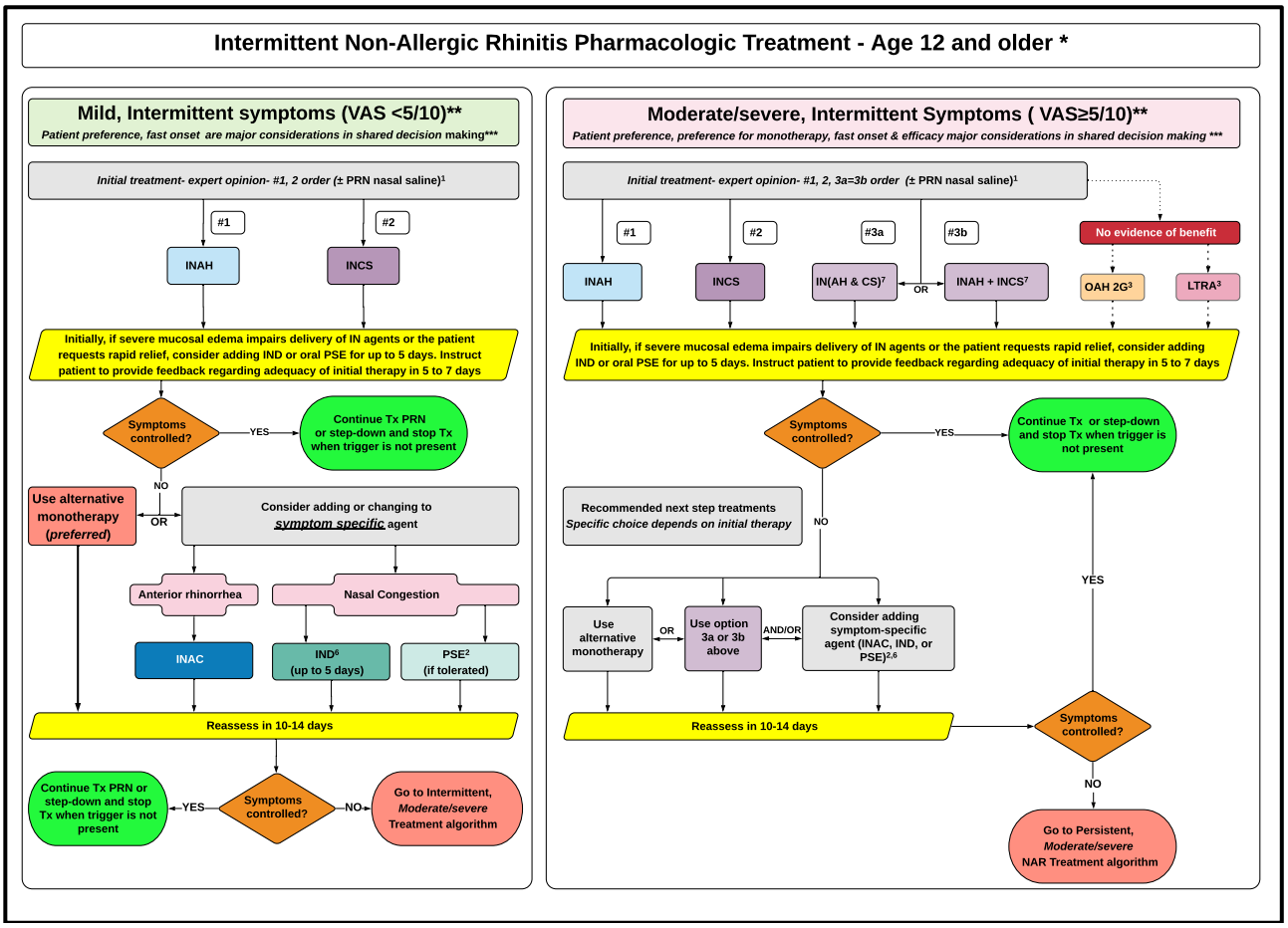
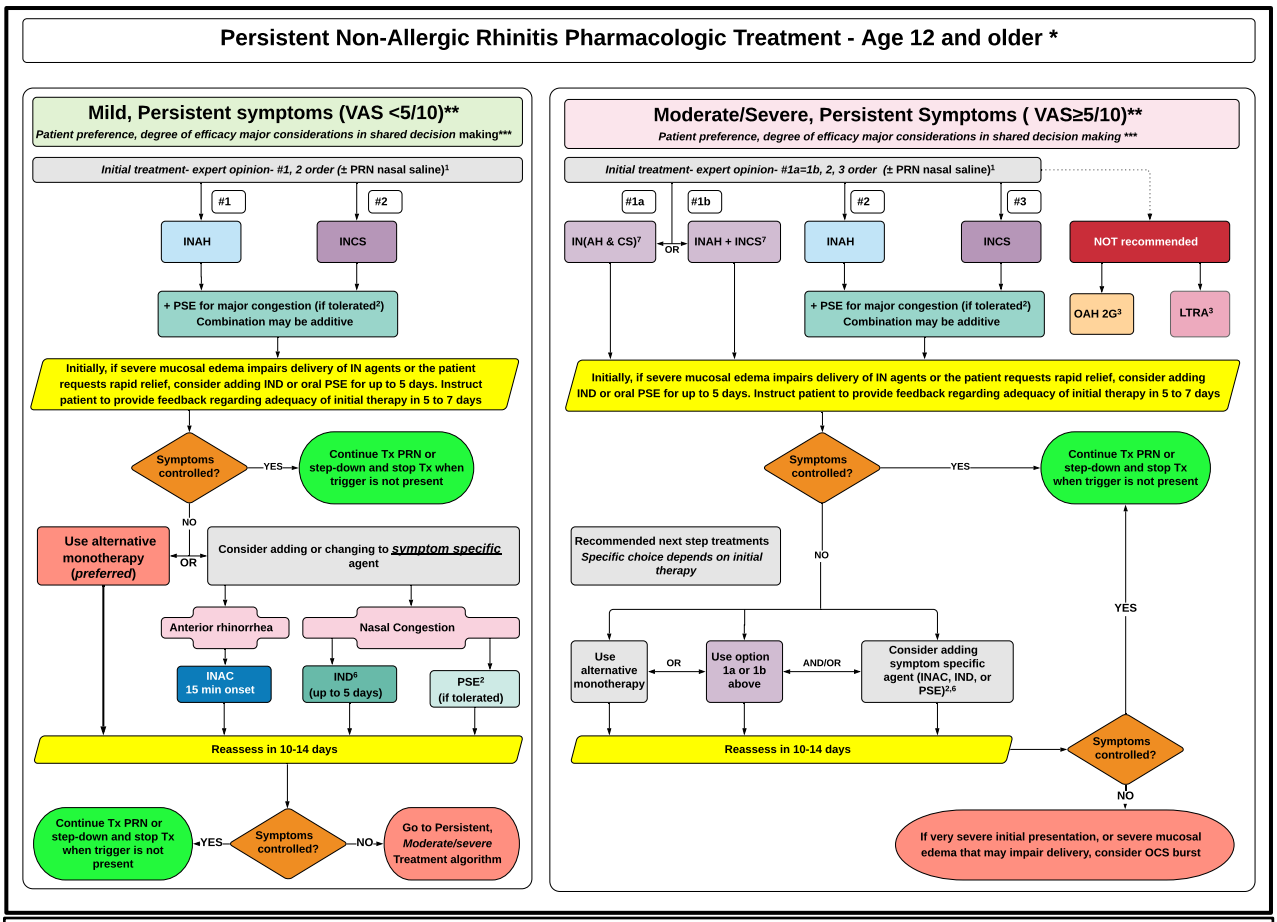


Figure 5: Algorithm Persistent Nonallergic Rhinitis



LEGEND FOR ABBREVIATIONS

- INAC Intranasal anticholinergic
- INAH Intranasal antihistamine
- IN cromolyn Intranasal cromolyn
- INCS Intranasal corticosteroid
- IN(AH & CS) Intranasal antihistamine and corticosteroid administered by a single device
- INAH+INCS These two preparations administered by separate devices
- IND Intranasal decongestant
- LTRA Leukotriene receptor antagonist
- OAH 2G Oral antihistamine,2nd generation
- OCS Oral corticosteroid
- PSE Pseudoephedrine
- VAS Visual analogue scale

* Recommendations for PNAR (perennial non-allergic rhinitis), VMR (vasomotor rhinitis)/idiopathic rhinitis do not necessarily apply to NARES, gustatory, senile, atrophic rhinitis. Onset of action studies have not been conducted for NAR for most medications. While most of the meds listed in the algorithm are approved for use in children < age 12, comparative trials have, for the most part, been limited to those equal to or greater than 12 yrs of age. The principles of treatment of children are the same as for adults, but special care must be given to dosage adjustment, adverse effects, and long-term safety.

** Severity of rhinitis, based upon symptoms and degree of overall control can be assessed by the patient using a visual analogue scale (VAS) of 1-10/10, with 10 being the most severe. Alternatively, the patient and provider can define "mild" as normal daily activities, sport, leisure, work, school, and sleep and no troublesome symptoms. "Moderate-severe" would indicate that one or more of these items are abnormal or impared.

*** Meds in JTFPP expert opinion suggested order, based upon major considerations noted.

FOOTNOTES FOR INTERMITTENT AND PERSISTENT NONALLERGIC RHINITIS

1. Order considers relative efficacy, but INCS monotherapy may be preferred when monotherapy and/or avoidance of adverse taste from INAH are desired. INCS may be preferred over INAH monotherapy when dosed over several days as INCS may become more effective with longer use.
2. PSE, if tolerated without significant adverse effects e.g. insomnia, irritability, aggravation of hypertension and cardiac arrhythmias
3. Unlikely to adequately control symptoms
6. IND, caution advised when used > 5 days due to risk for rhinitis medicamentosa (rebound congestion), although some evidence that concomitant INCS use can minimize risk of rebound. Consider INCS + IND if IND is to be used > 5 days
7. No studies compare INCS/INAH administered in a single device as 1 spray each nostril twice daily versus individual medications administered consecutively, each dosed as 1 spray each nostril twice daily. Preference for using a single device is based primarily on convenience. Using the two individual medications would be preferred primarily due to affordability.

Allergen immunotherapy and Allergic Rhinitis

<u>Consensus Based Statement # 33:</u> We suggest that allergen immunotherapy (subcutaneous or sublingual) be offered through shared decision-making to patients with moderate to severe allergic rhinitis who 1) are not controlled with allergen avoidance and/or pharmacotherapy or 2) choose immunotherapy as the preferred method of treatment, e.g., due to the desire to avoid the adverse effects, costs, or long-term use of pharmacotherapy, and/or 3) desire the

potential benefit of immunotherapy to prevent or reduce the severity of co-morbid conditions, such as asthma.
Strength of recommendation: Conditional
Certainty of evidence: Moderate

Consensus Based Statement # 34: We suggest that allergen immunotherapy (subcutaneous or sublingual) be considered for patients with controlled mild and moderate asthma with coexisting allergic rhinitis.
Strength of recommendation: Conditional
Certainty of evidence: Moderate

Allergen immunotherapy (AIT) is effective for the treatment of AR. (511-513) AIT should be considered for patients with allergic rhinitis who have specific IgE antibodies to clinically relevant allergens, and its use depends on the degree to which symptoms can be reduced by avoidance and medication, the amount and type of medication required to control symptoms, the adverse effects of medications, and patient preference(511-513). A high-quality meta-analysis from 2017 reported doubtful evidence that AIT can prevent the development of new allergen sensitizations (as this could not be confirmed in the sensitivity analysis)(514); however, its short-term potential to reduce the risk for the development of asthma in patients with AR, could be confirmed. (514)

A previous 2013 AHRQ meta-analysis reviewed 74 references and concluded that allergen subcutaneous immunotherapy (SCIT) is effective for reducing symptoms of AR and allergic conjunctivitis in adults (High strength of evidence). (515) Reviewing 60 studies, the authors concluded that sublingual immunotherapy (SLIT) reduces the symptoms of allergic rhinoconjunctivitis in adults (Moderate strength of evidence). (515) The 8 studies that indirectly compared SCIT to SLIT in adults showed that SCIT is superior to SLIT for symptom reduction in allergic rhinoconjunctivitis (Low strength of evidence). (515) A more recent head-to-head double-dummy, double blind RCT with grass pollen SCIT versus tablet SLIT showed minor numeric superiority of SCIT over SLIT (not significant). (516) In pediatric studies SCIT was effective in reducing rhinitis symptoms (Moderate strength of evidence) and conjunctivitis symptoms (Low strength of evidence) and SLIT reduced rhinoconjunctivitis symptoms. (Moderate strength of evidence). (515) The overall body of evidence showed that both SCIT and SLIT were safe and effective treatments for AR. (Moderate to High strength of evidence.) (515)

A systematic review and meta-analysis of the economic impact of SCIT and SLIT in adults and children with SAR was undertaken by the National Institute for Health Research in the United Kingdom. Economic modelling suggested that, when compared with symptomatic treatment, both SCIT and SLIT may become cost-effective at a threshold of $28,000-42,000 /quality-adjusted life-year (QALY) after 5-6 years of treatment. (517) In the US, using a Florida Medicaid claims analysis, SCIT in children and adults conferred significant health care cost savings within 3 months of initiating treatment and a 38% lower 18-month mean total health care costs. (518) A systematic review of the safety of SCIT (45/74 SCIT studies reported safety data) reviewed that the most common adverse effects, reported by 5-58% of patients were mild, local

reactions. (515) Pooled data, using a variety of grading systems, found that general symptoms (such as headache, fatigue, arthritis) were reported by 44% of patients and that respiratory-related systemic reactions were reported following 15% of the injections, a reaction rate far higher than that experienced by most US allergists. (515) The same study reported thirteen anaphylactic reactions, but no deaths. (515) A recent survey of AAAAI and ACAAI members, using the World Allergy Organization's classification system for systemic reactions (Grade 1-4) found an overall stable systemic reaction rate of 0.1% (Grade 1-4), 1/million allergy injections Grade 4 (most severe) reactions, and one fatality/23.3 million allergy injections. (519) There is insufficient evidence to determine the efficacy or safety of SCIT in select subpopulations, e.g., the elderly, pregnant women, racial and ethnic minorities, inner-city residents, rural residents, in patients with immunodeficiency and autoimmune disorders, and individuals with severe asthma. However, consensus by experts is that there is no absolute lower or upper age limit for initiation of immunotherapy, that AIT can be continued but generally not be initiated in pregnancy, and that SCIT can be considered in patients with immunodeficiency and autoimmune disorders. (513) Certified allergists' experience in large groups of such patients has been reported. (520) Limited evidence suggests that SCIT may be more beneficial in patients with mild asthma than in those with severe asthma. (519)

In general, the clinical indications for AIT for AR and asthma are similar for adults and children. Studies of children receiving AIT have demonstrated significant improvement in symptom control for asthma and AR and a reduction in airway responsiveness to cat and house dust mite allergens and reduction in pharmacy, outpatient, and total health care costs. (513) Discordant data about a decrease in the risk of developing asthma and new sensitizations has already been commented on above. (512)

When clinically indicated, the decision to initiate AIT depends upon a number of factors, including but not limited to patient's preference/acceptability, adherence, medication requirements, response to avoidance measures, and the adverse effects of medications. (521) The risks and benefits of administration of AIT with patients who are concurrently taking β-adrenergic blocking agents and ACE inhibitors and/ or have serious underlying medical conditions needs to be assessed. (520, 522) SCIT should be administered in a setting where procedures that can reduce the risk of anaphylaxis are in place and where the prompt recognition and treatment of anaphylaxis is ensured. (513) The first dose of SLIT is administered in a clinical setting under medical supervision but is, thereafter, administered by the patient at home. Clinical and physiological improvement can be demonstrated shortly after the patient reaches a maintenance dose. Patients should be evaluated at least every 6 to 12 months while receiving AIT. While many patients experience sustained clinical remission of their allergic disease after discontinuing AIT, others may relapse. A decision about continuation of effective AIT should generally be made after the initial period of 3 to 5 years of treatment. (523) At this point, for an individual patient, the decision to continue or discontinue treatment should be based upon the severity of disease, benefits sustained from treatment, and convenience of treatment.

Currently in the US, there are four tablet preparations for SLIT: a single pollen grass tablet, a 5-grass pollen tablet, a ragweed tablet, and a dust mite tablet. Several meta-analyses conclude that SLIT is effective in the treatment of AR and allergic asthma in adults and children and SLIT has been included in the Global Initiative for Asthma (GINA) treatment algorithm since 2017. Adverse reactions to SLIT, primarily local oral mucosal, are very common, systemic reactions are rare, and there have been no reported fatalities due to SLIT. (524)

Alternative medicine therapies

There is a body of literature reporting on the use of alternative medicine in AR. While alternative trials show promise as other optional therapies for AR, they suffer from many limitations. These include: the lack of standardized acupuncture protocols, lack of standardized outcome evaluations, methodological deficiencies, and small trial numbers. These limitations suggest that these positive outcomes should be interpreted with caution and that further research is needed before recommending alternative therapies for AR.

Acupuncture

Consensus Based Statement #35: We cannot make a recommendation for or against the use of acupuncture for the treatment of allergic rhinitis.
Strength of Recommendation: N/A
Certainty of Evidence: Ungraded due to lack of adequate studies

Developed in China 5000 years ago, acupuncture is one of the oldest medical interventions, yet little is known about its mechanism of action. Researchers have postulated alterations in immune or nervous system function with release of endorphins and changes in inflammatory and regulatory cells and their cytokine profiles, but none have been convincingly demonstrated. In a 2009 systematic review, acupuncture was found to be effective for treating seasonal allergic rhinitis based on symptom scores in only 1 of 4 studies when compared to a sham acupuncture. In another 4 studies on PAR, 2 studies showed improvements on symptom scores and a meta-analysis of the studies showed superiority over sham procedures. The authors concluded the evidence for acupuncture is mixed and larger sample size studies are needed. (525)

A systematic review of acupuncture for AR included related publications in both English and Chinese languages and identified 13 papers (of 174) that met inclusion criteria. (526) The studies involved 2365 participants with both SAR and PAR. The control groups included sham or no acupuncture and outcome measures included nasal symptom scores, relief medication scores, and quality of life measures. Compared to control, acupuncture led to significant reductions in nasal symptoms, intake of relief medications, and specific serum IgE levels. There was a trend in favor of active therapy in ameliorating quality of life measures. Another systematic review evaluated AHP in both English and Chinese literature and identified 20 trials (out of 1460) that met inclusion criteria and involved 2438 participants with allergic rhinitis where AHP was compared to placebo or western medicine. (527) In general, the analysis

showed that AHP was superior to placebo and not different from western medicine in control of symptoms and quality of life.

A randomized controlled trial with 12 sessions of acupuncture over 4 weeks in Australian patients with SAR showed improvements in symptom scores and quality of life compared to sham acupuncture. (528) An accompanying editorial questioned the clinical significance of these findings though, as only selected symptom scores of sneezing and itching were improved. (529) In the largest and highest quality multicenter study, 422 birch and grass allergic patients were randomized to 12 real or sham acupuncture sessions over 8 weeks. There was an improvement in quality of life scores and antihistamine use, but these did not meet predefined levels for clinical significance. (530) Finally, In the largest pediatric study to date, 72 Chinese children were randomized to twice weekly real or sham acupuncture for 8 weeks with an improvement in symptom scores but not medication use, IgE levels, or blood or nasal eosinophil levels. (531)

In conclusion, the results of acupuncture for allergic rhinitis are mixed, at best modest, and of uncertain clinical importance. However, it is very safe, with no serious adverse results reported in any studies.

Herbal medications

Consensus Based Statement #36: We cannot make a recommendation for or against the use of specific herbal products for the treatment of allergic rhinitis.
Strength of Recommendation: N/A
Certainty of Evidence: Ungraded due to lack of adequate studies

One alternative medical therapy is Chinese herbal medicine (CHM), which has been used for centuries to treat nasal symptoms related to allergic conditions. Studies can be hard to interpret as they use different products and methodologies, and many are industry funded. A review of one such CHM, Yu ping feng san, identified 22 randomized controlled trials (out of 1244 records) with 2309 participants with AR. (532) Control groups included placebo, pharmacotherapy, and the combination of CHM and pharmacotherapy and treatment periods ranged from 2-8 weeks. Results were limited in the placebo control trials and suggested a trend for benefit from CHM in a very small number of studies. When CHM was compared to pharmacotherapy, there was no superiority of CHM to antihistamines or intranasal steroids. There was also a hint of superiority of CHM when used in combination with pharmacotherapy compared to pharmacotherapy alone. Reported adverse events were mild and transient. Another review analyzed CHM in PAR and identified 7 randomized controlled trials (out of 266 studies) including 533 patients treated between 2 weeks and 3 months. (533) Compared to placebo, CHM significantly reduced nasal symptoms with a moderate side effect profile which lasted a short time.

A 2007 systematic review examined 16 randomized controlled trials with 10 different products and found evidence that *Petasites hybridus* (butterbur) improves symptoms and quality of life

comparably with a non-sedating antihistamine.(534) A proposed mechanism of action for *Petasites hybridus* (butterbur) is inhibition of the synthesis of cysteinyl leukotrienes by an ingredient, petasin 1, but there is no evidence for the mechanisms of possible action for other proposed herbal remedies. Studies with Aller-7, a mixture of 7 Indian plants suggested improvement in some symptoms, but this was inconsistent across studies and contradicted in other studies.(534) Studies of 3 Chinese herbal preparations showed some positive results in symptom scores; however, in one study only sneezing was significant.(534) Furthermore, another study reported that it required 5 weeks of herbal treatment to reach statistical significance.(534) The authors state there is moderately strong evidence to support the use of butterbur but that for Chinese herbal products independent replication is necessary. (534) More recently, a 2012 meta-analysis of 7 trials showed an improvement in symptom scores with traditional Chinese herbal medicine (533), but in a 2018 meta-analysis of 11 trials there was improvement in quality of life, but not symptom scores. (535)

The 2012 National Health Interview Survey showed 32.2% of US adults used complementary health approaches, including herbal medicines, in the previous year. (536) Physicians need to question patients on their use of these products as they can have toxicity and drug-herb interactions. The National Institute of Health has a webpage devoted to butterbur stating that raw, unprocessed butterbur plant contains pyrrolizidine alkaloids (PA) which can cause liver injury, recommending that only products certified "PA free" should be used. There is potential for allergic reactions to butterbur in patients sensitized to ragweed, chrysanthemums, marigolds, and daisies. (537) While butterbur has the most promising data, more studies are needed to demonstrate the efficacy and safety of herbal medicines before we can endorse them.

Rhinitis in Pregnancy

In summary, since the 2008 Rhinitis updated practice parameter (1) publication, there is interval information available that raises new safety concerns about use during pregnancy of intranasal triamcinolone and intranasal decongestants and additional evidence that supports and extends our previous recommendation to avoid oral decongestants. However, there is additional information that supports safety in pregnancy of most other common medications used for rhinitis.

FDA pregnancy classification

Starting in June 2015, the FDA replaced its old pregnancy (A,B,C,X) classification for newly approved medications with a more narrative discussion in Product Information for Risk Summary, Clinical considerations, and Data headers under the pregnancy subsection. Medications approved after June 2001 will be gradually phased in. Most allergic rhinitis medications were approved prior to this and will retain the old A through X classification. Unfortunately, there is still little high-quality evidence from prospective randomized trials supporting the safe use of pharmacologic agents in pregnancy, but we do have some additional information from cohort studies and clinical reviews since our 2008 JTFPP Rhinitis Update. (1)

Intranasal corticosteroids

As stated in the 2008 JTFPP Rhinitis Update, budesonide carries the old B FDA classification based upon the large Swedish birth registries which showed its safety. Other intranasal steroids still have the old C classification but there is new data supporting the safety of mometasone and fluticasone during pregnancy. Although most intranasal corticosteroids are generally considered safe during pregnancy, an exception is triamcinolone, which was associated with a higher rate of congenital respiratory defects in a large Canadian prospective cohort study. (538), although a chance finding cannot be ruled out.

Intranasal antihistamines

There is little data on the safety of intranasal antihistamines in pregnancy.

Nasal saline

A randomized study of pregnant women with AR demonstrated that nasal saline lavage is safe and effective, with significant reduction in rhinitis symptom score, daily antihistamine use, and nasal resistance. (539) Nasal saline therefore is a good first line option

Oral antihistamines

There is further evidence of the fetal safety of antihistamines and as a whole, oral antihistamines still appear to be safe for use in pregnancy. Cetirizine was not associated with increase rate of major malformations or increase teratogenic risk. (540) A study using the UCB Pharma Patient Safety Database up to February 2015 reaffirmed the safety of cetirizine in pregnancy. (541) A study using data from a multicenter case-control surveillance program of birth defects in North America did not support previously posited associations between antihistamines and major congenital anomalies. (542) Loratadine does not appear to increase the risk of hypospadias in male offspring. A 2014 systematic review found the most safety data for loratadine, including no evidence of increased risk of hypospadias. (543) A 2013 multicenter case-control surveillance program of birth defects in North America (544)(543)found no association between common antihistamines and birth defects, notably diphenhydramine, loratadine, and chlorpheniramine. (542)

Oral and intranasal decongestants

Oral decongestants should be avoided because of the risk for gastroschisis. (1)The Sloan Birth Defects Study confirmed an association between oral pseudoephedrine and gastroschisis. This same review also found an association between topical decongestants such as oxymetazoline, when used in the first trimester, with gastroschisis and pyloric stenosis as well as second trimester renal collecting system anomalies. In addition, an association between first-trimester exposure to phenylephrine, an oral decongestant, and endocardial cushion defects was described. (545) Epidemiologic studies have identified increased risk of birth defects involving the heart, eyes, ears, gut, abdominal wall, and feet when oral decongestants have been used during the first trimester of pregnancy. However, the number of reported cases is very small, considering the fact that up to 7.8% of pregnant women report using oral decongestants. There has been described a possible association of gastroschisis with the use of both pseudoephedrine (RR 2.1- 3.2)(546, 547) and phenylpropanolamine (RR 10.0) (547) during the first trimester of pregnancy. Pseudoephedrine use in the first trimester of pregnancy has also

been associated with limb reduction defects. Phenylephrine has also been associated with endocardial cushion defects (OR 8.0), ear defects (OR 7.8), and pyloric stenosis (OR 3.2). (545) However, a Swedish prospective study looked at the use of these two decongestants during early and late pregnancy in 2474 and 1771 women, respectively, and no teratogenic effects were reported. (548)

The adverse effects of oral decongestants taken during the second and third trimesters appear to be much less compared to early pregnancy, but caution should be used throughout pregnancy and prolonged use avoided.

Based on the low or variable benefit of using decongestants during pregnancy and the potential catastrophic harm of having a birth defect, the workgroup and JTFPP are making a strong recommendation against their use during the first trimester of pregnancy, despite the lack of a strong certainty of the evidence. The JTFPP is not make a recommendation for or against their use during the 2nd and 3rd trimester of pregnancy reflecting the lack of studies reporting catastrophic harm but the remaining low magnitude of benefit for their use. The clinician should involve shared decision-making with each patient when considering the use of oral decongestants during pregnancy.

Leukotriene receptor antagonists

Montelukast carries the old B FDA pregnancy classification and has reassuring observational data mostly from asthma studies. Since the 2008 JTFPP Rhinitis Update was published, a large Danish observational study from 1998 to 2009 found no increased risk of congenital malformations with montelukast. There was, however, an association with lower birth weight and gestational age in children and increased preeclampsia and gestational diabetes in mothers using montelukast. This may be explained by increased asthma severity in the montelukast group. (549) Other human studies have shown montelukast and other leukotriene receptor antagonists (e.g. zafirlukast) are not associated with an increased rate of major malformations in offspring. (550-552)

Allergen immunotherapy

As previously stated, subcutaneous immunotherapy should not be started in pregnancy, but may be continued. While no recommendation on sublingual immunotherapy can be made yet, there is one prospective observational study in which 185 pregnant Indian patients were treated with SLIT, (newly initiated in 24 and continued treatment in 161) with no increase in birth defects seen in 6 years of follow-up. (553)

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