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Phenotypes and endotypes of rhinitis and their impact on management: a PRACTALL report

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Abstract

Rhinitis is an umbrella term that encompasses many different subtypes, several of which still elude complete characterization. The concept of phenotyping, being the definition of disease subtypes on the basis of clinical presentation, has been well established in the last decade. Classification of rhinitis entities on the basis of phenotypes has facilitated their characterization and has helped practicing clinicians to efficiently approach rhinitis patients. Recently, the concept of endotypes, that is, the definition of disease subtypes on the basis of underlying pathophysiology, has emerged. Phenotypes/endotypes are dynamic, overlapping, and may evolve into one another, thus rendering clear-cut definitions difficult. Nevertheless, a phenotype-/endotype-based classification approach could lead toward the application of stratified and personalized medicine in the rhinitis field. In this PRACTALL document, rhinitis phenotypes and endotypes are described, and rhinitis diagnosis and management approaches focusing on those phenotypes/endotypes are presented and discussed. We emphasize the concept of control-based management, which transcends all rhinitis subtypes.

Rhinitis is an umbrella term used to describe nasal symptoms such as nasal congestion/obstruction, rhinorrhea, sneezing, and pruritus resulting from inflammation ('itis') and/or dysfunction of the nasal mucosa. Rhinitis is one of the most common medical conditions, with significant morbidity and a considerable financial burden (1). Rhinitis constitutes a risk factor for asthma and is associated with chronic conditions such as rhinosinusitis (2). Besides airway symptoms, the general impact of rhinitis such as sleep impairment, decreased work productivity and school performance, behavioral deviation, and psychological impairment should not be underestimated (3, 4). Different forms of rhinitis are associated with a significant burden. Patients suffering from severe rhinitis experience significant impairment of their quality of life. A recent report suggests that AR is a risk factor for traffic safety (5).

Rhinitis can be the result of diverse aetiologies, most commonly infections and immediate-type allergic responses, but also other triggers including irritants, medications, hormonal imbalance, and neuronal dysfunction. Rhinitis is classically divided into 3 major clinical phenotypes: allergic rhinitis (AR), infectious rhinitis, and nonallergic, noninfectious rhinitis (NAR) (6), with the possibility of a combined (mixed)

presentation in some patients (7, 8). In addition to the concepts of *phenotype*, that is, grouping based on distinct clinical patterns, disease classification by *endotype* has recently been proposed, that is, grouping based on distinct mechanistic pathways. Endotype classification has the potential to explain some of the observed variability in both clinical presentation and treatment response. Phenotypes can be dynamic and overlap or may develop into one another. For phenotype characterization, various clinical criteria can be used (age of onset, severity, symptom pattern/frequency, triggers etc.) and increasingly complex unbiased clustering approaches are being developed, but have yet to be applied in rhinitis in contrast to the current situation with asthma (9, 10). The need for performing and optimizing such clustering analyses stems from accumulating evidence, but also some speculation, that each group would be differentially responsive to both available and future treatments.

Another expectation is that practicing physicians who often opt to employ 'empirical' management approaches, not entirely consistent with guidelines (11, 12), will develop better skills in diagnosing and treating these conditions. In this PRACTALL consensus document, experts of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology report the current understanding of rhinitis phenotypes and endotypes, and propose diagnostic and therapeutic algorithms, which take into account the current phenotypic knowledge and may be useful in clinical practice for both primary and specialist cares (Fig. 1). Furthermore, a new disease control-defined paradigm is presented, which is complementary to the ARIA temporal/severity classifications, and may help drive clinical decisions once fully validated (13). Ongoing research will help fine-tune these approaches, leading toward the application of stratified and personalized medicine in this field.

Definitions, classifications, phenotypes, and endotypes of rhinitis

There have been several attempts to define and classify the whole or part of the spectrum of conditions that fall under the rhinitis umbrella (6, 7, 14, 15). Unfortunately, the terminology and classifications we use show inconsistencies in medical literature, resulting in challenges in research communication or clinical practice. For instance, the term rhinitis implies inflammation, but some rhinitis phenotypes are devoid of an influx of inflammatory cells (15). Furthermore, allergic rhinitis may have, according to different reports (16, 17), both an IgE and a non-IgE component. In addition, the definition of allergic rhinitis implies a causal role of specific allergen exposure, but fails to address the cases where IgE sensitization does exist, but does not seem to play a causal role.

The resolution of such issues is beyond the scope of this document. A wide consensus is necessary to commit to one or another classification system, which needs to cover all relevant cases. We hope that this document will contribute one further step toward such a consensus by offering a view on rhinitis phenotypes based on observable characteristics and also on endotypes based on clearly defined mechanisms.

Phenotypes can be described on the basis of disease severity (mild, moderate/severe, severe combined upper airway disease—SCUAD (18)), disease duration (acute or chronic, intermittent or persistent (17)), temporal pattern (seasonal or perennial), predominant symptom ('runners' vs 'blockers' (19)), disease control (controlled or uncontrolled (20)), apparent trigger (allergen, infectious agent, drug, etc. (21–23)), and response to specific treatment (steroid responsive or unresponsive (24)). Additional phenotypes may be based on common comorbidities (respiratory allergy, rhinoconjunctivitis) that would define allergic rhinitis and asthma in the same patients. In some cases, phenotypes can be identical to certain endotypes, when definition is based on pathology (nonallergic rhinitis with eosinophilia syndrome—NARES,) or pathophysiology (allergic rhinitis), for which there can be corresponding biomarkers.

Below we describe a number of relatively well-defined phenotypes and, wherever possible, their potential association with endotypes. It is important to note that some of these phenotypes overlap and that until we are able to identify all endotypes that result in a particular phenotype, this problem will continue to exist.

Infectious rhinitis

Most infectious rhinitis is viral, acute, and self-limiting, also called 'common cold' (25, 26); it is, however, sometimes complicated by secondary bacterial superinfection (27). Several conditions, including the presence of a foreign body or septal perforation, and/or nose picking, may predispose to prolonged infectious rhinitis, often of bacterial etiology.

Another form of infectious rhinitis is *fungal rhinosinusitis,* an entity that consists of numerous subtypes including *invasive (a*cute invasive, granulomatous invasive, and chronic invasive) and *noninvasive* forms (saprophytic fungal infestation, fungal ball, and eosinophilic fungal rhinosinusitis including allergic fungal rhinosinusitis)(28).

Chronic rhinosinusitis

The *chronic* rhinosinusitis phenotype requires persistence of a specific set of symptoms for at least 12 weeks and is further classified into chronic rhinosinusitis *without* (CRSsNP) or *with* nasal polyps (CRSwNP) (26). Some evidence suggests that a bacterial superantigen response to chronic infection (primarily with *S. aureus*) may underlie some forms of chronic rhinosinusitis, constituting an endotype of the disease (29–32). A potential role of biofilms of *S. aureus* in the pathogenesis of CRS is currently under investigation (33). Some additional interesting hypotheses on CRS pathogenesis include the possibility of primary defective epithelial barrier (34, 35) as well as autoimmunity (36).

Allergic rhinitis

In its strict sense, allergic rhinitis (AR) is an inflammatory condition caused by an IgE-mediated response to environmental allergens such as pollens, dust mites, cockroaches,

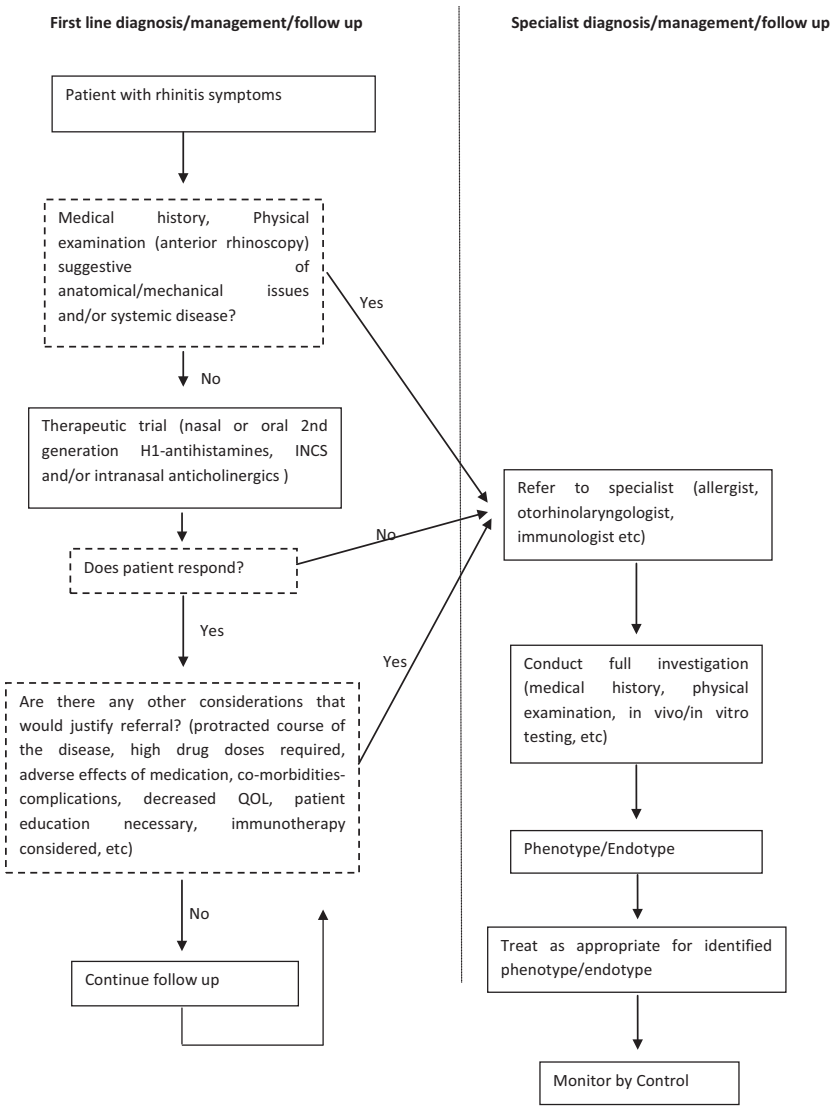

Figure 1 Simple algorithm for rhinitis management in primary and specialist care. The majority of rhinitis patients will be managed in the community; an effective mechanism for directing the right patient to the specialist is necessary.

animal dander, molds, and occupational allergens (37). Its pathophysiology has been described in detail and understood better than any other rhinitis phenotype/endotype (37–41). Subphenotypes of AR include the traditional 'seasonal' and 'perennial' groups denoting temporal patterns, but also symptomatic sensitization to the respective seasonal or perennial allergens (8, 21). The ARIA classification by symptom duration (intermittent or persistent), as well as by severity according to the effect on quality of life (mild or moderate/severe), has attempted to address AR phenotyping (17, 42–44). The proposed limits for the definition of persistent rhinitis (4 days a week and 4 consecutive weeks a year), although tested in large patient groups (45), are arbitrary and should be understood as suggestions. Both temporal phenotype classifications (seasonal/perennial and intermittent/persistent) have their merits and drawbacks and can be useful in clinical practice. An additional temporal phenotype, 'episodic rhinitis,' is associated with sporadic exposures to the culprit allergen. Additional AR phenotyping could be based on the pattern of sensitization (monosensitized vs polysensitized (46)) or the existence of concurrent asthma. Indeed, the unified airway concept is well documented and there is a strong correlation between the upper and lower respiratory tract allergy symptoms. Thus, the concomitant presence of asthma could affect the course of AR (and vice versa) and could also dictate different treatments for AR (47).

Local allergic rhinitis and NARES

Local *allergic rhinitis* (LAR) has recently been suggested to be a distinct rhinitis endotype characterized by symptoms similar to AR associated with *local* (nasal) allergen-specific

IgE (sIgE), but with no evidence of *systemic* sIgE. Although some studies have proposed that LAR could be an 'early AR' condition (48), a recent study demonstrated that LAR does not evolve to AR after a 5-year follow-up (49). The immunological characteristics of LAR are a localized Th2 inflammatory response, driven by the nasal production of specific IgE (48, 50–53) and nasal accumulation of eosinophils, basophils, mast cells, and $CD3^+/CD4^+$ T cells (51, 52, 54). Similar to AR, LAR can be classified as seasonal, perennial, intermittent, persistent and mild, and moderate/severe (48). More studies are needed to evaluate its underlying mechanisms and confirm its prevalence in different countries. Patients respond to nasal corticosteroids and oral antihistamines, and a recent study using specific immunotherapy showed promising results (55). Given the presence of eosinophilia in the nose without other signs of infection or systemic IgE sensitisation, it cannot be excluded that LAR may be identical or overlap with the nonallergic rhinitis with eosinophilia syndrome (NARES), which currently tends to be less favored in the literature (7).

Nonallergic rhinitis

Noninfectious, nonallergic rhinitis (NAR) is a heterogeneous group of nasal conditions with rhinitis symptoms. The diagnosis is made by history and by clinical exclusion of an endonasal infection and signs of allergic sensitization (56, 57). The different criteria employed for classification of its subtypes and the differing terminology across studies have led to substantial obstacles in conducting reliable epidemiologic research, but usually around half of the adult rhinitis patients (20–70%) are considered to have NAR (58–60).

At least 6 subphenotypes can be discerned within the context of NAR: drug-induced rhinitis, gustatory rhinitis, hormone-induced rhinitis, rhinitis of the elderly, atrophic rhinitis, and idiopathic rhinitis (61). The latter is the most prevalent subtype of NAR and has been known under numerous names over the years (56, 61): idiopathic rhinitis (IR) (62), nonallergic, noninfectious perennial rhinitis (NANIPER (63)), intrinsic rhinitis (64), vasomotor rhinitis (VMR) (65), and, as recently proposed, nonallergic rhinopathy (7). These subphenotypes are discussed below:

Idiopathic Rhinitis (vasomotor rhinitis)

Idiopathic rhinitis (IR) is the most prevalent NAR subphenotype (62), but is still a diagnosis of exclusion (58, 62, 66) and ongoing research is required to define specific endotypes with corresponding usable biomarkers. Its prevalence is difficult to estimate due to inconsistent terminology, but may represent as many as 70% of NAR cases (56, 58, 61). Several investigators have proposed that this is a disorder of the nonadrenergic, noncholinergic (NANC) or peptidergic neural system (67, 68), with inconsistent literature data on the concomitant inflammatory component (50, 69). Nasal symptoms may be triggered by a variety of stimuli (episodic phenotype (59, 60, 70)) which include tobacco smoke, odors, changes in climate/barometric pressure/temperature/relative humidity, automobile emission fumes, nonspecific irritants, and alcohol (21, 23, 62, 71). Nasal symptoms may also be persistent/perennial with no clearly identifiable triggers (21–23) and no deterioration upon exposure to typical IR precipitators (7). Subphenotyping IR on the basis of triggers has been attempted (such as *irritant-sensitive* and *weather/temperature-sensitive*), albeit due to the sheer number of triggers the value of such a classification is uncertain (23, 70). Nevertheless, the concept of *irritant-induced* rhinitis may be seen as an umbrella phenotype including not only an IR subphenotype, but also overlapping with occupational rhinitis phenotypes as well as other rhinitis entities. Overall, IR probably encompasses a number of additional subphenotypes and endotypes and there is an urgent need for systematic research to untangle this entity (72). Given the fact that the majority of the patients with idiopathic rhinitis and allergic rhinitis present with nasal hyper-reactivity (70), the presence of hyper-reactivity does not discriminate between IR and AR.

Hormonal rhinitis

Hormonal rhinitis can be further subphenotyped in rhinitis of pregnancy and menstrual cycle-associated rhinitis (7, 73). Raised levels of estrogen are thought to cause nasal congestion by vascular engorgement (74), although this has yet to be definitely established (22, 74). Other potential endotypes may involve vasodilation by increased beta-estradiol and progesterone, which affect mucosal H1 receptors (75) and eosinophil function (74, 76). Rhinitis of pregnancy is a common condition (7) and is more prevalent among smokers (77). Another subphenotype of 'hormonal rhinitis' which, however, has not been clearly documented (78) may be associated with acromegal*y* due to increased levels of human growth hormone causing nasal mucosal hypertrophy (74, 79). Other suggested phenotypes such as those linked with thyroid pathology have been suggested to exist but rarely occur (14, 37).

Gustatory rhinitis

Foods can provoke rhinitis symptoms as part of a generalized IgE-mediated allergic reaction (80–84). However, they can also cause a distinct nonallergic, noninflammatory rhinitis phenotype, gustatory rhinitis (85). Its symptoms follow ingestion of certain (often hot and spicy) foods (86). Stimulation of the nonadrenergic, noncholinergic, or peptidergic neural systems may be involved, but its response to anticholinergic treatment could also indicate that this entity represents a hyper-reactive state of efferent cholinergic reflexes (80, 85). Gustatory rhinitis is further classified into post-traumatic, postsurgical, cranial nerve neuropathy-associated, and idiopathic endotypes (80, 84). The latter is the most common and is frequent in the general population (80).

Drug-induced rhinitis

Drugs can provoke rhinitis symptoms as part of a generalized IgE-mediated allergic reaction. Otherwise, drug-induced rhinitis can be classified into four subtypes, those related to *systemic* pharmaceutical treatment (*local inflammatory* type, *neurogenic* type, and *idiopathic* type (87)) and *rhinitis medicamentos*a, a distinct phenotype caused by excessive use of

intranasal decongestant sprays (87, 88). The local inflammatory type is commonly caused by aspirin and other NSAIDs (22, 87), and is exemplified by AERD (89), also termed NSAIDs-exacerbated respiratory disease (NERD) (90), and its pathogenesis is currently believed to involve inhibition of cyclooxygenase-1 (COX-1) and subsequent overproduction of cysteinyl leukotrienes (87). Chronic rhinosinusitis with nasal polyps is often seen in patients with AERD (91). *The neurogenic type* is mediated by the vascular effects of alpha- and beta-adrenergic antagonists, which down-regulate the sympathetic tone (clonidine, guanethidine, doxazocin methyldopa, etc.) (22, 87), as well as by phosphodiesterase-5 selective inhibitors (sildenafil, adalafil, vardenafil, etc.) (79, 87, 92). The *idiopathic type* is invoked by several different drug classes (angiotensin-converting enzyme inhibitors (93), calcium channel blockers, antipsychotics (22, 87), etc.), via currently unclear mechanisms (87). Finally, *rhinitis medicamentosa* is caused by the prolonged use of local alpha-adrenergic agonist vasoconstrictors, possibly through the nasal tissue hypoxia and negative neural feedback (7, 61, 94, 95). Concurrent use of intranasal corticosteroids may prevent this problem (96, 97).

Rhinitis of the elderly

Rhinitis of the elderly (senile rhinitis) is clinically characterized by clear rhinorrhea not associated with a specific trigger and is considered to be the result of cholinergic hyper-reactivity. Although the pathophysiology is not clear, age-related changes in connective tissue (such as collagen atrophy and weakening of the septal cartilage) and/or vascular deficiencies (leading to reduced nasal blood flow) could be involved (8, 79, 98).

Atrophic rhinitis

Atrophic rhinitis is classified as *primary* or *secondary* (7), with the former endotype mainly affecting people from areas with warm climates (22, 99). It is characterized by nasal mucosal and glandular atrophy (7) and, commonly, by bacterial colonization (100). The secondary endotype has a similar clinical presentation, but is caused by extensive surgical removal of tissues, trauma, or chronic granulomatous disorders (7, 101).

Occupational rhinitis

Occupational rhinitis may bear characteristics of either or both the allergic and nonallergic rhinitis phenotypes (102). This form emerges due to workplace exposure to airborne agents, whose nature defines further classification into the following variants i. *Nonallergic occupational* rhinitis, which is further subdivided *into irritant-induced* rhinitis (associated with neutrophilic nasal inflammation and believed to be neurogenic (103)) and *corrosive rhinitis* (caused by exposure to a high concentration of toxic chemical gases and entailing diffuse mucosal damage (104)) ii. *Allergic occupational* rhinitis which when caused by high molecular weight agents is IgE-mediated and is characterized by eosinophilic mucosal inflammation (103, 105, 106), whereas when caused by low molecular weight agents may include endotypes that are IgE-mediated or non-IgE-mediated adaptive immune responses (102).

Neurogenic rhinitis endotype

This endotype could constitute an umbrella term encompassing part of idiopathic rhinitis, gustatory rhinitis, and other phenotypes with a strong neurological component. The organs that participate in the generation of the symptoms of rhinitis are under neural control, and all symptoms can occur upon neural stimulation (94). As discussed under the various rhinitis phenotypes, up-regulation of the neural apparatus of the nose presenting as neural hyper-responsiveness can occur as a result of chronic inflammation, as in allergic rhinitis, but also possibly as a result of chronic irritant stimulation or even on an idiopathic basis. Neural hyper-responsiveness may theoretically involve various aspects of the nervous system such as the afferent function of sensory nerve endings, the parasympathetic efferent tone and the magnitude of parasympathetic reflexes (primarily controlling the glands of the nose), and the sympathetic tone (which primarily controls arteriovenous anastomoses and vascular engorgement) and even an element of 'central neural sensitization' (107). An additional aspect of neural hyper-responsiveness may be the release of increased amounts of inflammatory neuropeptides by sensory nerve endings leading to neurogenic inflammation (108). Upregulation of one or more of these pathways may partially underpin AR, IR, gustatory rhinitis, or some forms of occupational rhinitis (109, 110). The involvement of transient receptor potential vanilloid (TRPV) receptors in these mechanisms is currently under investigation (111).

Some phenotypes involving nasal neural hyper-responsiveness can be identified by cold dry air provocation (112, 113), a nasal challenge that stimulates capsaicin-sensitive sensory nerves (109, 114, 115). Such phenotypes could therefore be associated with a distinct, but as of yet an incompletely characterized endotype. A considerable proportion of idiopathic rhinitis may fall under this category (72). We propose that this endotype is referred to as *neurogenic rhinitis*. Ongoing research is required to define potential subphenotypes that are driven by this pathophysiology. Criteria for such characterization could include a positive cold dry air challenge and/or response to treatments such as capsaicin and anticholinergic drugs.

Diagnosis and phenotyping of rhinitis

Although, in most cases, the diagnosis of rhinitis is rather straightforward when based on clinical symptomatology, phenotyping can be challenging. Medical history, physical examination, and some laboratory investigations can guide in this respect.

Medical history

A history of atopy, concurrent allergic disorders, symptoms from the lower respiratory system, and predominance of

sneezing and pruritus support an AR diagnosis (Table 1). LAR shares symptoms and typical temporal patterns with AR (48, 116) and is also often associated with pertinent comorbidities. History findings compatible with NAR may include nasal obstruction and rhinorrhea without itch or sneezing, smoking, hormonal relationship, correlation with use of medication, no correlation with allergen exposure, and no family history of allergies and overuse of nasal decongestants (117, 118). Ocular symptoms are seen as typical of AR; however, a potential role for a recently proposed naso-ocular reflex (119) remains to be investigated. The most common symptom of rhinitis caused by structural/mechanical abnormalities is a sense of congestion, either because of true blockage or because of development of a turbulent flow pattern (37). Quality of life could be assessed in all rhinitis phenotypes. However, phenotyping on the basis of clinical history alone is not recommended, as there is typically considerable overlap (56).

Physical examination

The typical findings of the 'allergic nasal mucosa' together with a history of positive reports to allergen exposure are

Table 1 Diagnostic considerations. Medical history, physical examination, and *in vitro–in vivo* findings for rhinitis phenotypes

	Medical History	Physical examination	*In vitro–in vivo* tests
Allergic rhinitis	• Symptoms: Obstruction, rhinorrhea, sneezing, and pruritus • Seasonal symptoms (58), preponderance of sneezing and pruritus (48) • Family history of atopy (8) • Early onset (< age 20) • Concurrent allergic conjunctivitis (6), atopic dermatitis, asthma (79, 293), food allergy (58), and obstructive sleep apnea syndrome (OSAS) (153–155)	• *Allergic shiners:* dark discolorations of the periorbital skin • *Demie–Morgan lines*: folds of the lower eyelid, • *Allergic crease:* horizontal wrinkle near the tip of the nose • *Gothic arch:* narrowing of the hard palate • Mucosa: pallor, edema, hyperemia, and clear discharge when patient is symptomatic. Possibly unremarkable if asymptomatic	• Skin prick tests (SPTs) with commercial allergen solutions (56) • Serum allergen-specific IgE tests • Nasal smears for eosinophils (> 10%) (not routinely employed and with considerable overlap) (52)
Local allergic rhinitis	• Symptoms: watery rhinorrhea, pruritus, obstruction, and sneezing • Early onset (116) • Family history of atopy • Often associated with conjunctivitis and asthma (51, 52, 294).	• No clinical/endoscopic evidence of rhinosinusitis	• Nasal smears for eosinophils (not routinely employed and with considerable overlap) • Allergen provocation test and/or specific IgE and tryptase in nasal lavage (not routinely employed) (48, 51, 52, 54, 293–298).
Non-allergic rhinitis and infectious rhinosinusitis	• *IR and gustatory rhinitis:* sneezing, pruritus, and ocular involvement uncommon (21, 22, 80, 84, 299) • *CRSwNP and atrophic rhinitis:* Hyposmia/anosmia common (14, 26, 101) • *Chronic rhinosinusitis:* headache and facial pain common (26) • *CRSwNP and IR*: usually adult onset (22, 61, 79, 300) • *Gustatory rhinitis:* may appear at any age (86). • *IR:* more prevalent in women (22, 61) • *Rhinitis of pregnancy:* mainly congestion during the last 6 weeks of pregnancy and up to 2 weeks post-partum (301). • *AERD:* deterioration of symptoms when receiving aspirin or other NSAID, concurrent asthma (89)	• *Atrophic rhinitis:* mucosal atrophy, foetor, crusts, and perceived congestion inconsistent with observed nasal patency (99) • *Chronic Rhinosinusitis:* endoscopic findings of polyps and/or mucopurulent discharge/edema/ mucosal obstruction primarily in middle meatus are a prerequisite for the diagnosis (27) • AERD: endoscopic findings of polyps (89)	• *Chronic rhinosinusitis:* CT findings are a prerequisite for the diagnosis of chronic rhinosinusitis if endoscopic picture is inconclusive (302, 303) • *Atrophic rhinitis and rhinoshinusitis:* objective and subjective olfactory evaluation (14, 101, 304) • *AERD:* nasal/oral aspirin challenges (6, 305)

supportive, albeit not specific (120), for AR (79) (Table 1); anterior rhinoscopy and/or endoscopy should always be performed as it may reveal mucosal and anatomical pathology (e.g., septal pathology, turbinate/adenoid hypertrophy, nasal tumors/trauma/foreign object, polyps, granulomata) and/or findings indicative of a distinct rhinitis phenotype/endotype (Table 1)(121, 122). It remains a clinical challenge to determine what part of the nasal symptoms, such as obstruction, is caused by anatomical abnormalities as opposed to mucosal problems.

In vivo/*in vitro* investigations

Skin prick tests (SPTs) (56) and/or specific IgE tests are important for AR/NAR discrimination (79). Nasal provocations may offer help in cases where phenotyping is difficult. For instance, when IgE tests do not provide a diagnosis in patients with high suspicion of having AR, allergen-specific nasal provocation can be considered, especially before indicating allergen immunotherapy. Nasal allergen challenges could also help identify patients with LAR (52, 123), although diagnostic thresholds are not currently available. Nasal cold dry air challenge may be used to test for neural hyper-responsiveness in cases of NAR—this would indicate the presence of the neurogenic rhinitis endotype (112, 124–127). However, similar to nasal allergen challenges, research is required to establish clear diagnostic cutoffs. Other nasal provocations such as with histamine and methacholine are less useful (112, 124–127). In some forms of occupational rhinitis, provocation with the suspected irritant can offer significant diagnostic help (128). In fact, nasal challenges are considered to be the gold standard in diagnosing occupational rhinitis and are typically performed in a clinical setting that attempts to simulate work environment in a dose-dependent manner, but can be also carried out in the workplace (129).

In summary, the main indications for allergen provocation testing are to demonstrate the causal role of an allergen, to identify the clinically relevant allergen(s) in polysensitized subjects, to evaluate the effects of a treatment, and to assess the role of occupational allergens. However, due to the lack of established diagnostic thresholds, the results are often unclear; hence, these challenges are mainly carried out in specialized centers.

Nasal challenge with aspirin is not an allergen challenge, as an IgE-mediated mechanism is not involved. Nevertheless, it is used to diagnose aspirin hypersensitivity with respiratory manifestations. The nasal challenge with aspirin was introduced later than the oral and bronchial challenges and can be used in patients with severe asthma in whom oral or bronchial aspirin challenges are contraindicated (122).

There is no place for radiologic imaging in the diagnosis of rhinitis. The exclusion of rhinosinusitis, however, can be made on the basis of either a nasal endoscopy or computerized tomographic scanning (CT scan).

Bacteriological analyses of nasal and sinus samples are not recommended for a routine rhinitis and/or rhinosinusitis diagnostic workup, as the clinical relevance of identified microorganisms is often unclear. In patients with nasal obstruction, nasal patency can be evaluated objectively via several methods (peak nasal inspiratory flow, rhinomanometry, acoustic rhinometry, etc.), all of which have intrinsic advantages and disadvantages (79, 122, 130).

Differential diagnosis of rhinitis

Structural/mechanical abnormalities

Anterior septal deviation commonly accompanied by contralateral compensatory turbinate hypertrophy may cause nasal obstruction and is also common in children with cleft palate (6). In infants and young children, adenoidal hypertrophy and pharyngonasal reflux typically manifest with congestion (37, 131), whereas *choanal atresia*, a congenital disorder involving blockage of the nasal passage, can go unnoticed for long, if unilateral (132, 133) (Table 2). Nasal tumors (e.g., midline granulomas (134)) are uncommon (121), but should be considered if symptoms of unilateral obstruction, epistaxis, hyposmia/anosmia, and facial pain are present, as well as in the presence of foul-smelling discharge and an endoscopic picture of necrotic tissue. Nasal polyps are often a cause of mechanical obstruction.

Systemic diseases

Ciliary dysfunction impairs mucous clearance and can manifest early in life as an autosomal recessive disorder (primary) or be caused by viral infections and/or pollutants (secondary) (135, 136) (Table 2). *Cystic fibrosis* is another autosomal recessive disorder that is present at birth and can underpin rhinitis symptoms. Eosinophilic granulomatosis with polyangiitis (EGPA) (formerly known as *Churg–Strauss syndrome)*, an autoimmune multi-organ vasculitis, is characterized by asthma and rhinitis (137), while another form of multi-organ vasculitis, *granulomatosis with polyangiitis (GPA)* (formerly known as Wegener's granulomatosis), commonly manifests with nasal, sinus, and ear symptoms (138). Nasal symptoms underpinned by granulomatous inflammation and amyloid deposition can also occur in *sarcoidosis* and *amyloidosis,* respectively (139, 140). Finally, *relapsing polychondritis* is a rare condition often associated with autoimmune disorders, which typically presents with nasal and ear pain, hearing loss, and arthralgia (141).

Management of rhinitis

Rhinitis management comprises a pharmacological component and a nonpharmacological one, entailing avoidance of disease-triggering factors, patient education, allergen immunotherapy, and occasionally surgical treatment. Management can be stratified on the basis of each patient's discrete phenotype. In this section, we present the therapeutic options that are supported by current evidence for different rhinitis phenotypes. To evaluate treatment out-

Table 2 Rhinitis differential diagnosis

Rhinitis differential diagnosis	
Structural/Mechanical abnormalities	Systemic disease
• **Septal deviation** *unilateral- obstruction, sleep apnea, and epistaxis*	• **Primary ciliary dyskinesia (PCD)** *recurrent respiratory infections, Kartageners syndrome (situs inversus, chronic rhinosinusitis, and bronchiectases), and low nasal and tidally exhaled NO (6, 123) diagnosis through biopsy and electron microscopy examination of cilia (14)*
• **Turbinate hypertrophy** *unilateral obstruction, often contralaterally to septal deviation* (6)	
• **Nasal tumors** *epistaxis, hyposmia/anosmia, facial pain, otalgia, recurrent ear infections, and unilateral obstruction. Lymphadenopathy, weight loss, fever, general malaise, endoscopic picture of necrotic tissue, and foul-smelling discharge*	• **Cystic fibrosis** *thick, viscous secretions, recurrent infections, often radiologic evidence of sinus disease (8), and concurrent nasal polyps (2). diagnosis through genetic and sweat testing*
• **Adenoidal hypertrophy** *congestion, mouth breathing, nasal speech, and sleep apneic episodes/snoring (3)*	
• **Pharyngonasal reflux** *apneic spells, secondary rhinitis (caused by return of ingested liquids (8)), and recurrent pneumonia due to aspiration*	• **Eosinophilic Granulomatosis with Polyangiitis (formerly Churg–Strauss syndrome)** *asthma, blood eosinophilia, mononeuropathy/polyneuropathy, migratory pulmonary infiltrates, paranasal sinus disease, and tissue eosinophilia (2)*
• **Nasal polyps** *anosmia, unilateral obstruction, sleep apnea, and typical endoscopic picture of polyps*	
• **Choanal atresia** *mild symptoms if unilateral (5), severe symptoms if bilateral (often involving generalized cyanosis(123)*	• **Granulomatosis with polyangiitis (formerly Wegener's disease)** *obstruction, rhinorrhea, crusting, ulcerations, and epistaxis, often secondary bacterial sinusitis* (6, 7)
• **Nasal trauma/foreign object** *may present with unilateral obstruction/epistaxis, olfactory impairment*	• **Sarcoidosis** *obstruction, nasal crusting, anosmia, epistaxis, lymphadenopathy, and malaise* (8, 9).
• **Cerebrospinal fluid rhinorrhea** *clear watery secretion, headaches, and olfactory impairment. b-2 transferrin protein assay suggestive of the condition (10, 11).*	• **Amyloidosis** *obstruction, nasal discharge, epistaxis, and post-nasal drip*
• **Nasal valve problems** *including external valve dysfunction (collapse, stenosis) and internal valve dysfunction*	• **Relapsing polychondritis**

comes and simplify monitoring, we suggest that a measure of ***rhinitis control*** should be used (Table 3). Although rhinitis *control* is essentially 'lack of symptoms,' there is currently no single definition for it, as its determination depends on the specific tools that are being employed (CARAT, RCAT, VAS scores for total nasal symptoms etc. (142–145)). Nevertheless, the 'control' approach has the potential to streamline rhinitis treatment as, unlike 'severity,' can be applied to patients already on medication (20). Most of the control tools devised so far focus on measurements of daily or nocturnal symptoms, symptom magnitude (that is, the patient perception of how bothersome their symptoms are), impairment in everyday activities, and the need for increased medication (142–144). The time period of assessment ranges from one (142) to four weeks (143) prior to consultation, with the latter likely being long enough to assess changes, but also short enough to be less affected by recall bias. These tools are thoroughly described and compared in a recent publication (13). Evaluation of rhinitis control can be based on a number of criteria (Table 3), including a patient-reported metric of QOL (i.e., impairment in sleep or daily activities), symptoms (congestion, rhinorrhea, sneezing, pruritus, post-nasal drip), objective measurements (peak nasal inspiratory flow, rhinomanometry, etc.), and an easily applied test to evaluate nasal patency ('closed mouth test,'

Table 3 Practical assessment of rhinitis control

Rhinitis Control Criteria	Controlled
Symptoms	*No* symptoms (congestion, rhinorrhea, sneezing, pruritus, post-nasal drip)
QOL	*No* sleep disturbance
	No impairment in daily life (school/work and leisure)
Objective measures	Normal peak nasal inspiratory flow
	'*Closed mouth test*' normal*
	(if available) Objective tests to asses nasal patency normal

- Criteria apply to the last four weeks before consultation
- Presence of rhinitis comorbidities (asthma, sinusitis, obstructive sleep apnea syndrome) should be assessed, as their exacerbations may affect rhinitis control.
- Requirement for increased use of rescue medication indicates loss of control
- Any deviation from these criteria indicates loss of control and up-stepping in the treatment algorithm may be considered.
- Use clinical judgment regarding the symptom-free time that is required before considering step-down.

*The patient is asked to close his/her mouth and breathe solely through the nose for 30 seconds.

Table 3). It should be noted that any requirement for increased use of rescue medication should also indicate loss of control (13). Finally, the presence of rhinitis comorbidities could also affect control, as 10% to 40% of rhinitis patients have comorbid asthma (146) and many of them have obstructive sleep apnea syndrome (OSAS), diseases whose severity/control appear to be linked with that of rhinitis (147–155).

The control assessment approach is intended to be a practical guide in the clinical setting for all rhinitis patients regardless of phenotype or endotype, and to supplement the several tools that are currently validated for assessment of rhinitis control. A stepwise management approach of allergic rhinitis based on control is shown in Fig. 2. Such an algorithm can be in principle considered for other rhinitis phenotypes, but, at this stage, this may be premature given the limitations in our understanding and treating NAR and its subphenotypes and endotypes.

Pharmacotherapy

Medications have different indications and effectiveness in different rhinitis phenotypes.

Control medications

Intranasal corticosteroids. INCS are the cornerstone of AR management and have been shown to be superior to combinations of oral H1-antihistamines (AHs) and leukotriene receptor antagonist (LTRAs) (156, 157), or to either drug alone (158–160). The modern INCS are safe when given in recommended doses in adults and in children (161), and potentially effective on an as-needed basis, as shown in studies that compared *prn* administration with nonsteroid regimes or placebo (79, 162–164); however, continuous administration may be superior (165, 166). They may also be efficient for the treatment of NARES, due to the underlying eosinophilic inflammation (7, 22, 48, 61), although evidence is still inconclusive, and also for the management of chronic rhinosinusitis *without polyps* (167–169), although they are more useful for the phenotype of CRS *with* polyps (170). Although not conclusive, there is some evidence suggesting that INCS are appropriate for the management of rhinitis medicamentosa, which is refractory to mere discontinuation of the offending nasal decongestant (79, 87, 171–173).

Oral antihistamines. First-generation oral antihistamines are no longer recommended, due to well-documented adverse effects (174). Conversely, second-generation oral AHs are recommended, as they have strong H_1 receptor selectivity, weak anticholinergic action, minimal potential for sedation, fast onset, and long half-lives (8, 79). They also have some anti-inflammatory properties and are not subject to tachyphylaxis/tolerance (21). Oral AHs are effective for the management of AR, although they are less potent than INCS (160), and probably offer limited additional benefit when combined with them (79, 175, 176). One study noted an additive effect of co-administration of oral AH with intranasal steroids for the treatment of NARES (177), but further research is required on such a regimen. Second-generation AH are of limited value for idiopathic rhinitis (22, 61); the use of first-generation AH for IR is also not supported by strong evidence, despite the presence of some anticholinergic activity, which can, theoretically, suppress nervous system-induced rhinorrhea (59).

Intranasal antihistamines. Intranasal antihistamines (IAI) antagonize H_1 receptors, exert a local anti-inflammatory effect (21), are effective for nasal congestion (178), and have a rapid onset of action (179). Azelastine and olopatadine (180, 181) are at least as effective as oral AH for AR (182–184), although they are still inferior to intranasal corticosteroids (185). Azelastine is efficient, and FDA approved for the treatment of idiopathic (vasomotor) rhinitis (61, 186, 187). Intranasal antihistamines may also be useful for occupational rhinitis (79, 103). Potential therapeutic pathways in regard to NAR are currently under investigation (72).

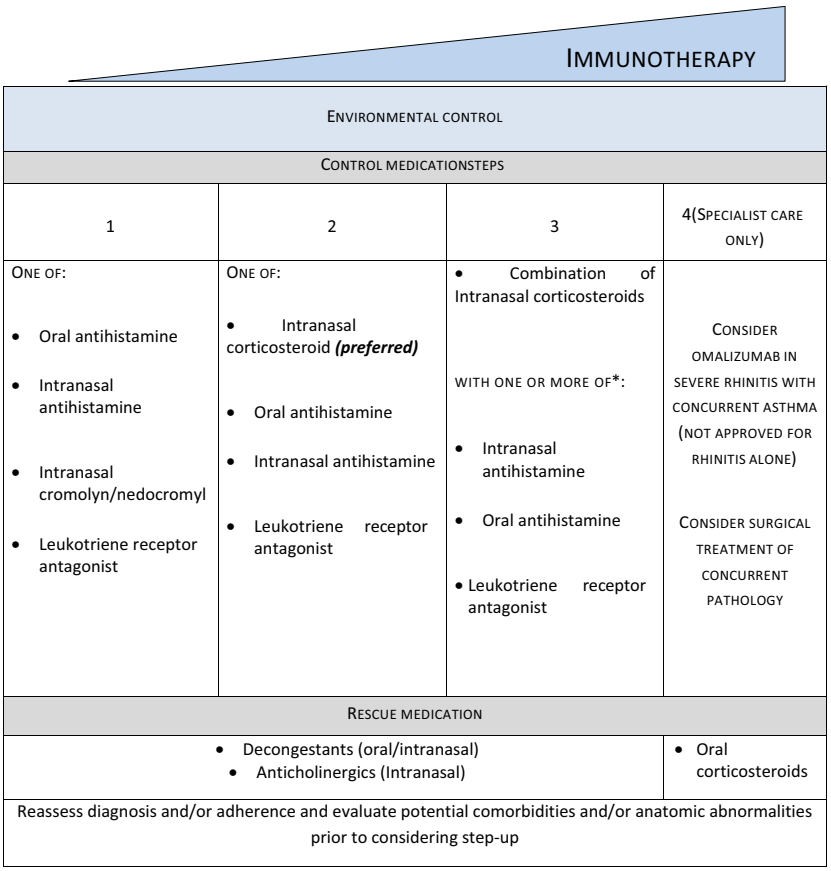

Figure 2 Stepwise treatment algorithm for *allergic rhinitis* based on control. Step-up is indicated if symptoms remain uncontrolled and step-down if control is achieved with the employed regimen. Although the control principle may be valid for other rhinitis phenotypes as well, specific medications should be adjusted accordingly. *There is little evidence of additional efficacy of the INCS/oral AH or INCS/LTRA combinations over INCS alone, but there is stronger evidence for the INCS/intranasal AH combination.

Combination of intranasal corticosteroids plus intranasal antihistamines. Whereas combination regimes of *oral* AHs with INCS do not appear to be superior to either agent alone (79, 175, 176), the addition of IAH to INCS has been shown to confer extra benefit (188, 189). In fact, a novel fixed-combination therapy of azelastine and fluticasone has shown promise as first-line treatment for moderate to severe rhinitis (190–193).

Leukotriene receptor antagonists. The LTRA montelukast is comparably effective to oral AHs (with loratadine as the usual comparator), and the combination with oral AHs may have a small additive effect (194–199). In patients with rhinitis and asthma (i.e., the vast majority of patients with allergic asthma), montelukast may be advantageous over AHs because of its potential to offer benefits in both conditions (200). Montelukast has a very good safety profile. There is weak evidence that leukotriene modifiers could be beneficial as adjunctive (201, 202) or even sole treatment (203) for nasal polyps, or could be used to control nasal symptoms of AERD (204). This warrants further research.

Rescue medications

Oral decongestants. In both AR and NAR, if nasal obstruction is the predominant symptom, a short course of oral adrenergic agents (pseudoephedrine and/or phenylephrine) could be considered as rescue medication (21, 79). However, these pharmaceuticals have a less favorable safety profile (8, 79), leading some to recommend that these agents should not be used regularly (17), should be avoided in young children, and should be used with caution in adults of over 60 years of age and in any patient with cardiovascular conditions (79).

Intranasal decongestants. These include vasoconstrictor sympathomimetic (alpha-adrenergic agonist) agents (e.g., phenylephrine, oxymetazoline, xylometazoline). These agents can be used as rescue medication for any rhinitis phenotype with congestion as a predominant symptom (205). They do not have anti-allergic or anti-inflammatory action and do not suppress itching, sneezing, or nasal secretions (79); importantly, they are not recommended for long-term therapy because, in a significant percentage of patients, tolerance

and/or rhinitis medicamentosa could appear as early as 3 days into treatment (8, 21, 206). Although there are reports of safe administration of up to 4 weeks (207, 208), especially in combination with nasal corticosteroids (96, 97), a maximum of 5–10 days of use is currently recommended (17, 79).

Intranasal anticholinergics. If rhinorrhea is predominant, ipratropium bromide, an antimuscarinic agent, could be considered (17). This pharmaceutical class is of limited value for the control of sneezing or nasal obstruction (8, 61), but is highly effective for improving rhinorrhea in most phenotypes associated with increased secretions (80, 209–213). It could therefore be useful for neurogenic rhinitis endotypes, including rhinorrhea-predominant rhinitis of the elderly, idiopathic rhinitis (61, 210, 214), gustatory rhinitis (80), and cold air-induced rhinorrhea (209, 212), or even for the neurogenic component of acute viral rhinosinusitis (211, 213, 215, 216). Ipratropium does not induce tolerance (21) and, in recommended doses, has few local adverse effects (79) and minimal —f any—systemic side-effects (217). It has an additive therapeutic effect to both oral AHs and INCS (210) with no increased risk of adverse events (79).

Oral corticosteroids. This is a last resort treatment and should be utilized strictly short term and for symptoms refractory to all other appropriate therapeutic modalities. A short burst of oral corticosteroids may help to resolve severe intractable symptoms of AR (218, 219) or to wean patients off topical nasal decongestants when discontinuation causes refractory rebound symptoms (87). Oral steroids may also be useful for chronic rhinosinusitis with nasal polyps (220, 221) possibly in regimes including intranasal steroids (222). Also, this drug class has a more integral role in the chronic treatment of systemic diseases, which can present with nasal symptoms, such as EGPA (223, 224), relapsing polychondritis (225, 226), and GPA (227).

Nasal irrigations. A commonly used adjunct treatment for most rhinitis phenotypes is nasal irrigations with isotonic or hypertonic saline (21). Such treatment may assist in mucus clearance (228, 229) and removal of inflammatory mediators (230). Saline rinses are the cornerstone of atrophic rhinitis management (101, 231) and are valuable for chronic rhinosinusitis treatment (232, 233) and for the control of nasal symptoms of cystic fibrosis (234). The evidence that nasal irrigation benefits AR is limited (235) and further research is warranted. Furthermore, it remains unclear whether hypertonic saline provides a better effect, as compared to normal saline (229, 236).

Other treatments

Nasal surgery. In patients suffering from nasal blockage despite medical treatment for rhinitis, physicians should evaluate the improvement of the nasal flow by various means of intervention such as septal correction, reduction in the inferior turbinate, valve surgery opening the nasal valve, and/or closure of septal perforation.

Application of various surgical reduction techniques is typically necessary to treat turbinate hypertrophy (237–240). Septoplasty is commonly carried out to correct septal deviation. Adenoidal hypertrophy is treated with the surgical removal of the enlarged adenoids (adenoidectomy), while endoscopic sinus surgery for CRS with and without nasal polyps is undertaken in those who fail to respond to maximal medical treatment (130). Finally, vidian nerve neurectomy, although rarely indicated, can be a last resort option for the treatment of idiopathic rhinitis (241).

The success of all surgical procedures mentioned above largely depends on the indication.

Capsaicin. Capsaicin, the pungent agent in hot pepper, causes selective degeneration/desensitization of peptidergic sensory C-fibers of the nasal mucosa that is reversible over time (242). Due to this mode of action, capsaicin has shown promise for rhinitis phenotypes that encompass a strong neurogenic component and could be assigned to *a nonallergic neurogenic endotype*, such as IR (243–249), and rhinitis induced by cold air. Although capsaicin is easy to prepare by the local pharmacist, its use in clinical practice is limited as commercial preparations with well-defined content are not available.

Intranasal cromolyn/nedocromil. These pharmaceutical agents are primarily used for *prophylaxis* in AR, as they are supposed to stabilize the membrane of mast cells, thereby inhibiting their degranulation (21, 250). They have an excellent safety record (8, 79). However, they are inferior to topical corticosteroids and probably topical AHs (8, 251), as they exert no effect on already released inflammatory mediators (79). Due to their *modus operandi,* they are expected to offer limited benefit for the treatment of any *nonallergic* rhinitis phenotype (252), albeit evidence is inconclusive (253).

Omalizumab. This humanized monoclonal anti-IgE antibody has been shown to reduce both nasal and ocular symptoms of AR in a dose-dependent manner (254, 255). Although its mode of action would not support any significant effect on *nonallergic* rhinitis phenotypes, it has shown some promise for patients with polyps and concomitant asthma, possibly by removing IgE against S. aureus enterotoxins (32). Omalizumab is not currently approved for AR treatment, and its high cost and injectable route of administration herald a role that should probably be confined in the most severe side of the AR spectrum.

Other regimes. For AERD, aspirin desensitization followed by long-term daily aspirin treatment can be considered, if tolerated (22, 87, 256, 257).

Avoidance and education

Depending on the specific rhinitis phenotype, the term 'avoidance' could encompass environmental control measures (in AR, irritant-induced rhinitis, and idiopathic rhinitis), abstaining from certain foods (in gustatory rhinitis),

avoiding certain drugs (in drug-induced rhinitis), and/or making changes in lifestyle/workplace (in occupational rhinitis). In fact, avoidance is the mainstay of treatment for drug-induced and gustatory rhinitis. For AR, multifaceted interventions in the home, school, or workplace can be effective (258, 259). However, single allergen avoidance measures are often not effective (260), probably due to the difficulty of achieving adequate avoidance. It may be easier to avoid some perennial allergens (e.g., cats, dogs, and other furry pets) as compared to others (e.g., dust mites, molds, cockroaches, and rodents (79)). It is even more difficult to avoid seasonal airborne pollen, as pollen spores can travel great distances and their daily levels depend on the interplay of various factors (e.g., wind, temperature, and humidity) (79). Airborne irritants such as sulfur dioxide, nitrogen dioxide, particulate matter, tobacco smoke, volatile organic compounds, and others (258, 261, 262) should also be avoided—if possible—in most rhinitis phenotypes. If identifiable by the patient, avoidance of precipitators can be of value in idiopathic rhinitis. Whereas some of these triggers are avoidable (e.g., tobacco smoke, perfumes), others are not (e.g., weather shifts). For occupational rhinitis, modification of the workplace and mask usage may be beneficial (79, 103) to avoid complete removal of the patient from this environment.

Overall, and although improved strategies for successful avoidance are still an unmet need, avoidance of precipitating agents can be feasible and important in certain contexts. However, patients often do not perceive the clinical value of such measures (263) and education about the importance of environmental control should be prioritized (264). It is in fact likely that proper education will not only allow for better environmental control but will also improve a key aspect of the patients' health behavior, that is, adherence to their prescribed treatment. For instance, it has been shown that immunotherapy patients are commonly ill-informed about their treatment and may have unrealistic expectations (265, 266): This could partly underlie the low level of *compliance* seen in both SCIT and SLIT (267–269). Indeed, in patients receiving SLIT it has been demonstrated that more effective communication in the form of higher frequency of office visits was associated with greater adherence (270). Also, patient compliance in the use of intranasal corticosteroids (and efficiency of use) is often dictated by factors relating to the physician clearly addressing the patients' concerns about topical corticosteroids and offering concise guidance on the administration technique, to avoid preventable treatment failures (271–273). Therefore, adequate information should be provided and the patients' goals and expectations must be discussed (274).

Allergen immunotherapy

Allergen immunotherapy (AIT) is an effective treatment for AR (275). Criteria to be considered prior to initiation of therapy include patient preference/acceptability, expected adherence, medication requirements, response to avoidance measures, allergen extract availability, and adverse effects of medications and cost (276). Although AIT is currently underutilized (277), it is a therapeutic modality appropriate for both adults and children (278, 279) and can lead to disease remission that is typically sustainable for years after discontinuation of treatment (280, 281). Furthermore, AIT can simultaneously be effective in the management of asthma and allergic rhinoconjunctivitis (276, 282), has the potential to prevent sensitizations to new allergens (283), and may also prevent the development of asthma (284, 285). Initially, AIT was exclusively administered by subcutaneous injections (SCIT), but more recently introduced sublingual dosing (SLIT) is effective (286, 287), although data are inconsistent about whether SCIT and SLIT have comparable effectiveness (288–291). The role of AIT was comprehensively reviewed in a recent PRACTALL document (292).

Conclusions

Although the importance of identifying different phenotypes of a single disease has been well recognized both in a clinical and in a research context, the importance of classification based on *endotypes* has only recently begun to be appreciated. From this perspective, rhinitis is a disease which presents with numerous clinical pictures and which is based on even more pathophysiological mechanisms. Disentangling these often overlapping entities may facilitate the design of improved approaches for the diagnosis and treatment of this prevalent condition.

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Author contributions

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Conflicts of interest

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