Practice parameter

Rhinitis 2020: A practice parameter update

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This comprehensive practice parameter for allergic rhinitis (AR) and nonallergic rhinitis (NAR) provides updated guidance on diagnosis, assessment, selection of monotherapy and combination pharmacologic options, and allergen immunotherapy for AR. Newer information about local AR is reviewed. Cough is emphasized as a common symptom in both AR and NAR. Food allergy testing is not recommended in the routine evaluation of rhinitis. Intranasal corticosteroids (INCS) remain the preferred monotherapy for persistent AR, but additional studies support the additive benefit of combination treatment with INCS and intranasal antihistamines in both AR and NAR. Either intranasal antihistamines or INCS may be offered as first-line monotherapy for NAR. Montelukast should only be used for AR if there has been an inadequate response or intolerance to alternative therapies. Depot parenteral corticosteroids are not recommended for treatment of AR due to potential risks. While intranasal decongestants generally should be limited to short-term use to prevent rebound congestion, in limited circumstances, patients receiving regimens that include an INCS may be offered, in addition, an intranasal decongestant for up to 4 weeks. Neither acupuncture nor herbal products have adequate studies to support their use for AR. Oral decongestants should be avoided during the first trimester of pregnancy. Recommendations for use of subcutaneous and sublingual tablet allergen immunotherapy in AR are provided. Algorithms based on a combination of evidence and expert opinion are provided to guide in the selection of pharmacologic options for intermittent and persistent AR and NAR. (J Allergy Clin Immunol 2020;146:721-67.)

Key words: *Allergic rhinitis, nonallergic rhinitis, vasomotor rhinitis, local allergic rhinitis, food allergy antihistamines, corticosteroids, ipratropium, allergen immunotherapy, decongestants*

Abbreviations used

AH:	Adenoidal hypertrophy
AIT:	Allergen immunotherapy
AR:	Allergic rhinitis
CBS:	Consensus based statements
CHM:	Chinese herbal medicine
CRS:	Chronic rhinosinusitis
CT:	Computed tomography
DBPC:	Double-blind, placebo controlled
DP:	*Dermatophagoides pteronyssinus*
FDA:	US Food and Drug Administration
GRADE:	Grading of Recommendations, Assessment, Development and Evaluation
INAH:	Intranasal antihistamines
INCS:	Intranasal corticosteroids
JTFPP:	Joint Task Force on Practice Parameters
LAR:	Local allergic rhinitis
LTRA:	Leukotriene receptor antagonist
NAPT:	Nasal allergen provocation test
NAR:	Nonallergic rhinitis
NARES:	Nonallergic rhinitis with eosinophilia syndrome
NSAID:	Nonsteroidal anti-inflammatory drug
NSD:	Nasal septal deviation
OAS:	Oral allergy syndrome
PAR:	Perennial allergic rhinitis
QOL:	Quality of life
SAR:	Seasonal allergic rhinitis
SCIT:	Subcutaneous allergy immunotherapy
sIgE:	Serum-specific IgE
SLIT:	Sublingual immunotherapy
SLIT-D:	Sublingual immunotherapy administered by liquid drops
SLIT-T:	Sublingual immunotherapy administered via tablets
TRPV1:	Transient receptor potential vanilloid 1
VAS:	Visual analog scale
VMR:	Vasomotor rhinitis
UACS:	Upper airway cough syndrome

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EXECUTIVE SUMMARY

This comprehensive practice parameter for allergic and nonallergic rhinitis provides updated guidance on diagnosis, assessment, selection of monotherapy and combination pharmacotherapy options, and allergen immunotherapy. Food allergy testing and parenteral corticosteroids are not recommended. Key new and updated recommendations are emphasized (Table I).

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 pathogenic mechanisms, as allergic or nonallergic, and differentiated from conditions that have overlapping symptoms of rhinitis.

Rhinitis phenotypes

Although the term rhinitis connotes inflammation, and allergic rhinitis (AR) and some types of nonallergic rhinitis (NAR) are associated with inflammation (eg, nonallergic rhinitis with eosinophilia syndrome [NARES], infectious rhinitis), some forms of NAR such as vasomotor rhinitis (VMR) 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 with and without 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 United States annually, can have a major impact on quality of life (QOL), and poses a substantial economic burden on society. It also is often associated with and can potentially impact asthma, allergic conjunctivitis, rhinosinusitis, 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% of US children.[3,4] Canadian data support an even higher prevalence of up to 20% of the population having physician-diagnosed AR.[5] Chronic NAR has been estimated to affect 17% to 52% of adults while up to 34% of patients with rhinitis in the United States may have a combination of AR and NAR, often referred to as "mixed rhinitis."[6-10]

QOL in rhinitis

Issues of QOL associated with rhinitis include disturbed sleep; daytime somnolence and fatigue; irritability; depression; impairment of physical and social functioning; and attention, learning, and memory deficits. Thirty-five percent to 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 1 in 4 of adult US respondents report they are unable to sleep or are

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Resolving conflict of interest: The JTFPP is committed to ensuring that all guidelines are based on the best scientific evidence at the time of publication, and that such evidence is free of commercial bias to the greatest extent possible. Before confirming the selection of the work group chairperson and members, the JTFPP discusses and resolves all relevant potential conflicts of interest (COIs) of each work group member. The JTFPP recognizes that experts in a field are likely to have interests that could come into conflict with the development of a completely unbiased and objective guideline. Therefore, a process has been developed to acknowledge potential COIs when making specific recommendations. To preserve the greatest transparency regarding potential COIs, all members of the JTFPP and work group complete a COI form prior to the development of each document and again prior to the guideline submission for publication.

During the review process there are additional measures to avoid bias. At the work group level, all the recommendations and discussion sections are reviewed by all work group members to ensure that content is appropriate and without apparent bias. If any recommendation or section is deemed to have apparent bias, it is appropriately revised, without the section author's involvement, in an attempt to remove potential bias. In addition, the entire document is also reviewed by the JTFPP and any apparent bias is acknowledged and removed at that level. For each and every recommendation, a vote is required by the work group and JTFPP, and any member with any perceived COI is recused from that vote (and so explained in the document). Any dissenting votes that cannot be resolved are described and explained in the document.

In a final stage of review, the practice parameter is sent to invited expert reviewers for review, selected by the AAAAI and the ACAAI. The document is also posted on the AAAAI and ACAAI websites for general membership and the public-at-large to review and offer comment. All reviewers must provide statements of potential COIs. Although the JTFPP has the final responsibility for the content of the documents submitted for publication, each reviewer's comments will be discussed and reviewers will receive written responses to comments when appropriate.

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Disclaimer: The AAAAI and the ACAAI have jointly accepted responsibility for developing "Rhinitis 2020: a practice parameter update." The medical environment is rapidly changing, and not all recommendations will be appropriate or applicable to all patients and may change over time. Because this document incorporates the efforts of many participants, no single individual, including members serving on the JTFPP, is authorized to provide an official AAAAI or ACAAI interpretation of this guideline. Any request for information or interpretation of this practice parameter by the AAAAI or ACAAI should be directed to the executive offices of the AAAAI and the ACAAI. Practice parameters and guidelines are not designed for use by the pharmaceutical industry in drug development or promotion. The JTFPP understands that the cost of diagnostic tests and therapeutic interventions is an important concern that may appropriately influence the evaluation and treatment selected for a given patient. The JTFPP recognizes that the emphasis of our primary recommendations regarding a medication may vary, for example, depending on third-party payer issues and product patent expiration dates. However, because a given test or a therapeutic intervention's cost is so widely variable, and there is a relative paucity of pharmacoeconomic data, the JTFPP is not always able to consider cost when formulating recommendations. In extraordinary circumstances, when the cost benefit of an intervention is prohibitive as supported by pharmacoeconomic data, commentary may be provided.

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TABLE I. What is new or newly emphasized in Rhinitis 2020?

Four new algorithms based on a combination of evidence and expert opinion can guide the clinician in the treatment of intermittent and persistent AR and NAR.
New tables assist in making (1) the differential diagnosis for rhinitis based on patient history and (2) the diagnosis and treatment for rhinitis-associated conditions or conditions that mimic rhinitis.
Cough is emphasized as a common symptom present in both AR and NAR.
New information is presented about LAR, possibly present in up to 25% of patients with rhinitis, and its response to both SCIT and SLIT, although more research is needed.
We recommend that food allergy testing not be performed in the routine evaluation of possible AR (Recommendation 4).
We recommend that the oral LTRA montelukast should only be used for AR in patients who have an inadequate response or intolerance to alternative therapies. Serious neuropsychiatric events that may include suicidal thoughts or actions have been reported in patients taking montelukast (Recommendation 7).
Either INAH or INCS may be offered as first-line monotherapy for NAR (Recommendations 12, 32).
Since the 2008 rhinitis update, additional studies support the use of combination INCS and INAH in AR and NAR (Recommendations 22-24).
Oral decongestants should be avoided during the first trimester of pregnancy (Recommendation 19).
Additional information is presented as to why first-generation antihistamines should not be used in AR, especially on a chronic basis, due to potential sedation, performance impairment, poor sleep quality, anticholinergic-medicated symptoms, and increased risk of dementia (Recommendation 6).
We continue to suggest that the use of intranasal decongestants generally be limited to short-term use to prevent rebound congestion that may occur with longer use. However, in limited circumstances discussed in the document, patients on regimens that include an INCS may be offered combination therapy with addition of an intranasal decongestant for up to 4 wk (Recommendations 16, 26).
SCIT and SLIT tablets are both effective for the treatment of AR and may help prevent and/or treat allergic asthma (Recommendation 34).
Neither acupuncture nor herbal medications have adequate studies to support a recommendation to use them in the treatment of AR (Recommendations 36, 37).

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.[12]

Limited available data report that health-related QOL is reduced in patients with NAR, with greatest reductions in patients with NARES.[13] A decreased sense of smell, present in both AR and NAR, can lead to a significant decrease in QOL, 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.[14]

Economic and societal burden of rhinitis

While the total direct medical costs of rhinitis are tremendous,[15,16] rhinitis is also a significant cause of lost work and school days and decreased work productivity/presenteeism (work interference) and school performance. Up to 10% of workers reported absenteeism because of their nasal allergies, and up to 25% reported presenteeism, with an estimated 23% to 33% decrease in productivity on days when allergies were at their worst compared with days when the respondent experienced no symptoms.[3] Increased symptom severity, decreased sleep quality and quantity, adverse effects on mental function, and treatment with soporific antihistamines negatively impact work productivity.[17]Appropriate therapy can substantially reduce both societal and employer costs. Lack of treatment, undertreatment, or nonadherence to treatment have been shown to increase direct and indirect costs.[18] AR can, by itself, introduce significant inattention, impairment of cognition, and decreased daytime school performance.[19]

AR, notably present in about 75% to 80% of all patients with asthma and in nearly 100% with allergic asthma, is associated with increased asthma-related hospitalizations and higher total annual medical costs.

Classification of AR: 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. Mild rhinitis severity is present when symptoms are not interfering with QOL 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 QOL 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).[20,22] This strict definition has some limitations; for example, a patient who has symptoms 3 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 nonallergic components contribute to rhinitis symptoms).

AR may also be classified by the temporal pattern of environmental exposure to a triggering allergen: seasonal (International Classification of Diseases, 10th Revision, J30.2, eg, from pollens, J30.1), perennial (year-round, eg, dust mites, J30.89 "other allergic rhinitis" and J30.9 "allergic rhinitis, unspecified"), or from episodic allergen exposures not normally encountered in the patient's environment, such as visiting a home with pets.[1] AR from animals (J30.81) therefore may be perennial with ongoing exposure, or occur only with episodic exposure.

In the United States, AR has traditionally been viewed as either seasonal (SAR) or perennial (PAR), and it is this classification system that the US Food and Drug Administration (FDA)[23] uses when approving new medications for AR. The reality is that a

patient may have both SAR and PAR, SAR or PAR with NAR (International Classification of Diseases, 10th Revision, J30 "vasomotor and allergic rhinitis"), intermittent symptoms with PAR, or persistent symptoms with SAR. 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 patients with AR, 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.[24] Since then, numerous studies have duplicated these findings in other regions.[25,26]

Local AR

In local allergic rhinitis (LAR), also referred to as entopy, there is (1) a clinical history of perennial and/or seasonal symptoms following allergen exposure, with (2) negative skin prick tests (and intradermal tests, when performed) and absence of serum-specific IgE (sIgE) antibodies but (3) a positive nasal allergen provocation test (NAPT) to aeroallergens.[27-30]

While a major study center in Europe has contributed the bulk of the research on LAR as discussed above, additional small studies from Australia,[31] Sweden,[32] Egypt,[33] and China[34,35] have supported their findings. There have been limited US studies, not all confirming these findings.[36,37]

A dual (immediate and late) response to NAPT had been noted in 37% to 70% of LAR.[38,39] 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% of patients.[39,40] When present in patients with SAR, an increase in nasal sIgE is noted both during NAPT challenge and during pollen season.[40] Likewise, in 1 dust mite LAR study of patients who had a positive NAPT-dust mite challenge, only 22% had nasal sIgE to dust mites.[38] 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.[41] Making the diagnosis can be challenging given the current low sensitivity of assays for the local sIgE and the need to conduct an in-office NAPT procedure.[42,43] Studies have suggested that the basophil activation test might serve as a surrogate marker of LAR, although currently this is available only as a research tool. It has been shown that using the basophil activation test with *Dermatophagoides pteronyssinus* (DP) extract and olive tree identifies 50% to 66%, respectively, of patients with NAPT-established LAR with a specificity of 93% and showing identical specificity for both LAR and AR.[44]

In some studies, using NAPT, up to 26% of all patients with rhinitis and up to 100% of patients with NAR have LAR.[31,32,35,36,45-48] In a population-based observational study that categorized all patients with rhinitis, over 25% and 63% were diagnosed to have LAR and AR, respectively, indicating that <12% had other types of NAR.[49] The coexistence of dual perennial LAR and SAR (skin prick test–positive) has also been described.[50,51] However, prevalence rates of LAR in China have been reported to be much lower (eg, 7.7%).[52] 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.[49,53,54] Local occupational rhinitis, diagnosed by nasal provocation studies, should be considered in workers with a convincing history but with negative immunological tests.[55]

The most frequently reported symptoms in patients with LAR are watery rhinorrhea, sneezing and itching, compared with congestion and mucoid rhinorrhea for patients with NAR.[49,56] While most patients with LAR are monosensitized, most commonly to dust mite, up to 37% are polysensitized to seasonal and/or perennial allergens.[46,49,57] Of particular interest is a significantly lower incidence (2.7%) of animal dander sensitization in patients with LAR compared with in patients with AR (31%).[49] The majority of adult patients with LAR have moderate/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.[39,49,58-60]

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 a reasonable consideration. SCIT has been successfully used to treat dust mite–, grass-, and birch-induced LAR in 2 different European centers.[40,60-62] A randomized, double-blind, placebo controlled (DBPC) parallel group study demonstrated that SCIT with DP in patients with LAR who are DP-sensitized 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.[62] Significant symptom improvement and nasal tolerance to NAPT-DP was noted as early as 6 months into treatment.[60] A small randomized DBPC 24-month trial of birch SCIT to patients with SAR produced a significant reduction in symptom medication score, a decrease in local sIgE, and an increase in IgG_4 levels.[40] 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.[40] An observational study using preseasonal grass SCIT demonstrated significant clinical improvement and increased NAPT nasal tolerance in all patients.[61] However, in this early study, 40% of the SCIT group developed positive skin prick tests after 6 months of treatment followed by sIgE and sIgG antibodies to grass after 12 months of treatment.[61] The same group completed a randomized DBPC study involving 56 patients with LAR to grass, established by either a positive NAPT or nasal sIgE ≥ 0.35 kU/L.[63] There was significant improvement in combined symptoms medication score and Rhinoconjunctivitis Quality of Life Questionnaire after 6 months of preseasonal treatment. The effect was sustained during the second year when year-round SCIT was used. There was a significant increase in serum IgG_4 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.[63] In

this controlled study, only 7.4% of the active versus 3% of the control group developed sIgE to grass at the end of year 1, showing that active SCIT treatment is unlikely to be creating systemic atopy.[63] A larger, prospective 10-year cohort study (2005-2016) of untreated patients with LAR showed a progressive worsening of the rhinitis, increased development of asthma, reduced QOL, and loss of allergen tolerance.[64] While a significant change was noted after 5 years,[53] this becomes progressively worse throughout the entire 10 years. The development of systemic atopy was not found to be significantly greater in patients with LAR (9.7%) versus in matched healthy controls (7.8%).[64]

While the literature supports LAR as a real entity, further large, multicenter, long-term, well-controlled studies with children and adults are needed to better define the prevalence, evolution, diagnosis, and treatment of LAR.

Nonallergic rhinitis

By definition NAR is defined as rhinitis that is independent of an IgE-mediated mechanism that includes VMR[65] (sometimes referred to as nonallergic rhinopathy or idiopathic rhinitis), infectious rhinitis, food-induced rhinitis,[66] hormonal rhinitis,[67] drug-induced rhinitis,[68] nonallergic occupational rhinitis,[69] atrophic rhinitis,[70] NARES,[26] and rhinitis of the elderly.[71] For this reason, "nonallergic noninfectious rhinitis" is a term sometimes used to describe this group of patients.[72] In reality, NAR can be acute or chronic, is often present in conjunction with AR ("mixed rhinitis")[73] and is frequently associated with hyperreactivity of the nasal mucosa.[74] In a study by Rondon et al,[49] compared with 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. The exact prevalence of NAR is unknown, but some estimates suggest that worldwide up to 200 million people have NAR.[72]

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.[75] VMR, often a diagnosis of exclusion, is frequently referred to as idiopathic rhinitis.[76] 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.[77]

"Idiopathic rhinitis" is sometimes used as an alternative term to VMR and usually excludes NARES.[78] 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.[79] In this practice parameter we do not use the term.

The diagnosis of VMR is based on exclusion of other forms of rhinitis, especially AR, 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 AR. Nasal challenge for VMR, to determine nasal hyperresponsiveness (eg, 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.[77,80] More recently, optical rhinometry with intranasal capsaicin challenge has been demonstrated to assist in the diagnosis of a subset of patients with VMR and nonallergic irritant rhinitis.[81]

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.[82] Support for this is partially based on the beneficial effects of ipratropium bromide and vidian neurectomy (the vidian nerve contains both the parasympathetic and the sympathetic innervation to the nasal mucosa).[82,83] Subjects with predominant rhinorrhea (sometimes referred to as cholinergic rhinitis) appear to have enhanced cholinergic glandular secretory activity that can be effectively reduced with the use of atropine and ipratropium bromide.[84,85] 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.[86-89] 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.[80]

However, somewhat conflicting research based on 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.[90] In clinical studies, when compared with controls, patients with irritant rhinitis have higher TRPV1 expression in the nasal mucosa and higher concentrations of substance P in nasal secretions.[91] From these data, the term "neurogenic rhinitis" has been proposed to replace VMR and idiopathic rhinitis 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.[75] 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.[1,92] 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 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.[93]

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 overprescribing antibiotics and a subsequent increase in 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 providers, despite often a lack of benefit and increased risk of adverse effects, including resistance.[94-105]

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.[99,106-108] In addition, because viral-induced infectious rhinitis/rhinosinusitis can cause sinus computed tomography (CT) scan changes that mimic acute bacterial rhinosinusitis, a CT scan should be deferred unless complications are a concern.[109-111] Up to 70% of children with viral infections[112] and as many as 87% of adults will have abnormalities on CT scan during the common cold.[113] Similarly, nasal culture and cytology of nasal secretions provide minimal assistance in distinguishing nonbacterial infections from bacterial rhinosinusitis and often positive bacterial cultures from the nose or sinus may represent colonization and not a pathogen.[93,114-116] 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.[93,114,117-124] 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 (CRS) are addressed in the most recent Joint Task Force on Practice Parameters (JTFPP) publication on rhinosinusitis.[92]

Unique populations susceptible to frequent or persistent and refractory infectious rhinitis include patients with anatomic abnormalities of the nares and sinuses, CRS with nasal polyps,[125] 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 *Staphylococcus aureus* bacterial infection of the nares and enlarged or infected adenoids.[126]

Food-induced rhinitis

Gustatory rhinitis. The main symptom is clear rhinorrhea after ingestion of food, especially hot and spicy foods.[127] The mechanism is thought to be a neurologic reflex of the noncholinergic, nonadrenergic system.

IgE-mediated food allergy and AR? Outside of the oral allergy syndrome (OAS),[128] discussed below, there is no evidence of IgE-mediated food-induced rhinitis symptoms without the presence of anaphylaxis with whole-body symptoms (eg, 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 <50%,[129] and recognizing that sensitization does not equate to clinical allergy, unnecessary food testing can lead to unwarranted food avoidance resulting in a reduced QOL, uncalled-for financial expenditure, and possible nutritional deficiency.[130,131] Testing with a "panel" of foods without attention to the medical history and epidemiology of AR, can result in mismanagement.[132]

While a high rate of sensitization to certain food (fruits, nuts, and vegetables), as demonstrated by skin prick tests or sIgE, is reported in patients with pollen-induced AR (eg, birch, mugwort, ragweed, and grass), most of these patients will not experience symptoms when ingesting cross-reacting foods.[133] Patient-reported prevalence of the OAS in patients with AR varies between 6% and 93%, generally being higher in adults versus children; females; patients having severe rhinoconjunctivitis symptoms, multiple pollen allergies, and longer duration of AR; and in geographical locations with high pollen levels.[133-137] 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%.[138] There have been, unfortunately, no studies in the United States that have adequately studied the prevalence of OAS including the development of rhinitis symptoms on 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.[139] In fact, compared with those without pollen-induced AR, patients with plant food reactions are at much lower risk of having systemic reactions if they have concurrent AR pollinosis.[140]

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.[141] Alcohol hyperresponsiveness correlates with the severity of the nasal inflammatory response, being greater in patients who have nonsteroidal anti-inflammatory drug (NSAID) exacerbated respiratory disease or CRS with nasal polyps (with or without asthma) than in patients with AR or CRS without nasal polyps.[141,142] 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 1 major contributing factor.[141] In some patients with AR, alcohol-induced symptoms may be intermittent (eg, only present during seasonal exacerbations), may appear 1 hour or later following ingestion, have a duration of >1 hour but <1 day, and may require between 1 and 3 drinks for symptom provocation.[142] For most affected patients, any alcoholic beverage can provoke symptoms; however, patients with CRS and without asthma have reported that wine may be worse than other alcoholic beverages.[142] Alcohol-induced symptoms in patients with NSAID-exacerbated upper respiratory disease have been reported to diminish following aspirin desensitization.[143] With the above-noted association of alcohol-induced rhinitis symptoms with CRS with nasal polyps, CRS without nasal polyps, 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 (eg, 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 with eosinophils may account for the greater prevalence and severity of rhinitis in females following puberty.[144] Rhinitis associated with pregnancy presents with congestion and while this may be secondary to an increase in estrogen and progesterone, the exact mechanism is not known.[145,146] Other endocrine diseases such as hypothyroidism and acromegaly also have been associated with nasal congestion.[72]

Drug-induced rhinitis

Drug-induced rhinitis can be classified based on proposed mechanism of action as local inflammatory, neurogenic, and idiopathic.[147] An acute inflammatory response may be induced following the ingestion of acetylsalicylic acid or other NSAIDs with isolated nasal symptoms or nasal symptoms as part of the NSAID-exacerbated respiratory disease with acute asthma symptoms and associated CRS 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 (eg, clonidine, reserpine, and methyldopa); (2) peripherally acting sympatholytic (eg, guanethidine and phentolamine); (3) ganglion-blocking (eg, trimethaphan); or (4) vasodilators, phosphodiesterase type-5 inhibitors (eg, sildenafil).[147] No mechanism has been clearly identified because there are many drugs that can produce nasal symptoms, such as calcium channel blockers, angiotensin-converting enzyme inhibitors, gabapentin, and psychotropics (eg, risperidone and chlorpromazine).[147,148] 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.[149-151] Overuse of topical decongestants can result in rhinitis medicamentosa, a form of drug-induced rhinitis, which is further discussed in the intranasal decongestants section.

Work-related rhinitis

Work-related rhinitis comprises (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 (preexisting or concurrent AR or NAR that is worsened by workplace exposures). Most occupational rhinitis is due to high molecular weight agents (>10 kDa) and is IgE- and T_H2 cell–driven. Low molecular weight (<10 kDa) occupational sensitizers may also induce occupational rhinitis symptoms through mechanisms without associated IgE.[72,152] Following specific inhalation challenge, when compared with low molecular weight agents, 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.[153] In work-exacerbated rhinitis, aggravation of rhinitis symptoms is often caused by nonallergic 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. 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.[154] Analogous to irritant-induced asthma/reactive airways dysfunction syndrome,[155] the predominant basis for making the diagnosis of reactive upper airways dysfunction syndrome is based on occupational history.

Atrophic rhinitis

Atrophic rhinitis is a chronic nasal condition associated with atrophy of the nasal mucosa and paradoxically presents with 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, such as Saudi Arabia, China, Africa, and India, and is uncommon in the United States and Europe.[156] One US study of patients with atrophic rhinitis categorized approximately 19% of them as having primary atrophic rhinitis; the mean age of this primary atrophic rhinitis group was 52 years.[156] 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 (eg, leprosy, sarcoidosis, or syphilis). Repeated, and often radical, sinonasal surgeries for CRS, allergic fungal rhinosinusitis, and/or nasal sarcoidosis produce a widening of the nasal vault, referred to as an "empty nose syndrome."[157] 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.[158,159]

Treatment has traditionally focused on reduction of crusting.[156,160] Conservative treatment can consist of nasal saline irrigation, glycerin-containing nose drops, nasal emollients, antibiotics, and vasodilators.[157] 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 procedure) or implanting prostheses submucosally to decrease nasal cavity size.[157,161]

However, a Cochrane review concluded there are no adequate randomized controlled studies of sufficient duration that compare these treatment options.[161]

NAR with eosinophilia syndrome

NARES was first was used in 1981 as a term to describe a case series of patients who were nonasthmatic that 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 >20% but with the absence of sIgE by skin and blood testing in all but 3 of 52 subjects. The original cohort included no patients with clinical evidence of CRS with nasal polyps. Oral aspirin and inhaled methacholine challenges performed on limited numbers of subjects were negative.[162] Onset of symptoms ranged from the first to fifth decades.

However, other systematic evaluations of nonallergic subjects with eosinophilic NAR 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 CRS, asthma, or perhaps NSAID-exacerbated respiratory disease.[7,163]

Blood eosinophilia is occasionally present in patients with NARES and the term "blood eosinophilic NAR" had been proposed but not routinely used to represent this possible condition.[164] The prevalence of NARES is unknown but is suspected to represent 1% to 5% of children and from 5% to 15% of adults with rhinitis.[7,165,166] One cluster analysis from a single center in Beijing characterized NARES in 23.6% of predominately adult subjects with chronic rhinitis.[167] Nasal eosinophilia persisted in children without allergies who were followed throughout the year including the winter season when not exposed to allergens.[166] Total nasal resistance and mucociliary transport time is increased in patients with NARES versus in healthy controls.[168]

The differential diagnosis of persistent nasal eosinophilia includes PAR with positive allergy skin or IgE blood tests, LAR, rhinosinusitis with nasal polyps, CRS without polyps, eosinophilic granuloma, allergic fungal rhinosinusitis, and NSAID-exacerbated respiratory disease.[169]

NARES is particularly responsive to corticosteroids.[7] In 1 uncontrolled study, montelukast 10 mg daily reduced nasal obstruction, rhinorrhea, sneezing, and nasal pruritus in subjects with NARES and asthma.[170] Intranasal cromolyn was studied and found to have no benefit in NARES.[171]

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 have been variable, ranging from 5% to 25% and the percentage may vary depending on specimen type.[172,173] Current clinical guidelines have not recommended routine assessments of nasal eosinophils.[1] The diagnosis of NARES should be considered in patients who are nonallergic and 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.

DIAGNOSIS AND MANAGEMENT OF RHINITIS

Methods and overview of the practice parameter guideline development process

This guideline contains systematically developed recommendations intended to optimize care of adult and adolescent patients (≥12-15 years of age) and to assist physicians and/or other health care practitioners and patients to make decisions regarding diagnosis and therapy for rhinitis. Even though many treatments are approved for younger children, the application of recommendations to children would be partially based on data extrapolation from adult studies and would therefore be less certain. This guideline updates "The diagnosis and management of rhinitis: an updated practice parameter" published in 2008.[1] This guideline was not intended to be a Grading of Recommendations, Assessment, Development and Evaluation (GRADE) document such as we published in 2017 to update for a limited number of questions for SAR.[174] Because GRADE documents require a comprehensive literature search, systematic review, and meta-analysis for each question, they require substantial resources, making it cost prohibitive to attempt to conduct a GRADE analysis for all of the questions for which clinicians would like an answer. In addition, for many questions, there is very limited evidence and the work group/Joint Task Force on Practice Parameters (JTFPP) must rely on expert evidence and opinion. Therefore, in this guideline, the only GRADE recommendations are those that were previously published in the 2017 rhinitis guideline update. The remainder of the recommendations are consensus-based statements (CBS), which are based, at best, on a recent literature search of PubMed to update or add to the 2012 rhinitis document. We have changed our method of grading our recommendations to be more transparent, choosing words that are used in a formal GRADE document, (eg, strong and conditional), to be consistent in terminology and to maintain a common thread. However, the use of these words do not imply that we are equating our recommendations to the rigor required by a GRADE document.

The strength of the CBSs 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 CBSs were based on the collective expert opinion and experience of the work group and JTFPP. We have provided the tabulated vote for and against each such statement.

The guideline development process involves several stages. The work group begins the process by developing a list of key clinical questions and topics to be addressed. At least 2 work group members are assigned to write and review each section. A PubMed literature search is completed to determine the most updated information for each CBS and discussion. The draft sections are reviewed by the work group chair and co-chair with subsequent revision by the authors. Subsequently, all sections are reviewed and revised by the entire work group 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 work group. The external review follows as described above under "resolving conflict of interest" in the preface (Tables II, III, and IV).

TABLE II. Grading the strength of the Consensus Based Statements (CBSs)

Strong CBS
The work group 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 work group 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 play a major role in arriving at the management decision.
● For policy makers—policy making will require substantial debate and involvement of many stakeholders.

TABLE III. Grading the certainty of evidence for each CBS

High = Further research is very unlikely to change our confidence in the estimate of effect. The recommendation is based on high-quality evidence, such as multiple highly rated randomized controlled trials, systematic reviews, or meta-analyses.
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 on somewhat limited evidence, such as reduced number or quality of randomized controlled trials or 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 on very weak evidence, such as nonexperimental studies, registries, or comparative studies.
Very low = Any estimate of effect is very uncertain. The recommendation is based largely on very low quality studies and/or on expert opinion.
CBS 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 work group members is indicated, with voting details provided if there were dissenting votes.

Clinical history and physical examination

Recommendation 1. *CBS:* 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

Recommendation 2. *CBS:* We recommend that for patients presenting with rhinitis symptoms, a review of all current medications should be completed to assess whether 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 work group and JTFPP.

Clinical history in patients with rhinitis. The most important single element for establishing the diagnosis of rhinitis, allergic or nonallergic, and differentiating it from other conditions with overlapping symptoms, is the clinical history.[1,20,175] 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 respiratory conditions (eg, asthma and chronic rhinitis with or without CRS) should be discussed. Because patients may not recognize symptoms of asthma, a history of symptoms suggestive of asthma (eg, wheezing, shortness of breath, chest tightness, and cough) should be sought, and if appropriate from symptoms, spirometry obtained. As noted earlier, AR coexists in about 75% to 80% of all patients with asthma, in nearly 100% of those with allergic asthma, and is a marker for more difficult-to-control or severe asthma. 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 health care 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.[176] The use of validated questionnaires is more beneficial for excluding than for confirming AR. The use of a validated 4-question screening tool has been shown to have a high negative predictive value for positive skin prick tests to common aeroallergens.[177] Furthermore, if a patient has a late onset of symptoms (age >45 years); no family history of allergies; no seasonality of symptoms or symptoms around cats, dogs, or other furry pets; and has trouble with nonallergic triggers such as deodorants/fragrances, the likelihood of having a

TABLE IV. JTFPP practice parameter CBSs and GRADE recommendations on the diagnosis and management of rhinitis

Recommendation no.	CBS or 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 whether 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 AR.	Strong	Ungraded
5	CBS: We suggest that the use of a validated instrument (eg, 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 first-generation antihistamine and are in favor of a second-generation antihistamine when prescribing an oral antihistamine for the treatment of AR.	Strong	High
7	CBS: We suggest that the clinician not select the oral LTRA montelukast for the initial treatment of AR due to reduced efficacy when compared with that of other agents. Furthermore, serious neuropsychiatric events that may include suicidal thoughts or actions have been reported in some patients taking montelukast. As advised by the FDA, montelukast should be used to treat AR only in patients who are not treated effectively with or cannot tolerate other alternative therapies.	Conditional	Very low
8	CBS: We recommend that the clinician not select an oral LTRA for the treatment of NAR.	Conditional	Ungraded
9	CBS: We suggest that for the treatment of very severe or intractable AR, the clinician may consider a short course (5-7 d) of oral corticosteroids.	Conditional	Very low
10	CBS: We suggest that for the treatment of very severe or intractable AR, the clinician not prescribe a depot parenteral corticosteroid for AR due to the potential risks of systemic and local corticosteroid side effects.	Conditional	Low
11	CBS: We recommend that the clinician offer INAH as an initial treatment option for patients with SAR.	Strong	High
12	CBS: We recommend that the clinician offer INAH as a first-line monotherapy option for patients with NAR.	Strong	High
13	CBS: We recommend that the clinician offer INAH as a first-line option for patients with intermittent AR.	Conditional	Ungraded
14	CBS: We recommend that when choosing monotherapy for persistent AR, INCS be the preferred medication.	Strong	High
15	GRADE: We recommend that for the initial treatment of moderate/severe SAR in patients ≥15 y of age, the clinician use an INCS over an LTRA. (Also see Recomendation 7.)	Strong	High
16	CBS: We suggest that the use of intranasal decongestants be short term and used for intermittent or episodic therapy of nasal congestion. (However, see also Recommendation 26.)	Conditional	Low
17	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 d of use.	Conditional	Ungraded
18	CBS: We suggest that oral decongestant agents be used with caution in older adults and children younger than 4 y 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
19	CBS: We recommend that oral decongestants be avoided during the first trimester of pregnancy.	Strong	Low
20	CBS: We suggest that in patients with PAR and NAR who have rhinorrhea as their main nasal symptom be offered intranasal ipratropium.	Conditional	Low for PAR; moderate for NAR
21	CBS: We suggest that intranasal cromolyn be offered as an option to be taken just prior to allergen exposure to reduce symptoms of AR from episodic allergen exposures.	Conditional	Very low
22	GRADE: We suggest that the clinician consider the combination of an INCS and an INAH for the initial treatment of moderate/severe nasal symptoms of SAR in patients ≥12 y old.	Conditional	High
23	CBS: We suggest that the clinician consider the combination of an INCS and an INAH for moderate/severe SAR and PAR that is resistant to pharmacologic monotherapy.*	Conditional	Moderate
24	CBS: We suggest that the clinician consider the combination of an INCS and an INAH for moderate/severe NAR that is resistant to pharmacologic monotherapy.*	Conditional	Low
25	CBS: We suggest that for patients taking an INCS who have persistent rhinorrhea, the clinician may consider the addition of intranasal ipratropium.	Conditional	Moderate
26	CBS: We suggest that patients with persistent nasal congestion unresponsive to an INCS or to an INCS-INAH combination be offered combination therapy with addition of an intranasal decongestant for up to 4 wk.	Conditional	Low

(Continued)

TABLE IV. *(Continued)*

Recommendation no.	CBS or GRADE recommendation	Strength of recommendation	Certainty of evidence
27	CBS: We suggest that for patients with AR and nasal congestion uncontrolled with an oral antihistamine, the clinician consider the addition of pseudoephedrine, when tolerated. (See Recommendation 18.)	Conditional	Moderate
28	CBS: We suggest that for SAR the clinician not combine the oral LTRA montelukast with an oral antihistamine for symptoms not controlled with an oral antihistamine. (See Recommendation 7.)	Conditional	Moderate
29	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 y of age with symptoms of SAR.	Strong	Moderate
30	CBS: We suggest that the clinician not prescribe the combination of an oral antihistamine and an INCS in preference to monotherapy with an intranasal steroid in all patients with SAR and PAR.	Conditional	Very low
31	CBS: We suggest against the addition of the oral LTRA montelukast to an INCS for AR, due to the lack of adequate evidence of improved efficacy and concerns for serious neuropsychiatric events from montelukast. (See Recommendation 7.)	Conditional	Very low
32	CBS: We suggest that the clinician offer an INCS as a first-line therapy for NAR.	Conditional	Low
33	CBS: We suggest that the clinician offer an INAH as a first-line therapy for NAR.	Conditional	Very low
34	CBS: We suggest that AIT (subcutaneous or sublingual tablets) be offered through shared decision making to patients with moderate/severe AR who (1) are not controlled with allergen avoidance and/or pharmacotherapy or (2) choose immunotherapy as the preferred method of treatment (eg, 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 comorbid conditions, such as asthma.	Conditional	Moderate
35	CBS: We suggest that AIT (subcutaneous or sublingual tablets) be considered for patients with controlled mild/moderate asthma with coexisting AR.	Conditional	Moderate
36	CBS: We cannot make a recommendation for or against the use of acupuncture for the treatment of AR.	N/A	Very low
37	CBS: We cannot make a recommendation for or against the use of specific herbal products for the treatment of AR.	N/A	Very low

N/A, Not applicable.
*"Resistant to pharmacologic monotherapy" assumes that the patient has been compliant and taken medication for adequate duration.

component of NAR before diagnostic skin or serologic testing is 98% predictive.[178] While the history has greater reliability and predictive value than solely relying on the physical exam, the combination of history and physical exam is still advised (Table V).[179]

Cough and rhinitis

Chronic cough, often defined as cough persisting for >4 weeks (children)[180] or >8 weeks (adults),[181] in patients who are immunocompetent and nonsmoking is usually due to upper airway cough syndrome (UACS), formerly referred to as postnasal drip syndrome; asthma; and/or gastrointestinal reflux disease, with UACS being the most common cause.[182-186] While the pathogenesis of chronic cough has often been attributed to some combination of upper airway inflammation, nasobronchial reflex, cold dry air stimulation, inflammatory mediators from the systemic circulation, or central and peripheral neuroplasticity, a clear pathway has not been shown experimentally.[187-189]

Cough as a consequence of rhinitis, especially AR, is often underappreciated, due in large part to a lack of high-level evidence. Overall, guidelines minimize or conclude that there is low-level evidence associating AR with cough without the presence of concurrent asthma.[179,190] Cough is often considered to be a comorbidity of AR rather than viewed as a direct symptom of AR. In 1 study, rhinitis was found to be an independent risk factor for the development of cough in adults.[191] Furthermore, in 1 large multinational observational study, 47% of patients with AR frequently reported cough as a symptom, although only 11% had cough as the main reason for seeking medical attention.[192] In a prospective study, cough as a symptom increased from mild intermittent to moderate/severe persistent AR.[193] Cough sensitivity has been described to be heightened in patients with AR, both during and outside of pollen season.[194,195] With up to 23% of patients with chronic cough having at least 2 contributing comorbidities (eg, AR with postnasal drip and gastroesophageal reflux disease), the complexity of managing chronic cough becomes magnified.[196]

The mechanism of cough in AR has often been explained both as a rhinobronchial reflex and as part of the UACS. In nasal challenge studies of patients with AR, cough was described most frequently in patients with PAR.[197] Patients with persistent AR report more postnasal drip along with more cough.[198] The mechanisms of cough from UACS in children may differ from adults and may differ among children of different age groups. In 1 Chinese study, rhinitis was the major pathogenesis in the school-age children, whereas it was adenoid hypertrophy in a group of preschool children, indicating that mechanical obstruction may be a major cause of UACS in some children.[199]

Frequently, cough in a patient with AR is related to concomitant asthma or nonspecific bronchial hyperreactivity, often undiagnosed. Furthermore, bronchial biopsy studies in patients with AR and without asthma have shown inflammatory cell infiltrate and active structural remodeling of the lower airways

TABLE V. Patient-reported symptoms and likely diagnosis

Symptom	AR	NAR	Acute upper respiratory tract infection	CRS without nasal polyps	CRS with nasal polyps
Rhinorrhea, sniffing	Very common, can be intermittent AR or persistent AR, most common symptom, clear watery	Common, but less than AR overall, but some subtypes have rhinorrhea as a major symptom	Common clear to purulent, watery to mucoid, associated with crust formation	Common, clear to mucoid	Common, clear to mucoid
Sneezing	Very common, intermittent and persistent AR, almost universal	Common, intermittent, less common than in AR, rarely persistent	Common	Very uncommon	Very uncommon
Hyposmia/anosmia	Occasional	Occasional	Common	Common	Very common
Nasal congestion/blocked nose, mouth breathing	Very common, persistent AR more than intermittent AR	Very common, usually persistent	Common	Very common	Very common, chronic, almost universal
Mouth breathing	Common	Common	Common	Occasional	Common
Ocular pruritus, watery discharge, red eyes	Very common	Uncommon	Uncommon	Very uncommon	Very uncommon
Postnasal drip	Uncommon, persistent more than intermittent AR	Very common	Common	Common	Occasional
Nasal/palate/ear itching	Common	Very uncommon	Very uncommon	Very uncommon	Very uncommon
Sore throat	Occasional, persistent more than intermittent	Uncommon	Common	Occasional	Uncommon
Constant clearing of throat	Uncommon	Common	Common	Common	Uncommon
Chronic cough	Common, persistent more than intermittent	Common, unless postnasal drip treated (persistent more than intermittent)	Common	Occasional	Uncommon
Bleeding of nose	Very uncommon	Uncommon	Very uncommon	Very uncommon	Very uncommon
Facial or sinus pain/ pressure	Very uncommon, persistent more than intermittent	Common	Common	Common	Uncommon
Eustachian tube dysfunction	Occasional	Occasional	Common	Uncommon	Uncommon
Snoring	Uncommon, persistent more than intermittent AR	Common	Common	Common	Common
Sleep disturbance/sleep apnea	Common, persistent more than intermittent AR	Common	Common	Common	Common
Headache as part of symptomology	Occasional	Common	Common	Common	Common

This table is developed based predominantly on expert opinion. Frequencies—very common, common, occasional, uncommon, very uncommon—are based on expert evidence and opinion.

similar to that of patients with asthma, thereby potentially contributing to cough in these patients.[200,201]

While intranasal corticosteroids (INCS) are often used to treat UACS, high-quality evidence is lacking. INCS have been shown to reduce cough sensitization in patients with AR.[202] Nasal-pharyngeal saline irrigation, compared with INCS, was shown to be more effective at reducing daytime and nighttime cough score and in lowering nasal lavage histamine and LTC_4.[203]

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 comorbid allergic or nonallergic condition (see Table VI for more details).[1,20,179] These comorbid conditions may include accompanying allergic conjunctivitis, otitis, eustachian tube dysfunction, CRS with and without nasal polyps, asthma, and/or atopic dermatitis.[1,204-206] Documentation of normal findings (eg, 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 (eg, pale, boggy nasal mucosa, allergic shiners, and pharyngeal hyperplasia) may support the diagnosis of AR, there are no pathognomonic findings that distinguish allergic versus nonallergic versus infectious rhinitis.[1,179,207,208] 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.[209] While conducting a physical exam is recommended by all major rhinitis guidelines to make the diagnosis of AR,[1,20,175] the very limited, low-quality research evidence that is available demonstrates a much lower sensitivity and specificity and high interpreter variability for

TABLE VI. Physical examination of patient presenting with symptoms compatible with rhinitis

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 AR or NAR).
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 AH, 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.

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. This table is modified from Table V in the 2008 rhinitis practice parameter.[1]

the physical exam when compared with the patient's history for making a diagnosis of AR, suggesting that both are essential to increase diagnostic accuracy.[179,209,210] Considering both the high prevalence of AR and NAR and the large number of differential diagnoses for rhinitis, perhaps the greatest benefit of completing the physical exam is to exclude the rare, but potentially life-threating diagnosis, intranasal tumor), which may even co-exist with AR.

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 does. 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 (eg, 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 (eg, deviated septum, rhinosinusitis with or without nasal polyps, foreign body, nasal septal perforation, or vocal cord dysfunction).

Differential diagnosis of rhinitis

The differential diagnosis of chronic rhinitis symptoms includes AR, NAR, 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 (NSD); and more uncommon conditions (Table VII). 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, >1 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 is a common cause of fixed nasal obstruction leading to nasal congestion.[211] It appears to be as common an anatomical cause of congestion as nasal valve collapse and turbinate hypertrophy.[212] It may cause bilateral or unilateral congestion and is often associated with nasal valve collapse and compensatory turbinate hypertrophy.[212-214] The importance and effectiveness of septoplasty for NSD does not appear to be universally accepted.[215,216]

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 two-thirds of the airflow resistance produced by the nose.[217] 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 do.[212] Hypertrophy can be primary (eg, from AR and NAR) or compensatory, often being associated with congenital or traumatic septal deviation.[213] While medical treatment for some causes of turbinate hypertrophy (eg, AR) 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.[218-220] When performing septoplasty for unilateral NSD, it is often necessary to also perform turbinate reduction

TABLE VII. Diagnosis and treatment of rhinitis-associated conditions or conditions that mimic rhinitis

Condition	History that may differentiate from rhinitis	Physical exam findings	Diagnostic studies	Treatment
CRS with nasal polyps	May have reduced sense of smell/taste; chronic congestion, nocturnal mouth breathing, NSAID-induced respiratory symptoms	Mucosal polypoidal changes that will not shrink with topical decongestant, nonpainful growths	Fiberoptic nasopharyngoscopy, sinus CT	Saline irrigation, consider short course oral corticosteroids, INCS, LTRAs, surgery, anti-IL-4/13 (dupilumab). Aspirin desensitization in aspirin/NSAID-exacerbated respiratory disease Research ongoing: anti-IL-5, IL-5 receptor antagonist, anti-IgE.
CRS without nasal polyps	Facial pain/pressure, headache, mucopurulent discharge, decreased sense of smell, postnasal drip, fatigue, poor sleep quality, depression	Mucopurulent discharge, facial tenderness, cobblestoning posterior pharyngeal wall	Fiberoptic nasopharyngoscopy, sinus CT, consider immune system evaluation	Evidence for treatment effectiveness may differ between CRS with and CRS without nasal polyps. Options include INCS, saline irrigation, chronic macrolide antibiotics (conflicting evidence), acute antibiotics for superimposed infection, surgery
Septal wall abnormalities, such as 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, such as 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 (ie, 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 and/or snoring, congestion as main or only symptom, possible sleep disturbance	Posterior nasal, pharyngeal fullness may be noted, adenoids may not be visualized on regular exam	Tympanogram, fiberoptic nasopharyngoscopy, lateral neck radiological studies, CT scan	INCS, LTRAs, 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 whether there is need for surgical leak closure

(Continued)

TABLE VII. *(Continued)*

Condition	History that may differentiate from rhinitis	Physical exam findings	Diagnostic studies	Treatment
Primary ciliary dyskinesia syndrome	Recurrent rhinosinusitis, otitis, sinus surgeries, diagnosis of rhinosinusitis with nasal polyps, atypical asthma, bronchiectasis	Findings compatible with CRS with or CRS without nasal polyps	Nasal nitric oxide; 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 CRS or chronic otitis

This table was developed largely based on expert opinion and is intended to offer considerations for the clinician.

surgery due to compensatory hypertrophy of the contralateral inferior turbinate.[221]

Cerebral spinal fluid leak. Cerebral spinal fluid leak usually presents as a unilateral clear rhinorrhea, without congestion, often worsened in the upright position, and increased in frequency following head trauma or surgery; however, some cases may be spontaneous.[222] Suggested diagnostic testing in the past included glucose determination, normally found in cerebral spinal fluid, 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.[222] For diagnostic confirmation and preparation for surgery, high-resolution CT and magnetic resonance cisternography are accurate, noninvasive, and complementary.[223] Treatment is often surgical in the form of endoscopic or open repair to prevent complications, which include meningitis.[222,224-226]

Adenoidal hypertrophy. Adenoidal hypertrophy (AH) is among 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.[227] The combination of clinical assessment (good specificity) with lateral x-ray (good sensitivity) is a good method for assessment of the degree of AH.[228] In addition, when feasible, the severity of AH can usually be adequately assessed by the nasopharyngolaryngoscope exam.[229] 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. Medical therapy includes topical nasal corticosteroids, which are 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.[230-232] When medical therapy fails, surgical removal should be considered. Young age and apnea hypopnea index >1 increase the likelihood that surgery will be necessary.[233]

Nasal foreign body. Nasal foreign bodies are common among young children.[234-236] Most cases present with unilateral congestion and foul-smelling purulent rhinorrhea. Foreign bodies are estimated to account for 30% of ear, nose, and throat emergencies of which 19% are intranasal.[234] Complications of nasal foreign bodies include infection, nasal perforation and epistaxis.[235] Of particular importance is the increase of nasal impaction with button batteries that can be corrosive and lead to septal perforation.[237] Removal may require general anesthesia, especially in cases of prolonged impaction because of associated inflammation.[238]

Ciliary dyskinesia. 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, that may present with cough, nasal congestion and symptoms of asthma, CRS with nasal polyps (in children and adults), bronchiectasis, recurrent otitis, rhinitis, and rhinosinusitis. In addition, infertility and situs inversus may complicate immotile-cilia syndrome. Unfortunately, there is no "gold standard" for the diagnosis of primary ciliary dyskinesia.[239] Most of the individual tests are subject to a false positive and/or a false negative result. An algorithmic-driven approach using a combination of tests has been published both by the European Respiratory Society and the American Thoracic Society.[240,241] Given a suggestive history and the exclusion of cystic fibrosis and immunodeficiency disorders, screening tests start the diagnostic process. In the past, screening tests included saccharine transit time or nasal challenge with tagged particles but these tests are no longer recommended. Currently, the first step in the European Respiratory Society algorithmic-driven approach is to obtain nasal nitric oxide and a nasal mucosal brushing for high-speed videomicroscopy analysis.[240] If these are equivocal or normal, a nasal mucosal brush specimen is sent for transmission electron microscopy and for cell culture and repeat high-speed videomicroscopy analysis.[240] If the results are still equivocal, genetic testing for known primary ciliary dyskinesia variants is then completed.[240] However, it is possible for the patient to have an unrecognized genetic defect. Many of the tests above described are only available in specialty centers. Additional testing methods (eg, inhalation of colloid albumin–tagged technetium Tc 99) are available only as a research tool.

Pharyngonasal reflux. 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.[242] The most common symptom of eosinophilic esophagitis is reflux, and eosinophilic esophagitis is frequently associated with rhinitis and especially symptoms of AR.[243] 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.[244,245]

Nasal/sinus tumor. Two recent documents from the World Health Organization address ear, nose, and throat tumors. A 2018 document discusses the classification of ear, nose, and throat tumors.[246] An earlier World Health Organization document from 2017 addresses clinical characteristics and imaging findings of benign masses of the nose and sinuses.[247]

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

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?**

Not at all	A little	Somewhat	A lot	All the time
☐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

FIG 1. Rhinitis Control Assessment Test. Reprinted with permission from Meltzer et al[265] and Nathan.[268]

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.

Recommendation 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.

Strength of recommendation: Strong

Certainty of evidence: High

Recommendation 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 AR.

Strength of recommendation: Strong

Certainty of evidence: Ungraded due to lack of studies addressing this specific issue.

Note: Unanimous vote in favor by work group 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[248] as he pioneered allergen immunotherapy (AIT). 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[76] 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 (ie, arms or back). Optimal results depend on use of potent test extracts and proficiency of the skin tester (ie, demonstration of coefficient of variation 30% at different periods). Intracutaneous tests are generally used for specific allergens (ie, 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 meta-analysis of 7 studies with 430 patients found that skin prick testing sensitivity was 85% and specificity 77%.[249] Intradermal studies were too few to give significant results. A large study from Turkey[250] compared intradermal with skin prick tests. Among 4223 patients with AR 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 with nasal challenge results. Other studies have suggested that in the presence of negative skin prick tests, positive intradermal tests to aeroallergens may often indicate

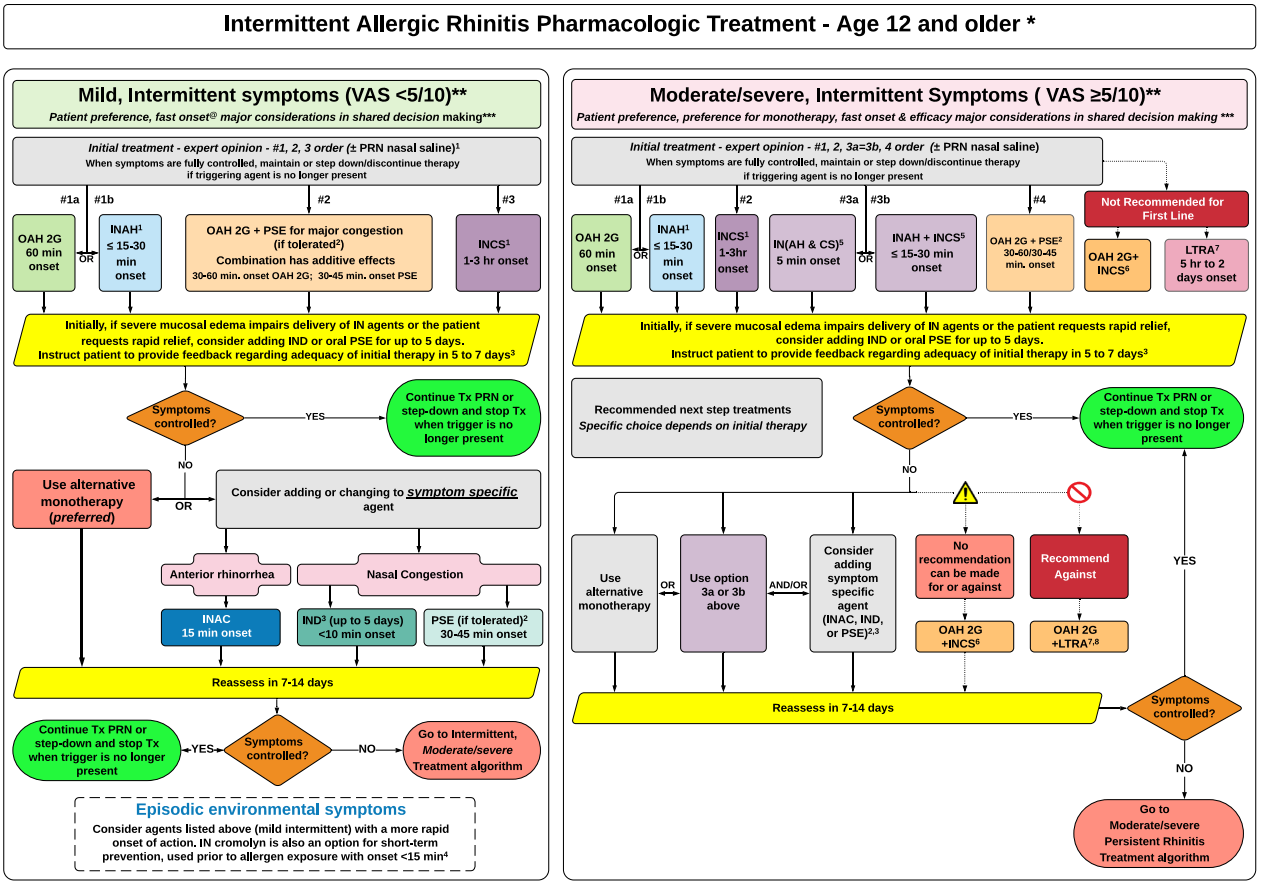

FIG 2. Algorithm for intermittent AR. *While most of the meds listed in the algorithm are approved for use in children <12 years old, comparative trials have, for the most part, been limited to those ≥12 years of age. The principles of treatment of children are the same as for adults, but special care must be given to dosage adjustment, adverse effects, and long-term safety. **Severity of rhinitis, based on symptoms and degree of overall control can be assessed by the patient using a VAS of 1 to 10, with 10 being the most severe. Alternatively, the patient and provider can define "mild" as normal daily activities, sport, leisure, work, school, sleep, and no troublesome symptoms. "Moderate/severe" would indicate that ≥1 of these items are abnormal or impaired. ***Medications are listed in the order suggested by JTFPP expert opinion based on major considerations noted. @See Table VIII for more details. [1]Order considers onset of action as well as relative efficacy. INCS monotherapy may be preferred when avoidance of adverse taste from INAH is desired. INCS may also 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, such as insomnia, irritability, or aggravation of hypertension and cardiac arrhythmias. [3]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. [4]IN cromolyn is recommended for 4-times-a-day dosing for persistent symptoms, has a slow onset of action of 1 to 2 weeks, has limited efficacy, but is very safe and may be preferred by some patients. However, it may be used just prior to episodic allergen exposure to blunt acute allergic response, with protective effect within 15 minutes. [5]No studies compare INCS/INAH administered in a single device as 1 spray in each nostril twice daily versus individual medications administered consecutively, each dosed as 1 spray in each nostril twice daily. Preference for using a single device is based primarily on convenience. Using the 2 individual medications would be preferred primarily due to affordability. There are no studies for onset using 2 devices; therefore, data from INAH are listed. However, onset may be similar to that of IN(AH & CS). [6]OAH 2G + INCS have not been shown to have any additive benefit over using just INCS. [7]Because serious neuropsychiatric events that may include suicidal thoughts or actions have been reported in patients taking montelukast, montelukast should generally be reserved for patients who have an inadequate response or intolerance to alternative therapies. [8]For OAH 2G + LTRA, there is lack of adequate of evidence of added efficacy to make a specific recommendation for or against this combination versus monotherapy. However, with the serious neuropsychiatric events reported with montelukast, this combination should rarely be used. *IN*, intranasal; *INAC*, intranasal anticholinergic; *IN(AH & CS)*, intranasal antihistamine and corticosteroid administered by a single device; *INAH+INCS*, these 2 preparations administered by separate devices; *IND*, intranasal decongestant; *OAH 2G*, oral antihistamine, second generation; *OCS*, oral corticosteroid; *PRN*, as needed; *PSE*, pseudoephedrine; *Tx*, treatment.

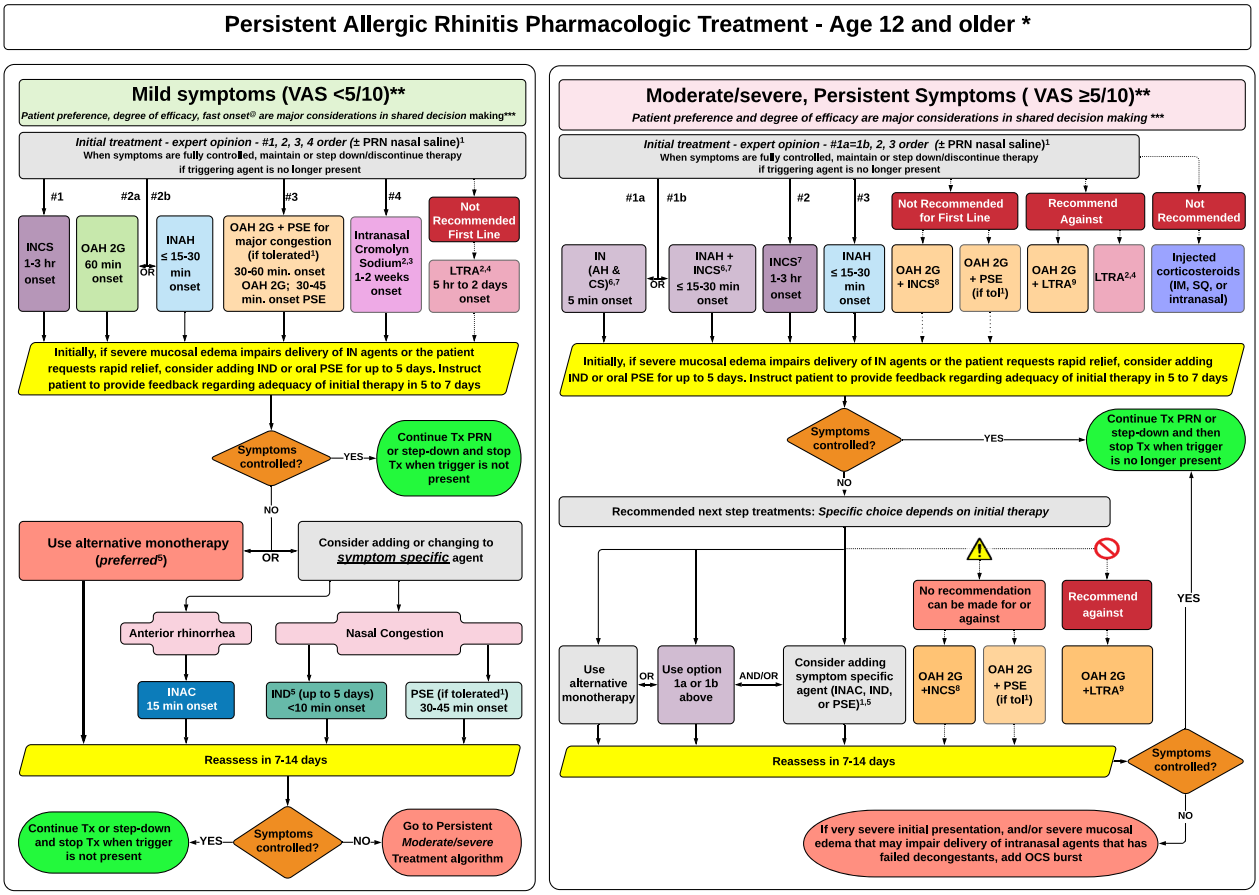

FIG 3. Algorithm for persistent AR. *While most of the medications listed in the algorithm are approved for use in children <12 years old, comparative trials have, for the most part, been limited to those ≥12 years of age. The principles of treatment of children are the same as for adults, but special care must be given to dosage adjustment, adverse effects, and long-term safety. **Severity of rhinitis, based on symptoms and degree of overall control can be assessed by the patient using a VAS of 1 to 10, with 10 being the most severe. Alternatively, the patient and provider can define "mild" as normal daily activities, sport, leisure, work, school, sleep, and no troublesome symptoms. "Moderate/severe" would indicate that ≥1 of these items are abnormal or impaired. ***Medications are listed in the order suggested by JTFPP expert opinion based on major considerations noted. @See Table VIII for more details about onset of action. [1]PSE if tolerated without significant adverse effects, such as insomnia, irritability, or aggravation of hypertension and cardiac arrhythmias. [2]Unlikely to adequately control symptoms. [3]IN cromolyn is recommended for 4-times-a-day dosing for persistent symptoms, has a slow onset of action of 1 to 2 weeks, has limited efficacy, but is very safe and may be preferred by some patients. However, it may be used just prior to episodic allergen exposure to blunt acute allergic response, with protective effect within 15 minutes. [4]Because serious neuropsychiatric events that may include suicidal thoughts or actions have been reported in patients taking montelukast, montelukast should generally be reserved for patients who have an inadequate response or intolerance to alternative therapies. [5]For IND, caution is 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. [6]No studies compare INCS/INAH administered in a single device as 1 spray in each nostril twice daily versus individual medications administered consecutively, each dosed as 1 spray in each nostril twice daily. Preference for using a single device is based primarily on convenience. Using the 2 individual medications would be preferred primarily due to affordability. There are no studies for onset using 2 devices; therefore, data from INAH are listed. However, onset may be similar to IN(AH & CS). [7]Order considers onset of action as well as relative efficacy. INCS monotherapy may be preferred when avoidance of adverse taste from INAH is desired. [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 of added efficacy to make a specific recommendation for or against this combination versus monotherapy. However, with the serious neuropsychiatric events reported with montelukast, this combination should rarely be used. *IM*, intramuscular; *OCS*, oral corticosteroid; *SQ*, subcutaneous.

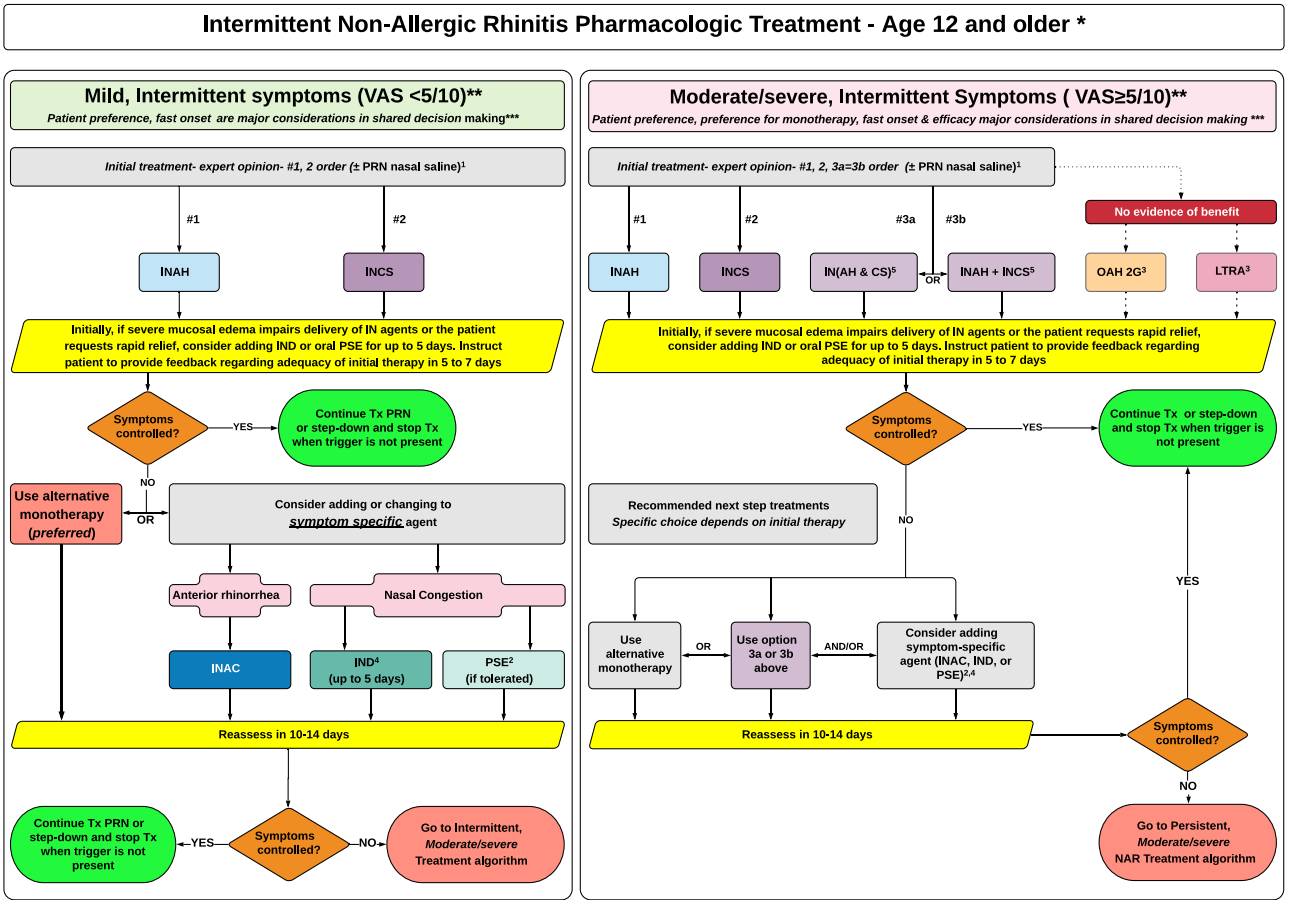

FIG 4. Algorithm for intermittent NAR. *Recommendations for perennial NAR, VMR, and/or idiopathic rhinitis do not necessarily apply to NARES, gustatory, senile, or atrophic rhinitis. Onset of action studies have not been conducted for NAR for most medications. While most of the medications listed in the algorithm are approved for use in children <12 years old, comparative trials have, for the most part, been limited to those ≥12 years 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 on symptoms and degree of overall control can be assessed by the patient using a VAS of 1 to 10, with 10 being the most severe. Alternatively, the patient and provider can define "mild" as normal daily activities, sport, leisure, work, school, sleep, and no troublesome symptoms. "Moderate/severe" would indicate that one or more of these items are abnormal or impaired. ***Medications are listed in the order suggested by JTFPP expert opinion based on major considerations noted. [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, such as insomnia, irritability, aggravation of hypertension, and cardiac arrhythmias. [3]No evidence of benefit for the treatment of NAR. [4]For IND, caution is 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. [5]No studies compare INCS/INAH administered in a single device as 1 spray in each nostril twice daily versus individual medications administered consecutively, each dosed as 1 spray in each nostril twice daily. Preference for using a single device is based primarily on convenience. Using the 2 individual medications would be preferred primarily due to affordability.

false positive results, and be unlikely to identify the presence of clinically signficant sensitivity.[251,252] In some cases of rhinitis, especially where LAR is suspected, a nasal allergen challenge can be helpful.[14,253]

Severity assessment including QOL by survey instruments and questionnaires

Recommendation 5. *CBS:* We suggest that the use of a validated instrument (eg 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. Some investigators have tried to translate the patient's assessment of severity using a visual analog scale (VAS) scale (ie, 0 to 10 where 0 is no symptoms and 10 is worst possible symptoms). The VAS is sensitive to detect changes in QOL for patients with AR,[254] but

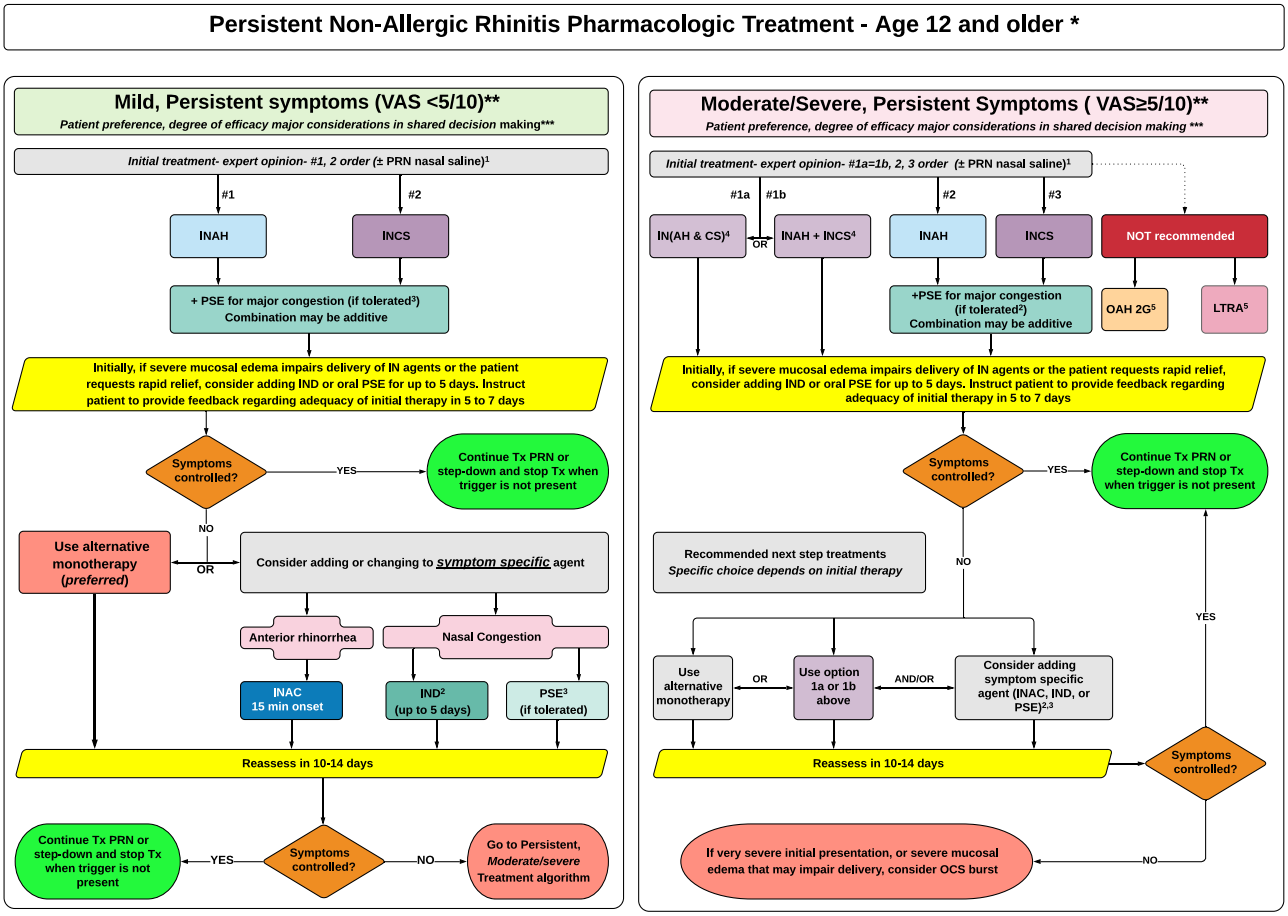

FIG 5. Algorithm for persistent NAR. *Recommendations for perennial NAR, VMR, and/or idiopathic rhinitis do not necessarily apply to NARES, gustatory, senile, or atrophic rhinitis. Onset of action studies have not been conducted for NAR for most medications. While most of the medications listed in the algorithm are approved for use in children <12 years old, comparative trials have, for the most part, been limited to those ≥12 years 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 on symptoms and degree of overall control can be assessed by the patient using a VAS of 1 to 10, with 10 being the most severe. Alternatively, the patient and provider can define "mild" as normal daily activities, sport, leisure, work, school, sleep, and no troublesome symptoms. "Moderate/severe" would indicate that ≥1 of these items are abnormal or impaired. ***Medications are listed in the order suggested by JTFPP expert opinion based on major considerations noted. [1]Order considers relative efficacy, but INCS monotherapy may be preferred when 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]For IND, caution is 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. [3]PSE if tolerated without significant adverse effects, such as insomnia, irritability, aggravation of hypertension, and cardiac arrhythmias. [4]No studies compare INCS/INAH administered in a single device as 1 spray in each nostril twice daily versus individual medications administered consecutively, each dosed as 1 spray in each nostril twice daily. Preference for using a single device is based primarily on convenience. Using the 2 individual medications would be preferred primarily due to affordability. [5]There is no evidence of benefit for the treatment of NAR.

the cutoff value for mild versus moderate/severe varies per study between 4 and 6.[255,256] Bousquet et al[255] identified 3052 patients with AR (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 that has no markings. The verbal anchors are "Not at all bothersome" (starting at 0) and "Very bothersome" (ending at 10 cm).[257] Receiver-operating curves found that this simple 1-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."[255] Subsequently a score of ≥5 has been used to represent moderate/severe.

A variety of QOL questionnaires, some specific to rhinitis and others being generic QOL instruments, have been used to assess AR severity.[190] Generic QOL scales offer comparison between different disorders and patient populations;[258] for example, adults with moderate/severe perennial rhinitis and moderate/severe asthma have equal functional impairment.[259,260] 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.[258,261] VASs may also correlate well with rhinitis symptom scores and QOL measures, leading to improved symptom control.[254] There is also a highly significant correlation between a VAS and the Rhinoconjunctivitis Quality of Life Questionnaire. A subsequent study further validated the VAS and determined that changes in the VAS of 23 mm were found to be clinically significant.[254] 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.[262,263]

Control of AR

In addition to assessing AR severity and the impact on QOL, assessing control is an important goal. As has been 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.[264] The Rhinitis Control Assessment Test, is a simple, reliable, self-administered 6-item questionnaire utilizing a 5-point Likert scale (Fig 1).[265-268] Developed to assist physicians in the assessment of patient rhinitis control in clinical practice, it also helps patients appreciate what rhinitis control is. The Rhinitis Control Assessment Test was developed and validated against total nasal symptom scores and the physician's global assessment. Subsequent work identified a cutoff score of 21 as representing good control, with a minimal important difference of 3. Downloadable forms for administering the Rhinitis Control Assessment Test are readily available online (eg, at AllergyAsthmaNetwork.org).

The Allergic Rhinitis Control Test is a validated 5-item self-assessment using a 5-point frequency scale with similarities to the Asthma Control Test.[103,269,270] The Control of Allergic Rhinitis and Asthma Test[25] is a validated 10-item questionnaire that was tested in patients consulting an allergist.[271-273] 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.[32,264]

PHARMACOTHERAPY

Review of monotherapy and then combination pharmacologic therapeutic options for rhinitis (with an emphasis on treatment of AR) is presented first. Thereafter a stepwise pharmacologic treatment of AR will be presented, using algorithms for intermittent (Fig 2) and persistent (Fig 3) AR. Similarly, pharmacologic treatment algorithms have been developed for the management of intermittent (Fig 4) and persistent (Fig 5) NAR.

Review of pharmacotherapy classes for rhinitis

Oral antihistamines. Recommendation 6. *CBS:* We recommend against prescribing a first-generation antihistamine and are in favor of a second-generation antihistamine when prescribing an oral antihistamine for the treatment of AR.

Strength of recommendation: Strong

Certainty of evidence: High

Oral antihistamines are of established benefit in AR. The overall efficacy of first-generation antihistamines (eg, diphenhydramine, hydroxyzine, chlorpheniramine) compared with less sedating or nonsedating second-generation antihistamines (eg, cetirizine and levocetirizine, fexofenadine, loratadine and desloratadine) for the management of AR 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 (eg, 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[274-276] and while driving[277-281] that can exist without subjective awareness of sedation,[282] and the use of first-generation antihistamines has been associated with increased automobile and occupational accidents.[277-281,283] Individual variation exists with respect to development of sedative effects with first-generation antihistamines.[276,284,285] One systematic review of first-generation antihistamines concluded that they induced nonamnestic deficits in attention and information processing.[286] One early study compared chlorpheniramine with placebo and found that drowsiness and dry mouth were greater with chlorpheniramine for the first 2 weeks, but after this time point, doses of chlorpheniramine <24 mg/day, compared with placebo, resulted in no significant difference in subjective drowsiness, dizziness, irritability, or dry mouth over the remaining 6 weeks of the study.[287] 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.[288-290] Tolerance to adverse central nervous system effects in an individual may or may not occur with regular daily use.[291] Although bedtime dosing of first-generation oral antihistamines has been suggested as a strategy to avoid daytime sedation, there can be residual central nervous system effects the next day because some agents have a very long terminal elimination half-life (>24 hours for chlorpheniramine).[292] Bedtime administration of first-generation antihistamines undesirably increased the latency to onset of restful rapid eye movement sleep and reduces the duration of rapid eye movement sleep.[291,293]

Beyond concerns about subjectively perceived side effects, among the anticholinergic side effects more recently reported in association with first-generation antihistamines is an associated higher risk of dementia. A 2015 US prospective population-based cohort study suggested a link between higher cumulative use of strong anticholinergics and the risk of developing dementia, with over 70% being diagnosed with Alzheimer's disease.[294] 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 for 1 to 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).[294] A longitudinal study showed that the use of anticholinergics in the elderly was associated with both reduced immediate recall and reduced executive functioning, which 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.[295] These findings further support use of second-generation antihistamines over first-generation antihistamines for AR.

Use of first-generation antihistamines in the treatment of NAR

Patients with NAR and AR experience similar symptoms including nasal congestion, postnasal drainage and rhinorrhea although through different mechanistic pathways.[296] Responses to various treatments in NAR and AR may vary.[297] A major symptom of patients with NAR that is frequently not well controlled despite combination topical nose sprays with anticholinergic activity is postnasal drainage.[296] There are no DBPC trials evaluating the therapeutic efficacy and safety of first-generation oral antihistamines such as chlorpheniramine maleate for the treatment of NAR/VMR. In a risk/benefit assessment, mindful of (1) the considerable concerns about safety of first-generation antihistamines as reviewed under discussion for Recommendation 6, and (2) recognition that it is not possible in a standard office setting to accurately assess development of some clinical adverse effects from these agents (eg, development of subtle changes in cognition or other potential central nervous system side effects such as decreased reaction time), some clinicians suggest that monitored use of first-generation oral antihistamines as an adjunctive anticholinergic agent may be considered in patients with NAR who have bothersome postnasal 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 postnasal 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,[298] individuals with existing known chronic disorders (dementia, Alzheimer's, benign prostatic hyperplasia) that would be complicated by their use or those working in occupations involving heavy machinery, driving, or flying.

Oral leukotriene receptor antagonists

Recommendation 7. *CBS:* We suggest that the clinician not select the oral leukotriene receptor antagonist (LTRA) montelukast for the initial treatment of AR due to reduced efficacy when compared with that of other agents. Furthermore, serious neuropsychiatric events that may include suicidal thoughts or actions have been reported in some patients taking montelukast. As advised by the FDA, montelukast should be used to treat AR only in patients who are not treated effectively with or cannot tolerate other alternative therapies.

Strength of recommendation: Conditional

Certainty of evidence: Very low

Recommendation 8. *CBS:* We recommend that the clinician not select an oral LTRA for the treatment of NAR.

Strength of recommendation: Conditional

Certainty of evidence: Ungraded as there are no studies.

Note: Unanimous vote in favor by work group and JTFPP.

LTRAs are modestly effective in the treatment of SAR and PAR.[299-302] Multiple systematic reviews have concluded that LTRAs have effectiveness similar to oral antihistamines with loratadine as the usual comparator,[301,303-306] but others find that LTRAs are less effective than antihistamines.[306] LTRAs are less effective than INCS.[301,304-306] Considering that the LTRA montelukast is equally or less effective than oral antihistamines for AR and is less effective than INCS (which would be preferred therapy for more severe AR because of greater effectiveness), clinicians should not routinely offer an LTRA as preferred therapy for patients with AR. Furthermore, as discussed below, serious neuropsychiatric events that may include suicidal thoughts or actions have been reported in some patients taking montelukast. As advised by the FDA, montelukast should be used to treat AR only in patients who are not treated effectively with or cannot tolerate other alternative therapies.[307] In such patients, when considering montelukast, a shared-decision making conversation should be utilized.

The use of an oral LTRA in combination with an oral antihistamine may be more effective than monotherapy with an LTRA (montelukast) for AR, although not all study results are consistent with this finding.[304,308,309] The combination of an oral LTRA and an oral antihistamine is similarly effective as monotherapy with an INCS for AR though it is likely more costly and burdensome to maintain.[310,311]

There is no evidence to support the use of LTRAs in NAR. There is no mechanistic rationale or expert opinion that supports the use of an LTRA in NAR.

Montelukast has been approved down to 6 months of age. It is not associated with somnolence and side effects are uncommon.[312,313] However, there are postmarketing 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.[314-317] Unexpectedly, a worldwide review of Individual Case Safety Reports associated with montelukast determined that completed suicides were reported more frequently for children than for adolescents or the total population.[316] Most studies are low-quality evidence, (eg, 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.[317] 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, compared with placebo, montelukast could result in significant improvements in both conditions and therefore can be considered an option for patients with both conditions.[310,318] However, due to the only modest efficacy and also the potential increased risks of montelukast compared with those of 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 INCS for AR.

Systemic corticosteroids

Recommendation 9. *CBS:* We suggest that for the treatment of very severe or intractable AR, the clinician may consider a short course (5-7 days) of oral corticosteroids.

Strength of recommendation: Conditional

Certainty of evidence: Very low

Recommendation 10. *CBS:* We suggest that for the treatment of very severe or intractable AR, the clinician not prescribe a

depot parenteral corticosteroid for AR due to the potential risks of systemic and local corticosteroid side effects.

Strength of recommendation: Conditional

Certainty of evidence: Low

While most clinicians will use a short course (5-7 days) of oral corticosteroids for severe or intractable AR, depot parenteral corticosteroids may be viewed as attractive because the duration of action of a single injection is 3 weeks or longer and is often adequate to treat an entire allergy season. However, there is concern that depot corticosteroids may lead to a higher risk for adrenal suppression than short courses of short-acting corticosteroids (eg, prednisone) dosed once daily. While head-to-head comparisons of short courses of oral corticosteroids versus single injections of depot corticosteroids have not been completed, studies have shown adrenal suppression following a single intramuscular injection of methylprednisolone acetate for AR.[319,320] The suppression is usually maximal at 72 hours but persists for up to 3 weeks.[319,320] Two systematic reviews looking at adrenal suppression from various administration forms, dosages, duration, and disease states found that while higher doses for longer duration increased the risk of adrenal suppression, there is no method of delivery, dosage, or duration for which the risk of adrenal suppression can be safely excluded.[321,322]

A large retrospective study of Danish National Registries found that in patients with AR, a minimum of 1 depot corticosteroid injection for at least 3 consecutive years was associated with an increased risk of osteoporosis and diabetes, with the largest risk increase seen within the first 2 years of annual use.[323] Although rare, local muscle atrophy and fat necrosis has also been described.[324,325] With such variability in the development of adrenal suppression, diabetes, osteoporosis, local side effects, and other steroid-induced adverse effects from one patient to another, the clinician is advised to always use the lowest dose of corticosteroids for the shortest period of time.

INTRANASAL AGENTS

Intranasal antihistamines

Recommendation 11. *CBS:* We recommend that the clinician offer intranasal antihistamines (INAH) as an initial treatment option for patients with SAR.

Strength of recommendation: Strong

Certainty of evidence: High

Recommendation 12. *CBS:* We recommend that the clinician offer INAH as a first-line monotherapy option for patients with NAR.

Strength of recommendation: Strong

Certainty of evidence: High

Recommendation 13. *CBS:* We recommend that the clinician offer INAH as a first-line option for patients with intermittent AR.

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 work group and JTFPP.

For relief of nasal symptoms of SAR, INAH are equal to or superior to oral antihistamines[326-328] and may benefit patients for whom oral antihistamine treatment fails.[328,329] INAH have a more rapid onset of action than INCS and oral antihistamines do,[326-332] are more effective than oral antihistamines in the control of nasal congestion,[320,327,331] and provide a favorable safety profile. Comparisons of INCS to INAH for reduction of nasal symptoms are conflicting, with some showing equality[333-335] and some showing superiority of INCS.[336] In a systematic review of INCS and INAH, INAH provide comparable relief of allergic eye symptoms.[337] Two INAH, azelastine and olopatadine, are approved by the FDA for the treatment of SAR. Azelastine is also approved for the treatment of PAR and VMR.

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.[338-340] 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.[90] In contrast to azelastine, intranasal olopatadine is a selective H1 receptor antagonist that has also been shown to have some mast cell–inhibitory properties, described with the olopatadine eye drop preparation.[341]

INAH have a rapid onset of action in AR ranging from 15 to 30 minutes, compared with an average of 150 minutes for oral antihistamines.[326-332,338] They have been shown to improve nasal as well as nonnasal AR symptoms and QOL.[330,331,342] Azelastine has also been shown to be clinically effective in controlling symptoms of NAR.[343] 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.[344]

Nineteen percent of patients treated with azelastine in the initial clinical trials reported bitter taste lasting around 30 minutes.[343] Subsequent studies found that 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 with what was reported in the pivotal trials (11.5% and 19.7%, respectively).[345] 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%).[65,346] In contrast to the pivotal SAR studies, somnolence was not an issue for patients with NAR using azelastine with sucralose compared with those using placebo (3.2% vs 1.0%).[338,340,343] While the initial clinical trials using a larger dose reported somnolence in around 11%,[347] more recent studies have found rates of 0.4% to 3%, which were equal or only slightly greater than in placebo groups.[346,348-351] 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%).[352-355]

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.[356] Moreover, their side effect profiles were comparable except for bitter taste, which was more pronounced for azelastine.[356] A randomized, double-blind, parallel-group, multicenter noninferiority study showed no significant difference between intranasal olopatadine and intranasal azelastine in controlling nasal symptoms in patients with nonallergic VMR.[357] No significant differences were observed for adverse events, including taste, or treatment satisfaction between treatment groups.[357] While taste aversion has been demonstrated to all INAH, 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 INAH.

Intranasal corticosteroids

Recommendation 14. *CBS:* We recommend that when choosing monotherapy for persistent AR, INCS be the preferred medication.

Strength of recommendation: Strong

Certainty of evidence: High

Recommendation 15. *GRADE:*[174] We recommend that for the initial treatment of moderate/severe SAR in patients 15 years of age and older, the clinician use an INCS over an LTRA. (Also see Recommendation 7.)

Strength of the recommendation: Strong

Certainty of evidence: High

INCS remain the most effective monotherapy for AR and are therefore recommended as preferred monotherapy for moderate/severe AR that have negative impact on QOL.[1,310,311,358-360] More recent guidelines continue to support this recommendation.[175,361] 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.[1,362,363]

The sensory attributes of INCS (aftertaste, nose runout, throat rundown, and smell) play an important role in patient preference and adherence to therapy.[364] To address some of these concerns, nonaqueous intranasal preparations with hydrofluoroalkane aerosol are now available for the treatment of AR in the United States.[365-367]

When given in recommended doses, INCS are not generally associated with clinically significant systemic side effects.[1] They have not been shown to affect the hypothalamic–pituitary–adrenal 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).[368] 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 INCS have been published;[369] however, adequately powered, blinded studies have not confirmed this adverse effect.[1,370] 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 AR using INCS.[371]

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.[1,175] Nasal bleeding with long-term use of topical nasal corticosteroids may approach 28%.[370] The epistaxis reported from INCS can be worsened by the use of anticoagulant agents.[372-375]

Septal perforations, although rare, have been reported.[1,175] Biopsy specimens from the nasal mucosa of patients with perennial rhinitis who have been treated with INCS continuously for 1 to 5 years showed no evidence of atrophy.[1,175]

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 NAR 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.[90,91,296,376-381] Clinical trials investigating the therapeutic benefit of capsaicin on patients with AR did not find a significant effect in reducing nasal hyperreactivity or in improving rhinorrhea.[382] Cochrane analysis for AR found only 1 small trial where intranasal capsaicin had a therapeutic benefit.[383] 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.[384] When used to treat NAR and VMR compared with placebo therapies, some studies have described significant therapeutic efficacy and safety of chronic usage of local capsaicin formulations.[385-390] Because all of these trials used different study designs and dosing regimens, the ability to compare primary endpoints is significantly limited.[385,387,388,391,392] 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).[393] Future well-conducted, large, randomized controlled trials are required to further assess the effectiveness of capsaicin using different concentrations and in patients with NAR who have mild, moderate, and severe symptoms.

Intranasal decongestants

Recommendation 16. *CBS:* 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

Recommendation 17. *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.

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 work group and JTFPP.

Intranasal decongestants, such as 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.[394,395] Oxymetazoline and xylometazoline cause similar decongestive effects with statistically significant beneficial changes in nasal resistance, nasal airflow, and nasal cross-sectional areas that provide clinically meaningful improvement in nasal congestion.[396] On average, the effect of oxymetazoline begins within 30 seconds.[397] Xylometazoline was found to have superior efficacy for nasal

decongestion compared with INCS in a 28-day AR study.[398] However, intranasal decongestants are not routinely recommended for continuous use because of the potential development of alpha-receptor tachyphylaxis and subsequent rhinitis medicamentosa.[399] 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.[399-404] 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.

Concomitant administration of intranasal decongestants and corticosteroids

Recent placebo-controlled studies of PAR and SAR demonstrated that concurrent administration of INCS and intranasal decongestants provided additional efficacy both subjectively in rapidity of onset compared with the corticosteroid alone and in magnitude of nasal congestion symptom score improvement compared with 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.[405,406] (Also see Recommendation 24 for related recommendation about combined use of intranasal decongestants and corticosteroids.)

Safety concerns about use of intranasal decongestants in pregnancy are discussed in the later section on rhinitis in pregnancy.

Oral decongestants

Recommendation 18. *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.

Strength of recommendation: Conditional

Certainty of evidence: Low

Recommendation 19. *CBS:* We recommend that oral decongestants be avoided during the first trimester of pregnancy.

Strength of recommendation: Strong

Certainty of evidence: 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.[407] For the management of concomitant SAR and mild/moderate asthma, the combination of an oral decongestant and a second-generation oral antihistamine, compared with placebo, significantly reduced both rhinitis and asthma symptoms.[408]

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.[409] 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 40 mg.[410-412]

Pseudoephedrine can result in adverse effects such as insomnia, loss of appetite, irritability, and palpitations.[413] 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 patients who are normotensive and those 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.[414] However, because of the variation in patient response, patients receiving oral decongestants should be followed for changes in blood pressure. Because of the potential for drug interactions, oral decongestants should be avoided in patients taking monoamine oxidase inhibitors,[415] used for psychiatric disorders and Parkinson's disease. 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.[407]

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.[416-418] 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.[419] 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

Recommendation 20. *CBS:* We suggest that in patients with PAR and NAR 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 PAR (0.03%) and NAR (0.03%), as well as for the common cold (0.06%).[420-422] 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.[423] Rhinorrhea is significantly reduced in chronic perennial rhinitis, VMR, gustatory rhinorrhea, and cold-induced rhinorrhea (eg, skiers nose), but with no significant effect on congestion or sneezing.[420,424-428] When ipratropium bromide was administered prior to nasal methacholine challenge in patients with AR and NAR there was reduced rhinorrhea and sneezing but there was no significant effect on airway resistance.[422,429] Rhinorrhea was significantly reduced not only in cold air exposure but also following ingestion of hot soup, leading the investigators to suggest that the nasal discharge is reflex-mediated.[430] In PAR, ipratropium bromide was effective in reducing rhinorrhea for 1 year when used on a continuous basis.[427] 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.[427,428] 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

Recommendation 21. *CBS:* We suggest that intranasal cromolyn be offered as an option to be taken just prior to allergen exposure to reduce symptoms of AR from episodic allergen exposures.

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 AR.[431,432] Intranasal administration of cromolyn sodium, compared with placebo, improves symptoms of SAR.[433-435] In PAR, with marked skin test responses,[436] benefit has been found in some but not all studies of patients with PAR.[437] Intranasal cromolyn may reduce nasal eosinophils in patients with AR.[438] Ten milligrams of intranasal cromolyn inhibited allergen-induced nasal airway resistance in 80% and 50% of subjects at 4 and 8 hours, respectively, after the administration of cromolyn, suggesting efficacy for around 6 hours.[439] A large 2-week multicenter, randomized, DBPC, 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.[431,435]

Nasal cromolyn administered just before allergen exposure can reduce development of symptoms of AR.[440-442] Therefore, nasal cromolyn can be useful in short-term prevention of development of episodic AR symptoms if administered just prior to anticipated 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.[431,435,443] However, there are a very limited number of cases suggesting the possibility of immediate, possibly IgE-mediated, reactions to disodium cromoglycate.[444,445]

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.[171] A placebo-controlled trial of intranasal cromolyn showed no benefit in VMR, although some anecdotal cases suggest benefit in isolated individuals with VMR.[446] Intranasal cromolyn was found to have no benefit on nasal polyps.[447]

Intranasal cromolyn has similar efficacy to oral antihistamines in the treatment of AR. However, intranasal cromolyn reduced nasal eosinophils in comparison to oral antihistamines.[438] Intranasal cromolyn may be less efficacious than levocabastine nasal spray in SAR.[448] Intranasal cromolyn is less efficacious than intranasal steroid sprays in SAR.[449]

Nasal saline

Nasal saline is commonly used as a treatment for rhinitis and rhinosinusitis in both children and adults. Nasal saline can be beneficial for moisturizing dry nasal passages and clearing out mucus. The preferred method of delivery—nose spray, bottle, pump, irrigation, or nebulizer; the volume; whether isotonic or hypertonic; and the dose frequency have not been established. The use of topical saline is associated with minimal side effects, such as burning, irritation, and nausea; has low cost; and has overall good patient acceptance.[450,451]

There is a risk of transmission of bacteria and parasites including development of fatal primary amebic meningoencephalitis from using tap water contaminated with *Naegleria fowleri.* The Centers for Disease Control and Prevention and FDA recommend that if tap water is used to prepare saline for nasal irrigation, water should be boiled for 1 to 5 minutes before cooling and use.[452,453]

A systematic review of studies on nasal sinus irrigation concluded that when performed regularly over a limited period of up to 7 weeks, there was a positive effect on all investigated outcome parameters in adults and children with AR.[454] A 2018 Cochrane review on saline irrigation for AR concluded that it may reduce patient-reported disease severity compared with no saline irrigation at up to 3 months in both adults and children with AR.[455] However, saline nasal irrigation alone is less effective than INCS alone for AR in children.[456,457]

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 on both scientific evidence and expert opinion. The algorithms were developed to assist the clinician in selecting the preferred monotherapy and determining when to consider specific agents for combination therapy.

INCS and INAH combined

Recommendation 22. *GRADE:*[174] We suggest that the clinician consider the combination of an INCS and an INAH for the initial treatment of moderate/severe nasal symptoms of SAR in patients age ≥12 years.

Strength of the recommendation: Conditional

Certainty of evidence: High

Recommendation 23. *CBS:* We suggest that the clinician consider the combination of an INCS and an INAH for moderate/severe SAR and PAR that is resistant to pharmacologic monotherapy.

Strength of recommendation: Conditional

Certainty of evidence: Moderate

Recommendation 24. *CBS:* We suggest that the clinician consider the combination of an INCS and an INAH for moderate/severe NAR that is resistant to pharmacologic monotherapy.

Strength of recommendation: Conditional

Certainty of evidence: Low

DBPC trials in AR have demonstrated that the combination of an INCS and INAH is more effective at reducing symptoms of AR and has a faster onset of action than the individual components do.[174] This has been demonstrated in 5 DBPC trials with a fixed combination of intranasal azelastine and fluticasone propionate in a single device (MP29-02, Dymista; Mylan, Canonsburg, Pa), in patients with moderate/severe SAR, ages ≥12 years[458-460] and 1 DBPC trial showed its superiority over

placebo in children 6 to 11 years old.[461] Its superior efficacy in reducing the PM 12 hour-reflective (daytime) total nasal symptom score over intranasal fluticasone was also demonstrated over the whole range of a 12-month randomized, open-label trial in patients with chronic rhinitis (PAR and NAR), although no NAR-subgroup analysis was presented.[462] A 6-week randomized trial of 162 patients with NAR demonstrated significantly greater ($P < .01$) reduction in nasal obstruction score with the combination of an INCS and an INAH compared with monotherapy with an INCS.[463]

However, as reviewed in the 2017 rhinitis GRADE document,[174] all these studies were designed to compare the use of combination therapy versus monotherapy as initial treatment of SAR and not as add-on therapy. 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 2 active substances, fluticasone propionate and azelastine. Slightly higher fluticasone area under the curve (AUC) $_{0\text{-tlast}}$ and C_{max} have been reported compared with those of commercially available intranasal fluticasone propionate.[464] Of note are the safety data reported from the above-mentioned 12-month trial, with MP29-02 1 spray per nostril twice a day, in which 8 of 404 patients were discontinued at 6 months, because of an adverse event (3 decreased serum cortisol, 3 cataract, 2 acne) versus 1 of 207 in the commercially available fluticasone group (cataract).[462,465] Other additional combination devices, currently not FDA-approved, including those that contain different INCS and INAH, have been studied.[466-472] Several of these studies confirm additive benefit over intranasal monotherapies.

INCS with intranasal ipratropium for control of rhinorrhea

Recommendation 25. *CBS:* We suggest that for patients taking an INCS 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 AR and NAR.[473]

INCS with intranasal decongestant

Recommendation 26. *CBS:* We suggest that patients with persistent nasal congestion unresponsive to an INCS or to an INCS/INAH 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 INCS and intranasal decongestants provides greater reduction in nasal congestion symptoms and greater improvement in nasal volume than that of an intranasal decongestant alone.[405,406] Furthermore, the combination tended to reduce nasal congestion faster than the INCS 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.[405,406] In addition, in a small study where 19 healthy subjects received intranasal decongestant for 2 weeks followed by the addition of INCS for 3 days, oxymetazoline-induced tachyphylaxis and rebound congestion were reversed by intranasal fluticasone.[474] 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 with placebo without the development of rhinitis medicamentosa.[475] A *post hoc* analysis demonstrated that the addition of oxymetazoline afforded significantly greater nasal congestion reduction in the AR compared with in the NAR subgroup.[475] Whereas the combination of an INCS and an INAH 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 AR and significant nasal congestion. At this time, existing evidence is scant and is not sufficient to support the prolonged use of the above-mentioned combination.

Oral antihistamine with oral decongestant

Recommendation 27. *CBS:* We suggest that for patients with AR and nasal congestion uncontrolled with an oral antihistamine, the clinician consider the addition of pseudoephedrine, when tolerated. (See Recommendation 18.)

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 are,[476-478] 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 indicated in Figs 2 and 3, pharmacologic options other than an oral antihistamine with an oral decongestant (eg, INCS or INAH) generally are preferred, but the selection to use an oral antihistamine with an oral decongestant may be made in a shared decision-making discussion. As presented in the rhinitis 2008 practice parameter,[409] pseudoephedrine is far superior to other decongestants; however, there are limited antihistamine-pseudoephedrine combinations (eg, 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 (eg, INCS).

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 1 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.[479]

Oral antihistamines with oral LTRAs

Recommendation 28. *CBS:* We suggest that for SAR, the clinician not combine the oral LTRA montelukast with an oral antihistamine for symptoms not controlled with an oral antihistamine. (Also see Recommendation 7.)

Strength of recommendation: Conditional

Certainty of evidence: Moderate

Some studies find the concomitant use of LTRA with various oral antihistamines provide additive benefit in reducing symptoms and improving QOL in patients with SAR,[301,480-484] while others have shown inconclusive or conflicting results, or no benefit over individual medications.[485,486] 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.[487]

Although some studies find that the concomitant administration of an oral LTRA and an oral antihistamine can have an additive effect, this approach is usually less efficacious than administering INCS as monotherapy.[304,305,309,310] 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 AR have coexisting asthma.[301] The combination of montelukast and a second-generation antihistamine may protect against seasonal decrease in some measures of lung function (eg, forced expiratory flow at 25% to 75% of forced vital capacity (FEF_{25-75}) in patients with AR.[488] 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.[489]

COMBINATION THERAPIES THAT HAVE NOT BEEN SHOWN TO BE CONVINCINGLY SUPERIOR TO MONOTHERAPY

Oral antihistamine with INCS

Recommendation 29. *GRADE:*[174] 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 with symptoms of SAR.

Strength of the recommendation: Strong

Certainty of evidence: Moderate

Recommendation 30. *CBS:* We suggest that the clinician not prescribe the combination of an oral antihistamine and an INCS in preference to monotherapy with an intranasal steroid in all patients with SAR and PAR.

Strength of recommendation: Conditional

Certainty of evidence: Very low

The evidence, as reviewed in the JTFPP 2017 rhinitis GRADE guideline,[174] looks at the initial use of monotherapy with an INCS or combination therapy of an INCS and an oral antihistamine for SAR in patients ≥12 years of age.[1] That review did not find significant increased symptom relief from the combination compared with relief from INCS 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, which is 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 INCS monotherapy rather than combination therapy.

Oral LTRAs with INCS

Recommendation 31. *CBS:* We suggest against the addition of the oral LTRA montelukast to an INCS for AR, due to the lack of adequate evidence of improved efficacy and concerns for serious neuropsychiatric events from montelukast. (Also see Recommendation 7.)

Strength of recommendation: Conditional

Certainty of evidence: Very low

There is no strong evidence to support use of oral LTRA in addition to an INCS. One study found no further benefit when an oral LTRA was added to an INCS for the treatment of AR.[490] 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.[491] With very weak evidence, suggesting on one hand a possible benefit and on the other no benefit, but with concerns for serious neuropsychiatric events from montelukast, the JTFPP suggests against the use of this combination.

AR pharmacologic treatment algorithms

In making decisions about selection of therapies for AR, we recommend that a clinician use guidance from an algorithm (see Figs 2 and 3) that is based on multiple considerations including relative effectiveness, onset of action, potential for adverse effects, patient preference, cost to patient, symptom severity, and whether a patient has intermittent or persistent AR. The stepwise progression and decision tree is based largely on expert opinion and cannot account for variable patient adherence in real-life experience. 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 on 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 AR. See discussion for each drug class or combination of drug classes for detailed review of data considered.

AR PHARMACOTHERAPY: ONSET OF ACTION

Onset of action for symptom relief may be an important consideration in selection of treatment (see Table VIII). 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 find quicker

TABLE VIII. Onset of action of pharmacological agents for AR

Agent	Study design	Onset of action	Maximal effect	First measure of onset	References for onset	References for peak action
Intranasal steroid/ antihistamine	EEU	5 min (azelastine/fluticasone propionate)	2 wk or greater	5 min	495	333
Intranasal decongestant-oxymetazoline	Peak nasal airflow	<10 min	? within an hour	10 min	496	
INAH	EEU	15 min (azelastine)	1 d to 4 wk	15 min	497,498	331,354
	EEU	30 min (olopatadine)	1 d to 4 wk	30 min	332,498,499	354
Intranasal anticholinergic	Methacholine challenge	15 min (ipratropium)	1 h	15 min	500	500
Oral antihistamine	EEU	30-90 min (desloratadine)		30 min	501	
	EEU	45 min (levocetirizine)		15 min	502	
	EEU	60 min (cetirizine)	1-8 d	15 min	497	503
	EEU	60-75 min (loratadine)	1-8 d	15 min	497,502,504	505
Oral antihistamine with decongestant	Single-dose park setting	30 min (loratadine/PSE)	Unknown	15 min	506	
INCS	EEU	1-6 h (ciclesonide)	2-4 wk	1 h	507,508	509
	EEU	2.5 h (mometasone)	4 wk	30 min	499	510
	EEU	3-8 h (budesonide)	2-4 wk	1 h	472,511	512,513
	2-wk seasonal study	8 h (fluticasone furoate)	2 wk	30 min	514	509,510,513
	Not EEU, park study or other	2-12 h (fluticasone propionate)	2-4 wk	2, 4, 12 h (meta-analysis)	515	512
LTRA	EEU	Within 5 h (montelukast)	By wk 2	5 h	516,517	518
Intranasal mast cell stabilizer	2-wk seasonal study	2 wk (cromolyn)	At least 2 wk	1 wk	435	435,519
Intranasal mast cell stabilizer before allergen exposure	EEU, nasal allergen challenge	Application 1-7 min before allergen exposure	N/A	≥10 min	442	N/A

EEU, Environmental exposure unit.

onset of action than outdoor park challenges do, and traditional field studies do not measure symptom relief until ≥12 hours after commencing treatment.[492-494] One cannot rely on a 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 to 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). 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. INCS 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 to 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 preexposure prophylaxis, treatment of current symptoms requires 1 to 2 weeks of treatment 3 to 4 times per day 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 to 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 VIII[331-333,354,436,442,495-519] 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 preexisting turbinate hypertrophy.

Pharmacotherapy for NAR

Recommendation 32. *CBS:* We suggest that the clinician offer an INCS as a first-line therapy for NAR.

Strength of the recommendation: Conditional

Certainty of evidence: Low to moderate

Recommendation 33. *CBS:* We suggest that the clinician offer an INAH as a first-line therapy for NAR.

Strength of the recommendation: Conditional

Certainty of evidence: Very low

The effectiveness of INCS has been reported in studies that have involved a large number of patients with NAR,[1] especially those with NARES.[353-355] INCS have also been reported to be effective in the treatment of VMR.[1,353,356] 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.[520] There is conflicting clinical research on whether inflammatory NAR responds better to INCS than does noninflammatory NAR.[521,522] A 2019 Cochrane review concluded that it

is unclear whether INCS, compared with placebo, reduce patient-reported disease severity in patients with NAR.[523]

Topical INAH, azelastine and olopatadine, have been shown to reduce symptoms of NAR.[524] Two 3-week multicenter, randomized, DBPC, parallel-group clinical trials (n = 223 study 1; n = 203 study 2) conducted in patients with VMR revealed numerical improvements in total VMR symptom score for azelastine compared with placebo from baseline (mean numerical change 1.54 vs 84, $P = .002$ in study 1; mean numerical change 1.54 vs 0.88, $P = .005$ 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%).[343] 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.[357] In this study, the investigators acknowledge that a limitation of this study was that subjects could have previously been on either study drug and enrolled after a washout period of 7 days.[357] 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 ($P < .05$).[80] 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 QOL.[525]

Less used and non-FDA-approved treatments include topically applied capsaicin (see intranasal capsaicin section), botulinum toxin A[526] injected or topically applied, and vidian neurectomy for severe refractory cases of VMR.[1] Botulinum toxin A[526] applied on the nasal mucosa or injected submucosally has been demonstrated to be effective in reducing hypersecretions and nasal congestion in VMR[527-530] but to a lesser degree than ipratropium bromide.[527] 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.[531]

NAR pharmacologic treatment algorithm

As with AR, we recommend that a clinician use guidance from an algorithm (see Figs 4 and 5) that is based on 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 stepwise progression and decision tree is based largely on expert opinion and cannot account for variable patient adherence in real-life experience. Compared with 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.

AIT and AR

Recommendation 34. *CBS:* We suggest that AIT (subcutaneous or sublingual tablets) be offered through shared decision making to patients with moderate/severe AR who (1) are not controlled with allergen avoidance and/or pharmacotherapy or (2) choose immunotherapy as the preferred method of treatment (eg, 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 comorbid conditions, such as asthma.

Strength of recommendation: Conditional

Certainty of evidence: Moderate

Recommendation 35. *CBS:* We suggest that AIT (subcutaneous or sublingual tablets) be considered for patients with controlled mild and moderate asthma with coexisting AR.

Strength of recommendation: Conditional

Certainty of evidence: Moderate

The basis for the preceding consensus statements about AIT is discussed below. Much more detailed discussion and additional recommendations about AIT are found in recent JTFPP parameter documents on AIT. (See allergyparameters.org.)

AIT is effective for the treatment of AR.[532-534] AIT should be considered for patients with AR 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.[532-534] 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);[535] however, its short-term potential to reduce the risk for the development of asthma in patients with AR could be confirmed.[535]

A previous 2013 Agency for Healthcare Research and Quality meta-analysis reviewed 74 references and concluded that allergen SCIT is effective for reducing symptoms of AR and allergic conjunctivitis in adults (high strength of evidence).[536] Reviewing 60 studies, the investigators concluded that SLIT reduces the symptoms of allergic rhinoconjunctivitis in adults (moderate strength of evidence).[536] 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).[536] A more recent head-to-head double-dummy, double-blind randomized controlled trial with grass pollen SCIT versus tablet SLIT (SLIT-T) showed minor numeric superiority of SCIT over SLIT-T (not significant).[537] 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).[536] The overall body of evidence showed that both SCIT and SLIT were safe and effective treatments for AR (moderate to high strength of evidence.)[536]

Currently in the United States, there are 4 tablet preparations for SLIT (SLIT-T): 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 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.[538]

The following text is a quotation from the JTFPP's 2017 practice parameter on SLIT: "Although alternative regimens and preparations for SLIT have been proposed and may be used off-label in the United States (eg, use of liquid SCIT extract for sublingual delivery or use of specific sublingual drops or other sublingual tablets), these products and formulations do not have FDA approval at present and have not been systematically studied in a rigorous manner in US populations. Use of such products or formulations as prescribed SLIT therapy is currently off-label, at a practitioner's discretion, and is without recommendation for any current particular indication in the US populations. Therefore, off-label use of aqueous SLIT extracts or any other non-FDA approved SLIT formulation is not endorsed."[538]

No head-to-head trials of SLIT administered via tablets (SLIT-T) and SLIT administered via liquid drops (SLIT-D) have been conducted and variations among the trials in scoring of symptoms and medication use preclude direct comparisons of treatment effects.[539] Four meta-analyses have provided indirect comparisons.[532,540-542] The symptom treatment effect was greater for SLIT-T versus SLIT-D in all 4 of the meta-analysis comparisons. The medication use treatment effect of SLIT-T was greater than that of SLIT-D in 2 of the comparisons, was less than SLIT-D in 1 comparison, and was comparable to SLIT-D in 1 comparison.

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 modeling suggested that, when compared with symptomatic treatment, both SCIT and SLIT may become cost-effective at a threshold of $28,000 to $42,000 per QALY after 5 to 6 years of treatment.[543] In the United States, 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.[544]

A systematic review of the safety of SCIT (45 of 74 SCIT studies reported safety data) reviewed that the most common adverse effects, reported by 5% to 58% of patients were mild, local reactions.[536] 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.[536] The same study reported 13 anaphylactic reactions, but no deaths.[536] A recent survey of American Academy of Allergy, Asthma, and Immunology and American College of Allergy, Asthma, and Immunology members, using the World Allergy Organization's classification system for systemic reactions (grades 1-4) found an overall stable systemic reaction rate of 0.1% (grades 1-4), 1 per 1 million allergy injections had grade 4 (most severe) reactions, and 1 fatality per 23.3 million allergy injections.[545]

There is insufficient evidence to determine the efficacy or safety of SCIT in select subpopulations, such as 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 AIT, 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.[534] Certified allergists' experience in large groups of such patients has been reported.[546] Limited evidence suggests that SCIT may be more beneficial in patients with mild asthma than in those with severe asthma.[545]

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.[534] Discordant data about a decrease in the risk of developing asthma and new sensitizations has already been commented on above.[533]

When clinically indicated, the decision to initiate AIT depends on 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. The risks and benefits of administration of AIT with patients who are concurrently taking beta-adrenergic blocking agents and angiotensin-converting enzyme inhibitors and/or have serious underlying medical conditions needs to be assessed.[546-548] 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.[534] 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 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.[549] At this point, for an individual patient, the decision to continue or discontinue treatment should be based on the severity of disease, benefits sustained from treatment, and convenience of treatment.

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

Recommendation 36. *CBS:* We cannot make a recommendation for or against the use of acupuncture for the treatment of AR.

Strength of recommendation: N/A

Certainty of evidence: Ungraded due to lack of adequate studies.

Developed in China 5000 years ago, acupuncture is among 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. A 2009 systematic review of randomized trials evaluated the effectiveness of acupuncture in preventing and treating allergic rhinitis.[550] Compared to sham acupuncture, only 1 of 4 SAR trials found acupuncture to be effective for reducing symptoms.[550] For PAR, 2 of 4 trials demonstrated symptom improvement. The investigators concluded that the evidence for acupuncture is mixed and larger well-controlled studies are needed.

A more recent systematic review and meta-analysis of acupuncture for AR treatment included publications in both English and Chinese languages and identified 13 papers (of 174) that met inclusion criteria.[551] 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 QOL measures. Compared with control treatment, acupuncture led to significant reductions in nasal symptoms, intake of relief medications, and sIgE levels. There was a trend in favor of active therapy in ameliorating QOL measures. Another systematic review evaluated alternative health practices in both English and Chinese literature and identified 20 (of 1460) trials that met inclusion criteria and involved 2438 participants with AR where alternative health practices were compared with placebo or Western medicine.[552] In general, the analysis showed that alternative health practices were superior to placebo and not different from Western medicine in control of symptoms and QOL.

A randomized controlled trial with 12 sessions of acupuncture over 4 weeks in Australian patients with SAR showed improvements in symptom scores and QOL compared to sham acupuncture.[553] An accompanying editorial questioned the clinical significance of these findings though, as only selected symptom scores of sneezing and itching were improved.[554] In the largest and highest quality multicenter study, 422 patients allergic to birch and grass were randomized to 12 real or sham acupuncture sessions over 8 weeks. There was an improvement in QOL scores and antihistamine use, but these did not meet predefined levels for clinical significance.[555] 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.[556]

In conclusion, the results of acupuncture for AR 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

Recommendation 37. *CBS:* We cannot make a recommendation for or against the use of specific herbal products for the treatment of AR.

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 (of 1244 records) with 2309 participants with AR.[557] Control groups included placebo, pharmacotherapy, and the combination of CHM and pharmacotherapy, and the treatment periods ranged from 2 to 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 with 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 with pharmacotherapy alone. Reported adverse events were mild and transient. Another review analyzed CHM in PAR and identified 7 randomized controlled trials (of 266 studies) including 533 patients treated between 2 weeks and 3 months.[558] Compared with placebo, CHM significantly reduced nasal symptoms with a moderate side effect profile that 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 QOL comparably with a nonsedating antihistamine.[559] A proposed mechanism of action for *P hybridus* 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.[559] Studies of 3 Chinese herbal preparations showed some positive results in symptom scores; however, in one study only sneezing was significant.[559] Furthermore, another study reported that it required 5 weeks of herbal treatment to reach statistical significance.[559] The investigators state there is moderately strong evidence to support the use of butterbur but that for Chinese herbal products independent replication is necessary.[559] More recently, a 2012 meta-analysis of 7 trials showed an improvement in symptom scores with traditional CHM,[558] but in a 2018 meta-analysis of 11 trials, there was improvement in QOL but not in symptom scores.[560]

The 2012 National Health Interview Survey showed 34% of US adults used complementary health approaches, including herbal medicines, in the previous year.[561] Physicians need to question patients on their use of these products as they can have toxicity and drug-herb interactions. The National Institutes of Health have a webpage devoted to butterbur stating that raw, unprocessed butterbur plant contains pyrrolizidine alkaloids, which can cause liver injury, and recommending that only products certified pyrrolizidine alkaloids–free should be used. There is potential for allergic reactions to butterbur in patients sensitized to ragweed, chrysanthemums, marigolds, and daisies.[562] 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.

SUBPOPULATIONS WITH RHINITIS

Pediatric patients and rhinitis

Rhinitis in children shares most of the pathophysiologic, clinical, diagnostic, and therapeutic characteristics observed in adults. The most frequent comorbidities of AR in children are allergic conjunctivitis, asthma, and atopic dermatitis.[21,563] AR is

unusual below 2 years of age. Infectious rhinitis is discussed in the earlier section on that topic. Nonallergic, noninfectious rhinitis in children generally presents with chronic nasal symptoms. In addition to more common symptoms and signs of rhinitis such as nasal obstruction, rhinorrhea (anterior or posterior), sneezing, and itching, children with rhinitis may present with snorting, throat clearing, cough, gaping mouth, eye rubbing, and dark circles under the eyes. Physical exam findings are further reviewed in Table VI. As discussed in the section on differential diagnosis, in infants and young children, nasal congestion or obstruction can result from structural problems, such as cleft palate and AH, or from functional processes, such as laryngopharyngeal reflux. Chronic mucopurulent drainage may suggest infectious rhinosinusitis. Purulent drainage, particularly if unilateral, bloody, or persistent, may result from an intranasal foreign body. The "allergic march" is a progressive natural history of atopic disease that may begin in infancy and early childhood with atopic dermatitis and food allergy, followed by AR and atopic asthma in older childhood and adolescence.

The therapeutic approach to treating children with rhinitis is similar to that of adults and includes allergen avoidance, AIT in appropriate cases (see Receommendations 34 and 35) for AR, and pharmacotherapy. Most pharmacologic treatments for AR are approved for children down to age 5 years, and many down to age 2 years or even younger. Special care must be given to dosage adjustment, adverse effects, and long-term safety. Controlled trials or real-world experience that have examined the comparative effectiveness, acceptance, and adherence of medication options are more limited in children than in adults. That said, there are data that adherence to nasal spray use may be a greater issue in younger children.[564] Historically there has been a shift in guidelines from recommending that oral antihistamines generally should be the first-line agents for treatment of AR in children to a broader approach that positions other agents including INCS as first-line considerations in shared decision making with patients and families.[565] Further discussion of considerations in children for different medication options are discussed within the recommendation discussion for each respective drug class.

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, with >40% of these patients rating their rhinitis as moderate/severe, and almost 70% experiencing ocular symptoms.[70] AR is the most common type of rhinitis in the elderly but is less frequent than its incidence in younger age groups. In addition to AR, 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,[566] angiotensin-converting enzyme inhibitors,[148,567-569] and possibly beta-adrenergic inhibitors[570] and phosphodiesterase inhibitors[571] can induce symptoms of rhinitis. (See earlier section on drug-induced rhinitis.)

Physiological changes due to aging result in alterations in neural, histologic, mucosal, and olfactory status that have direct impacts on the functioning of the nose.[572] 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.[573,574] 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.[575-578] Structural changes due to aging can also reduce nasal cartilage elasticity and tip support that can further interfere with nasal airflow.[578] Age-related reduced blood flow to the nasal mucosa, basement membrane thickening, and epithelial atrophy have also been described.[579,580] 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.[578]

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.[581] Second-generation oral antihistamines, INAH, leukotriene inhibitors, and INCS are effective and well tolerated in the elderly when used for an appropriate indication, but controlled data comparing efficacy in this population are lacking.[576] 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.[582] As noted below in the oral antihistamines section, a 2015 US 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.

Rhinitis in pregnancy

In summary, since the release of the 2008 rhinitis updated practice parameter,[1] interval information has become 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 the product information section for risk summary, clinical considerations, and data headers under the pregnancy subsection. Medications approved after June 2001 will be gradually phased in. Most AR medications were approved prior to this and will retain the old A through X classifications. 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,[1] budesonide carries the old B FDA classification based on the large Swedish birth registries that 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 INCS 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,[583] although a chance finding cannot be ruled out.

Intranasal antihistamines. There is little data on the safety of INAH 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.[584] 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.[585] A study using the UCB Pharma Patient Safety Database up to February 2015 reaffirmed the safety of cetirizine in pregnancy.[586] A 2013 study using data from a multicenter case-control surveillance program of birth defects in North America did not support previously posited associations between antihistamines, notably diphenhydramine, loratadine, and chlorpheniramine, and major congenital anomalies.[587] Loratadine does not appear to increase the risk of hypospadias in male offspring.[588] A 2014 systematic review found the most safety data for loratadine, including that there is no evidence of increased risk of hypospadias.[589]

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.[590] 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 (relative risk, 2.1-3.2)[591,592] and phenylpropanolamine (relative risk, 10.0)[592] 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 (odds ratio, 8.0), ear defects (odds ratio, 7.8), and pyloric stenosis (odds ratio, 3.2).[590] However, a Swedish prospective study looked at the use of these 2 decongestants during early and late pregnancy in 2474 and 1771 women, respectively, and no teratogenic effects were reported.[593]

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

Based on the low or variable benefit of using decongestants during pregnancy and the potential catastrophic harm of having a birth defect, the work group and the 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 making a recommendation for or against their use during the second and third trimesters 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[1] 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.[594] Other human studies have shown montelukast and other LTRAs (eg, zafirlukast) are not associated with an increased rate of major malformations in offspring.[595-597]

Allergen immunotherapy. As previously stated, subcutaneous immunotherapy should not be started in pregnancy, but may be continued. While no recommendation on SLIT 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.[598]

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