Allergic rhinitis

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Abstract | Allergic rhinitis (AR) is caused by immunoglobulin E (IgE)-mediated reactions to inhaled allergens and is one of the most common chronic conditions globally. AR often co-occurs with asthma and conjunctivitis and is a global health problem causing major burden and disability worldwide. Risk factors include inhalant and occupational allergens, as well as genetic factors. AR impairs quality of life, affects social life, school and work, and is associated with substantial economic costs. The Allergic Rhinitis and its Impact on Asthma (ARIA) initiative classified AR into intermittent or persistent and mild or moderate/severe. The diagnosis is based on the clinical history and, if needed in patients with uncontrolled rhinitis despite medications or with long-lasting symptoms, on skin tests or the presence of serum-specific IgE antibodies to allergens. The most frequently used pharmacological treatments include oral, intranasal or ocular H_1-antihistamines, intranasal corticosteroids or a fixed combination of intranasal H_1-antihistamines and corticosteroids. Allergen immunotherapy prescribed by a specialist using high-quality extracts in stratified patients is effective in patients with persistent symptoms. Real-world data obtained by mobile technology offer new insights into AR phenotypes and management. The outlook for AR includes a better understanding of novel multimorbid phenotypes, health technology assessment and patient-centred shared decision-making.

Allergic rhinitis (AR) is characterized by sneezing, nasal congestion, nasal itching and rhinorrhoea (nasal discharge) and is caused by immunoglobulin E (IgE)-mediated reactions to inhaled allergens. These immune reactions involve mucosal inflammation that is driven by type 2 cells[1,2]. AR seems to be the consequence of environmental exposures acting on a predisposed genetic background. AR is often co-morbid with asthma and/or conjunctivitis.

AR is one of the most common chronic conditions in high-income countries, with a prevalence of up to 50% in some countries[3]. By contrast, the prevalence is relatively low in low-income and middle-income countries (LMICs), although prevalence is increasing steadily in these counties. AR is a global health problem that causes major burden and disability worldwide. Indeed, AR contributes to missed or unproductive time at work[4] and school, sleep problems and, in children, decreased involvement in outdoor activities[5]. The economic effect of AR is often underestimated as indirect costs are substantial, but the effect of AR on work productivity is estimated to cost €30 billion to €50 billion per year in the European Union[4,6,7].

The diagnosis of AR is made by medical history and examination (physical examination and, if needed, nasal endoscopy) plus, in some patients, tests for allergen-specific IgE (skin prick tests or tests for serum-specific IgE). Available treatments include allergen avoidance, pharmacotherapy with H_1-antihistamines or intranasal corticosteroids (INCS) and allergen-specific immunotherapy (AIT). Many patients are dissatisfied with their treatment, for example, because management does not take the patient's needs into consideration, no cure is available, adherence to long-term therapy is poor and/or because the patient does not fully understand the condition. Real-world data obtained via mobile technology should offer new insights into the phenotypes and management of AR.

This Primer discusses the epidemiology, risk factors and genetic background of AR. In addition, it reviews the mechanisms of disease, diagnosis, prevention and management and the effect of AR on quality of life (QOL).

Epidemiology

Prevalence

For accurate prevalence estimates, AR needs to be distinguished from infectious rhinitis and non-allergic rhinitis. Two large multinational studies on the prevalence of allergic diseases were conducted from 1990 to 2010 in children (International Study of Asthma and Allergy in Childhood (ISAAC))[8] and adults (European Community

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Health Survey (ECRHS))[3]; however, more recent large studies have not been undertaken. Collectively, these studies demonstrated that AR often begins early in life, with a prevalence of more than 5% at 3 years of age. In the ISAAC phase III study (consisting of data from 236 centres in 98 countries), AR prevalence increased from 8.5% in individuals aged 6–7 years to 14.6% in those aged 13–14 years[8]. Overall, AR in children and adolescents was more prevalent in high-income countries, but the prevalence of severe symptoms was higher in LMICs[9]. In the ECRHS study (conducted in 35 centres in 15 countries), the age-standardized and sex-standardized prevalence of AR in people aged 20–44 ranged from 11.8% in Oviedo (Spain) to 46.0% in Melbourne (Australia)[3]. Of note, AR is more common in males before puberty, whereas it is more common in females after puberty; these differences are more pronounced in those with asthma and AR concomitantly[10]. In the US National Health and Nutrition Examination Survey III from 1988 to 1994, the prevalence of nasal symptoms during the previous 12 months was highest (~30%) in individuals aged 17–29 years and lowest (~10%) in those older than 60 years[11].

In general, the prevalence of AR has increased worldwide since the 1960s in parallel to the increase in the prevalence of atopy (that is, the tendency to produce IgE antibodies owing to genetic and/or environmental factors)[12,13]. The ISAAC also evaluated the change in prevalence of allergic diseases between 1994–1995 and 2002–2003 (REF.[8]). For the two age groups evaluated as part of this study (6–7-year-olds and 13–14-year-olds), the prevalence of AR increased from the 1990s to the early years of the first decade of the twenty-first century in many LMICs but decreased or had little change in western Europe. The reasons for the observed changes in prevalence are unclear[8].

Risk factors

Allergens associated with AR include pollens (tree, grass and weed, including ragweed), moulds and indoor allergens (house dust mites and animal allergens) and have a large geographical variability within and between countries[14]. Occupational AR includes both IgE (vegetal and animal proteins as well as certain chemicals) and non-IgE (isocyanates, persulfate salts and woods) mechanisms[15]. Risk factors for AR include antibiotic use, self-reported air pollution, exposure to farm animals (only in LMICs), exposure to cats and/or dogs, maternal and paternal smoking and vigorous physical activity in adolescents[16]. Of note, many of these risk factors are shared with asthma and atopic dermatitis[16]. Overweight and obesity are not associated with AR[17]. Of note, many of these exposures and lifestyle risk factors have not been established as major risk factors for AR[18]; for example, ambient air pollution and passive smoking do not seem to have a large effect on AR development, but pollution may be associated with increased AR severity[19].

The proportion of rhinitis in general that is attributable to atopy is ~50% in the overall population[20]. AR, asthma and atopic dermatitis often coexist in the same individual, partially due to a shared genetic origin[21,22]. Indeed, data from genome-wide association studies (GWAS) have demonstrated that allergic diseases and traits share a large number of genetic susceptibility loci, of which *IL33*, *IL1RL1* (also known as *IL33R*), *IL13–RAD50*, *C11orf30* (also known as *EMSY*)*–LRRC32* and *TSLP* seem to be important for multimorbid allergic diseases[18,23]. In addition, rhinitis was associated with TLR expression, whereas AR associated with asthma was associated with *IL5* and *IL33*, suggesting a different genetic cause for AR alone compared with multimorbid AR[24]. Further research is warranted to explore transcriptomic signatures as biomarkers for single and multimorbid allergic diseases.

Susceptibility loci for AR have various immune functions, such as the inflammatory adhesion process for *MRPL4* (19q13), in the activation, development and maturation of B cells and epithelial barrier function/regulatory T cell function for *BCAP* (also known as *PIK3AP1*; 10q24) and immune tolerance for *C11orf30–LRRC32* (11q13), whereas other loci have unknown functions, such as *FERD3L* (7p21)[23]. In addition, data from one large GWAS and HLA fine-mapping study found 20 new loci that were associated with AR, many of which had immune functions related to both innate and adaptive IgE-related mechanisms[25]. In that study, the estimated proportion of AR attributable to the key identified AR-associated loci was 39%, which is a relatively high estimate for a complex disease. Other GWAS analyses have found common genetic mechanisms in AR and non-allergic rhinitis[22,25,26].

Classification

Although historically AR has been categorized as seasonal and perennial, this distinction has not been well reproduced in epidemiological studies assessing

molecular allergens as most patients are polysensitized (sensitized to more than one allergen)[27]. Accordingly, the organization Allergic Rhinitis and its Impact on Asthma (ARIA) proposed replacing seasonality with intermittent and persistent rhinitis[1].

The large number of risk factors associated with AR suggest that the geographical variations in prevalence are due to a constellation of environmental factors varying between locations and time. These varying constellations of risk factors are also a plausible explanation for the time and place distribution of allergic multimorbidity[16]. No biomarker that can be used in clinical practice to predict the type (that is, phenotype or endotype) and severity of AR and the development of its common co-morbidities is available.

Multimorbidities and sensitization

Most patients with asthma have multimorbid rhinitis (AR or non-allergic rhinitis), whereas less than one-third of patients with AR have asthma associated with rhinitis[1]. The Mechanisms of the Development of ALLergy (MeDALL) study, which included 12 European birth cohorts, demonstrated that the coexistence of rhinitis with asthma and/or atopic dermatitis is more common than expected by chance alone, both in the presence and in the absence of IgE sensitization, suggesting that multimorbidity and IgE have different genetic mechanisms[28]. In addition, data from the MeDALL study suggested that type 2 signalling pathways represent a relevant multimorbidity mechanism of allergic diseases[22].

Many patients with AR also have conjunctivitis, but rhinitis and rhinoconjunctivitis seem to be two separate diseases[29–31] and should be differentiated. In addition, data from the mobile application MASK-air have identified an extreme pattern of uncontrolled multimorbidity (uncontrolled rhinitis, conjunctivitis and asthma during the same day)[32]. More recent classical epidemiological studies showed that ocular symptoms are more common in polysensitized patients[29] whether they have asthma or do not have asthma[30], ocular symptoms are associated with the severity of nasal symptoms[33], ocular symptoms are important to consider in severe asthma[33] and the severity of allergic diseases increases with the number of allergic multimorbidities[34].

Monosensitization and polysensitization represent different phenotypes of IgE-associated disease[35]. Polysensitization is associated with an earlier onset of allergy and with more severe symptoms compared with monosensitization. In addition, the multimorbidity polysensitization phenotype seems to occur at various ages and in various allergenic environments and may be associated with specific mechanisms of disease[36].

Mechanisms/pathophysiology

Allergen exposure, either topically intranasally or in an exposure chamber[37], can be used to study nasal allergic reactions, monitor symptoms and collect nasal secretions and serum for mediator measurements in response to the allergen[38] or nasal scrapings or biopsy from patients[39–41]. In addition, blood cells (such as basophils and antigen-specific T cells) and nasal mucosa tissue can be studied ex vivo[42] using different stimuli and interventions.

The nasal epithelium

The nasal mucosa is the primary air conditioner of the respiratory tract and the first line of defence against airborne infectious agents. For these roles, maintaining and restoring epithelial integrity and the ability to initiate immune responses are essential. In the presence of conditions or factors that impair mucosal integrity, the epithelium releases alarmins and other damage-associated molecular patterns that initiate repair mechanisms but can also induce protective inflammation. In AR, the same mechanisms may be active in inducing disease. For example, allergens with protease activity (such as Der p 1 in house dust mites) can directly compromise the epithelial barrier, whereas others (such as Der p 2 in house dust mites) can activate pattern recognition receptors; in both cases the epithelium can initiate innate immune responses through the release of alarmins such as IL-33, thymic stromal lymphopoietin (TSLP) or IL-25 (REFS[43–46]). Alarmins can, in turn, activate group 2 innate lymphoid cells (ILC2s), which rapidly produce in situ type 2 cytokines (IL-5, IL-13 and IL-4), therefore having a key role in the initiation and maintenance of type 2 adaptive immune responses, leading to IgE class switching and mucosal inflammation. Additional environmental factors are probably involved in the pathophysiology of AR through their effects on the nasal epithelium. These include pollutants (diesel exhaust particles[47] or other air pollutants[48]), irritants and infectious agents (*Staphylococcus aureus*[49] or viruses). The exact mechanisms through which those factors contribute to disease manifestation have not been elucidated.

Antigen presentation and sensitization

The allergic immune response begins with a sensitization phase when the patient is first exposed to an allergen without experiencing clinical symptoms (FIG. 1). During this phase, dendritic cells in the nasal mucosa take up the allergen, process it and transport it to the draining lymph node, in which the processed allergen is presented to naive $CD4^+$ T cells. Following antigen presentation, naive $CD4^+$ T cells are activated and differentiate into allergen-specific type 2 T helper cells (T_H2 cells)[50–55] that induce the activation of B cells and IgE class switching, which leads to B cell differentiation into plasma cells that produce allergen-specific IgE. IgE enters the circulation and binds through its Cε3 domain to the high-affinity IgE receptor (FcεRI) on the surface of effector cells (for example, mast cells and basophils). These processes lead to the formation of a pool of memory allergen-specific T_H2 cells and B cells. Although this constitutes the first step in the development of allergy, it is also an ongoing process as the mucosa becomes exposed to various allergens on a chronic, seasonal or episodic basis.

Symptom generation and inflammation

AR symptoms are caused by biochemical products released in the nasal tissue during an allergic reaction. When a patient who has been sensitized by previous exposure to the allergen re-encounters the causative

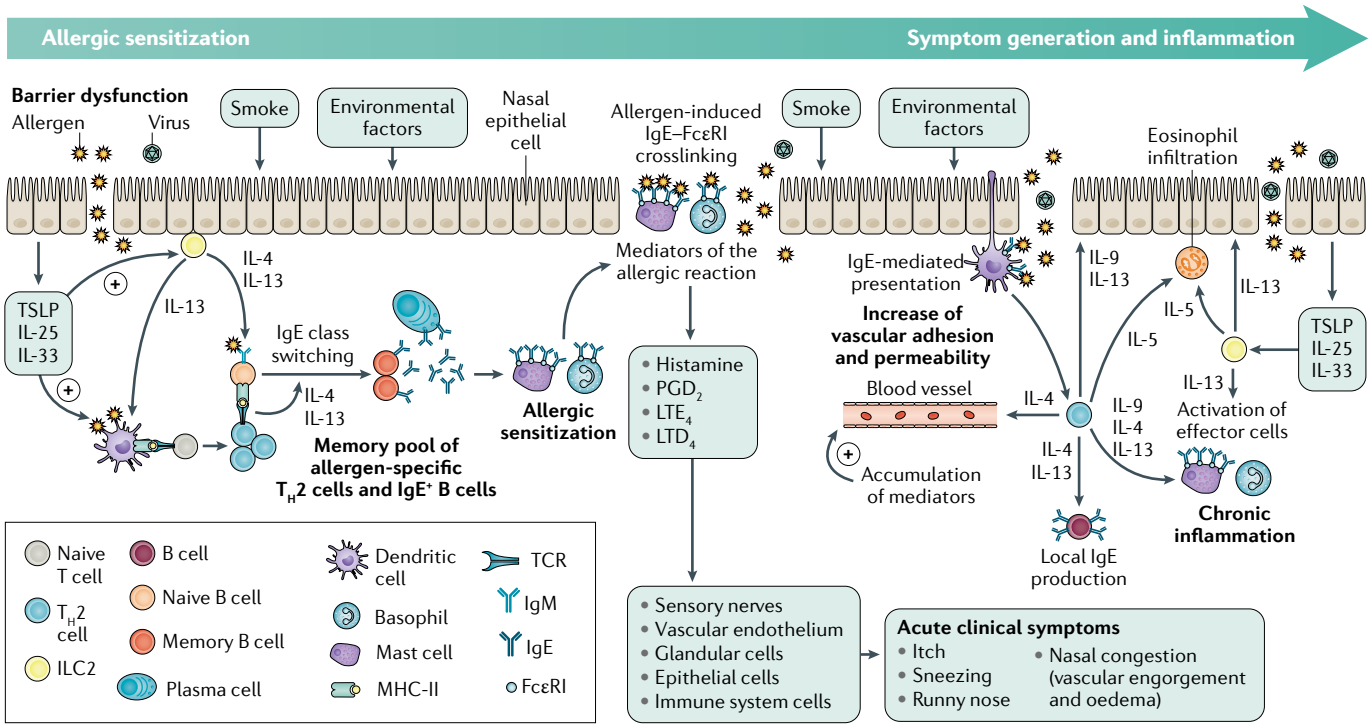

Fig. 1 | **Pathophysiology of allergic rhinitis.** During the sensitization phase, allergens are taken up by dendritic cells in the nasal mucosa and induce a series of events leading to the generation of plasma cells that produce allergen-specific immunoglobulin E (IgE) that binds to mast cells and basophils and to a pool of memory allergen-specific type 2 T helper cells (T_H2 cells) and IgE^+ B cells. In individuals who are sensitized to the allergen, subsequent allergen exposure activates basophils and mast cells in the nasal mucosa, triggering the release of allergic mediators (including histamine and sulfidopeptide leukotrienes), leading to the acute symptoms of allergic rhinitis. Subsequent cytokine production by memory allergen-specific T_H2 cells induces an inflammatory infiltrate (eosinophil recruitment) within a few hours, leading to more symptoms and changes in the functional aspects of the nasal mucosa that mimic chronic rhinitis. ILC2, group 2 innate lymphoid cell; LTD_4, leukotriene D_4; LTE_4, leukotriene E_4; MHC-II, class II major histocompatibility complex; PGD_2; prostaglandin D_2; TCR, T cell receptor; TSLP, thymic stromal lymphopoietin. Adapted with permission from REF.[51], Wiley.

allergen, the allergen binds to allergen-specific IgE on mast cells in the nasal mucosa, resulting in IgE and FcεRI crosslinking and subsequent mast cell activation and degranulation. This leads to the release of prestored and newly synthesized mediators, including histamine, sulfidopeptide leukotrienes (leukotriene C_4 and leukotriene D_4), prostaglandin D_2 and other products[52] (FIG. 1). These mediators interact with nasal sensory nerves, vasculature and glands, resulting in acute AR symptoms.

In addition to acute symptoms, experimental nasal exposure to an allergen in an individual with AR produces immediate signs of inflammation, such as plasma exudation and the development of a type 2 inflammatory infiltrate characterized by eosinophils, neutrophils and basophils and by a mononuclear infiltrate (primarily T_H2 cells)[56]. Indeed, classic type 2 cytokines — such as IL-4, IL-5 and IL-13 — can be detected in tissue and measured in nasal secretions several hours after allergen exposure[57,58] (FIG. 1). In the natural presentation of AR, the histopathology is quite similar to that after experimental allergen exposure, and activation of allergen-specific memory T_H2 cells by dendritic cells and other antigen-presenting cells such as B cells via mechanisms partially depending on IgE-facilitated allergen presentation is believed to play a critical role[49,50]. Activated allergen-specific T_H2 cells produce large amounts of IL-4, IL-5 and IL-13 that contribute to vascular permeability, the infiltration of eosinophils and other inflammatory cells into the nasal mucosa, local IgE production, increased mucus production, vascular leakage and expansion, and activation and differentiation of different subsets of T_H2 cells[40,42,43]. Of particular interest are antigen-specific T_H2 peripheral blood cells that display markers such as CRTH2, CD161 and CCR4 with very little expression of CD27. These cells, also known as $T_H2\alpha$ cells, are associated with AR severity and are characteristically suppressed by allergen immunotherapy[57]. Although the histology of AR shows a typical type 2 inflammation, there is little evidence of mucosal remodelling in contradistinction with asthma[46,52].

Although patients with AR experience acute symptoms on exposure to a known allergen, the natural symptomatic state can be chronic with relatively low fluctuations and frequently includes non-allergen triggers such as irritants and changes in environmental conditions. Experimental allergen provocations (nasal challenges), whether conducted by direct instillation of an allergen into the nasal cavities or through an environmental exposure unit, help identify a number of pathophysiological phenomena that offer better understanding of the overall clinical picture of AR. Acute symptoms are reduced within minutes but can persist

at lower levels for hours after allergen exposure or can recrudesce in a phenomenon known as the 'late-phase' reaction[59]. Late-phase reactions may explain why, after sudden exposure to a large amount of an allergen, a patient with AR may remain symptomatic for prolonged periods. Repetitive allergen exposure leads to another phenomenon, whereby progressively lower amounts of the allergen are required to elicit symptoms; this has been termed 'priming'[60]. Nasal priming may explain why, towards the end of a pollen season, patients with AR tend to become symptomatic even when exposed to very low levels of pollen. A third phenomenon is the induction of nasal hyper-responsiveness, where the nasal response (sneezing, rhinorrhoea and so on) to a stimulus that is not an allergen (for example, histamine) can be augmented by a prior allergen challenge. In the natural history of AR, this phenomenon may explain the high sensitivity of patients to irritants and to environmental changes[61].

Nasal priming may be caused by the increased accumulation of mast cells or basophils — which is a consequence of repeated allergen exposure — at the site of the allergic reaction in the nose[62], in addition to the induction of non-specific hyper-responsiveness at the 'end-organ' (nose) level. In addition, late-phase reactions and chronicity might also depend on the perpetuation of allergen-specific adaptive immune responses. Indeed, persistent symptoms following allergen challenge could be mediated mainly by the accumulation of allergic mediators in the nasal mucosa but also by the activation of allergen-specific memory T_H2 cells by dendritic cells and other antigen-presenting cells such as B cells via mechanisms partially depending on IgE-facilitated allergen presentation[63,64]. Activated T_H2 cells produce large amounts of type 2 cytokines that contribute to enhance all the local pathophysiological mechanisms described above, including the enhanced and sustained activation not only of tissue-resident mast cells but also of basophils infiltrating the nasal mucosa, which also might well contribute to the clinical symptoms after allergen-induced IgE crosslinking and subsequent release of mediators[50–52] (FIG. 1). Nasal late-phase reactions, priming and non-specific hyper-responsiveness are inflammation dependent and can be suppressed by nasal corticosteroids. However, the specific molecular and cellular events underlying these phenomena are not yet fully understood.

Role of nasal nerves

The nervous system has a key role in the nasal symptoms of AR. The nasal mucosa is densely innervated by adrenergic and cholinergic nerve fibres, and the epithelium is innervated by interdigitating sensory nerve endings, mostly nociceptors (receptors that respond to noxious stimuli)[65]. In addition, nasal chemosensory cells that express bitter taste receptors may reflect a specialized sensory nerve system that reacts to noxious stimuli and bacterial products[66]. Cholinergic and adrenergic nerve fibres are activated through central reflexes initiated at the nasal mucosa by sensory nerves, including nociceptor C fibres. Nasal C fibres and other sensory nerves express receptors for some mediators of the allergic response (such as histamine and bradykinin), and also express several transient receptor potential ion channels that are activated by noxious physical or chemical stimuli, such as low pH, high or low temperatures, CO_2 and hypertonicity. These fibres may also have a local effector function as they produce and release neuropeptides via axonal, antidromic reflexes[67]. However, the mechanism and clinical role are unclear. Nasal hyper-responsiveness seems to have a strong neural component[68]. Indeed, changes in the density and neuropeptide content of sensory nerves have been found in the nose of patients with AR. A putative mediator of these changes, nerve growth factor, is released on nasal allergen provocation[69] and can be found in nasal glandular epithelial cells and eosinophils in the nasal mucosa[70].

Diagnosis, screening and prevention

AR is often under-recognized owing to poor public awareness, limited access to allergologists and confounding diagnoses, such as the common cold[71]. The diagnosis of AR is made by considering a detailed history that is supported by examination findings (physical examination and, if needed, nasal endoscopy) and, if necessary, testing for allergen-specific IgE. Other tests such as nasal allergen challenge, CT scans, evaluation of nasal nitric oxide and ciliary beat frequency, nasal smears, nasal cultures and analysis of nasal fluid for β-transferrin) may be required to include or exclude different forms of rhinitis[72]. The ARIA guidelines propose classifying AR as intermittent or persistent depending on the duration of symptoms, with persistent rhinitis occurring for more than 4 days for 4 weeks at a time, and as mild or moderate to severe, depending on whether sleep and daily activities are affected or whether symptoms are troublesome[73] (FIG. 1). In addition, AR can also be classified as mild, moderate or severe[74].

Clinical history

The clinical history should note symptoms, particularly those that cause major problems, where and when they occur, and any exacerbating and relieving factors. Other symptoms in the chest, ears, throat, gut or skin, in addition to whether there is a patient history or a family history of allergic disease and/or immune problems, together with a review of treatments previously tried, those currently being taken and their efficacy, should all be noted.

All individuals are familiar with rhinitis because of the common cold. Rhinitis is defined clinically as having two or more of the following symptoms for more than 1 hour per day: nasal running, blocking, itching or sneezing. The diagnosis is made by an accurate history but can be missed owing to misperceptions such as symptoms being ascribed to frequent colds, mouth-breathing children having enlarged adenoids and secretions being missed when they pass posteriorly. Questioning patients with asthma regarding nasal function (such as the ability to breathe through the nose and to smell) should be undertaken as most patients with asthma have rhinitis or rhinosinusitis[73].

The clinical history may also provide a clue to the inciting allergen or allergens. Of note, long-term allergen

exposure is harder to diagnose than short-term exposure as the major symptom is often nasal blockage and postnasal discharge, with fewer obvious symptoms such as nasal itching, running and sneezing. Nasal inflammation can also cause non-specific nasal hyper-reactivity to non-allergic stimuli[75] and a poor sense of smell, among other multimorbidities[76]. Some pollen-sensitive individuals with AR may present with oral symptoms of pollen food syndrome, such as itchy mouth and throat after ingestion of the food[77].

Examination

An examination of the whole patient is necessary as rhinitis has important co-morbidities[76]. Children should have their growth assessed, as severe airway problems are associated with reduced growth, and the combined use of INCS and inhaled corticosteroids may reduce height at high doses[78]. The presence of facial features such as conjunctivitis, nasal allergic crease, allergic salute or double creases beneath the eyes (Dennie–Morgan lines) all suggest that the patient has an allergic diathesis.

Nasal examination is needed in patients with moderate to severe AR or in those with uncontrolled symptoms despite optimal treatment. This examination should include assessment of the external appearance followed by internal examination, preferably with a nasendoscope. An otoscope may suffice to examine the nose in children. The position of the nasal septum, as well as the size and colour of the inferior turbinates, should be noted, together with the appearance of the mucosa and the presence and nature of any secretions, polyps, bleeding, tumours, crusting or foreign bodies. The classic appearance of the nasal cavity in patients with AR is swollen pale bluish inferior turbinates with copious clear secretions; however, the nose may look normal, and these features are not restricted to AR. Of note, the mucosa may be slightly reddened in patients using INCS[72]. Referral to an ear, nose and throat specialist is advised for patients with nasal polyps, bleeding, unilateral disease, high crusting and septal perforations[79]. High crusting and septal perforations most commonly result from previous septal surgery but can also occur with cocaine abuse and vasculitides.

Asthma should always be assessed in patients with AR by asking patients about wheezing, shortness of breath and sleep disturbance plus, if needed, an objective measurement such as spirometry[80] and vice versa in patients with asthma owing to the frequent co-occurrence of these disorders. Patients should also undergo ear inspection as otitis media with effusion (also known as glue ear) may be a co-morbidity in children with rhinitis and in adults with severe forms of rhinosinusitis[81]. The general examination needs to also include skin examination for atopic dermatitis, and, in patients with obstructive rhinitis, assessment of thyroid function by checking for slow relaxation after the ankle jerk and for eye signs such as puffiness, redness and/or bulging, as hypothyroidism.

Tests

Whether further diagnostic testing for AR is required in all patients is disputed. Some clinicians do not recommend further testing in those with a clear history of nasal symptoms that are provoked by allergen exposure[82]. This occurs in most northern hemisphere patients allergic to pollen and with intermittent exposure to animal or occupational allergens but is not possible with long-term exposure, as with pollens in most tropical climates or indoor allergens such as house dust mites. By contrast, other clinicians recommend further testing in all patients with symptoms suggestive of AR. Testing for allergen-specific IgE using skin prick or blood tests[72] to identity the allergen can be performed to support the diagnosis and is mandatory when AIT is being considered as part of the treatment. Of note, the results from IgE testing need to be interpreted in the light of the clinical history, as both false-positive and false-negative results can occur[83]. In one meta-analysis of skin prick tests, the sensitivity ranged from 68% to 100% and the specificity ranged from 70% to 91% (REF.[84]).

Component-resolved diagnosis (that is, using purified native or recombinant allergens to identify IgE sensitivity to individual allergens) is not yet routine in AR diagnosis but may provide important information. For example, the detection of serum IgE antibodies to specific molecules (Phl p 1, Phl p 5, Bet v 1 or Pru p 3) could be used as a biomarker to predict AR persistence and the future onset of multimorbidities, such as asthma and/or pollen food syndrome[85–87]. Moreover, component-resolved diagnosis may be useful in understanding cross-sensitizations and in proposing AIT where specific molecular sensitization can guide the content of the vaccine[86].

Other diagnostic tests may be required to verify the diagnosis of AR or to make an alternative diagnosis. Additional tests include nasal allergen challenge, nasal cytology, nasal nitric oxide measurements and ciliary beat frequency analysis[72]. Nasal smear cytology is practised in some centres. The presence of a high number of eosinophils (although the necessary percentage of cells is debatable) suggests an inflammatory process but not necessarily AR (AR or non-allergic rhinitis with eosinophilia), which is likely to be corticosteroid responsive. Unilateral eosinophilia can occur so bilateral samples must be taken[88]. Nasal nitric oxide measurement is a simple and rapid test to discriminate AR, non-allergic rhinitis, and subgroups with acceptable sensitivity and specificity, but it can be done only in highly specialized centres[89].

Testing for local AR

Some patients with rhinitis who do not have systemic IgE sensitization identified via a skin prick test and serum allergen-specific IgE show nasal reactivity on a nasal allergen provocation test (whereby an allergen is entered into the nose). Nasal allergen provocation tests can be used when the history and systemic IgE results are not concordant, to monitor the progress of AIT and in research studies[90]. Local AR might be an independent rhinitis phenotype, although it is treated in the same way as AR[91].

Patients with rhinitis who have negative results on tests for allergy have non-allergic rhinitis, which can be caused by several factors that can broadly be divided into infectious and non-infectious factors. Tests to identify these factors are detailed in an EAACI position paper[72].

Box 1 | **Managing patients with AR during the COVID-19 pandemic**

The global spread of COVID-19 has caused sudden and dramatic changes in society and health care, including management of allergic rhinitis (AR). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) particles that are inhaled though the nose or the mouth bind to upper respiratory tract cells, and the nose is the first organ to be invaded[203]. In addition, SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2), and expression of ACE2 is lower in patients with allergic diseases, suggesting that they may be less prone to SARS-CoV-2 infection[204,205]. The effect of AR on COVID-19 is still a matter of debate, and no firm conclusion can be drawn[206]. Smell dysfunction and anosmia are common COVID-19 symptoms[207].

The allergy and immunology communities have quickly responded by mobilizing practice adjustments and embracing new paradigms of care to protect patients and staff from severe SARS-CoV-2 exposure[208–211] using telehealth[212]. Some recommendations regarding the treatment of AR in patients with COVID-19 have been made. For example, although oral corticosteroids are contraindicated in patients with COVID-19, they can be used without restriction in patients with AR and COVID-19 (REF.[213]). Practical recommendations were made to organize an allergy clinic[208]. In addition, Allergic Rhinitis and its Impact on Asthma (ARIA) and EAACI recommend stopping all forms of allergen-specific immunotherapy in patients with AR who have COVID-19 and continuing allergen-specific immunotherapy in patients with AR who do not have COVID-19 (REFS[214–216]). The possibility of expanding injection intervals in the continuation phase should be checked and may be beneficial. On the other hand, face masks may reduce the severity of AR symptoms[217].

As for any other chronic disease, is clear that the COVID-19 pandemic will profoundly change AR management owing to the infectivity of allergic patients, probable changes in management and major changes in health-care systems.

Mobile health

Mobile health tools use algorithms created using advanced statistics (neural networks) on data including medical diagnoses and questionnaire answers[92]. Very large numbers of patients can be studied with data obtained by mobile phones, and, in the future, mobile health added to machine learning may be useful for the screening of undiagnosed patients with AR in the general population.

Prevention

Many different attempts have been made to prevent allergic diseases, although most of these attempts have been unsuccessful. However, farm animal exposure in early life is a protective factor for allergic diseases in high-income countries[93] and also possibly in some LMICs, although the mechanisms are unclear[94]. In addition, early-life exposure to cats and dogs may prevent the development of allergy but results are not consistent[95]. The use of probiotics or prebiotics prenatally and postnatally has failed to reduce AR[96,97]. Moreover, the use of pharmacological therapies before allergen exposure cannot prevent the onset of symptoms in AR[98].

Management

Treatments for AR include education, allergen avoidance, pharmacotherapy and AIT[1,79,99]. Pharmacotherapy is effective in most patients and, when properly implemented, improves QOL; however, many patients do not follow prescriptions and are poorly adherent to pharmacotherapy.

No biologic has been approved for AR except omalizumab in Japan for *Cryptomeria japonica* allergy[100], and, owing to their costs and the prevalence of AR, newly developed biologics may be restricted to highly stratified patients with severe AR. Of note, some changes to the management of AR have occurred owing to the COVID-19 pandemic (BOX 1).

Education

As AR is a chronic condition that is caused by specific allergens, it is important for patients to try to identify allergens and/or environmental agents that may precipitate their AR. In addition, it is important for clinicians to inform patients of the importance of the correct use of intranasal sprays to ensure they correctly adhere to the therapy.

Allergen avoidance

When possible, avoiding or minimizing exposure to the causative allergens should be the first management step for AR. Although allergen avoidance may reduce symptoms of AR, it should never isolate individuals from social interactions. Data regarding the benefits of house dust mite avoidance in asthma are conflicting, and interventions designed to reduce house dust mites have unknown effectiveness[101]. For patients who are polysensitized, avoidance strategies are often challenging as it is difficult to eliminate all causative allergens or triggers[18]. Some classical, but often unproven allergen avoidance measures for AR include use of bed covers for house dust mite allergy, removing pets from the home, changing profession for occupational allergens or wearing masks for pollen allergy. An innovative approach is to feed cats with a cat food containing antibodies against Fel d 1 to reduce allergenicity of the cat[102].

Pharmacotherapy

Many pharmacological treatment options are available for the management of AR (TABLE 1). Oral and/or intranasal H_1-antihistamines, INCS and the fixed combination of INCS and H_1-antihistamines are all considered first-line treatments depending on the severity or burden of symptoms.

H_1-antihistamines. H_1-antihistamines for AR treatment are available in oral, intranasal and ocular formulations and are first-line treatments for patients with mild symptoms or those who do not want to use an INCS treatment. H_1-antihistamines block the action of histamine by acting as neutral receptor antagonists or inverse agonists of the histamine H_1 receptor[103]. Different H_1-antihistamines have different chemical structures, pharmacokinetics and potential for drug–drug and drug–food interactions, and they are classified into non-sedating, less-sedating and sedating groups on the basis of brain H_1 receptor occupancy[103]. The less-sedating second-generation oral H_1-antihistamines (such as desloratadine, loratadine, cetirizine, levocetirizine and rupatadine) and the non-sedating H_1-antihistamines (such as fexofenadine and bilastine) are well tolerated, safe and effective[104]. First-generation oral H_1-antihistamines should be avoided owing to adverse effects, in particular sedation, and are not recommended for AR treatment[103,105]. First-generation H_1-antihistamines have not been optimally studied as most trials of these therapies do not meet appropriate standards in terms of study design, meaning their relative efficacy is unknown[106].

Table 1 | **Treatment options for allergic rhinitis**

Treatment	Rhinorrhoea	Sneezing	Nasal itch	Nasal obstruction	Ocular symptoms	Onset of action
Oral H_1-antihistamine	++	++	+	+	+	1–3 hours
Intranasal H_1-antihistamine	++	++	+	+	0	<30 minutes
Ocular H_1 antihistamine	0	0	0	0	+++	15 minutes
Intranasal corticosteroid	+++	+++	+++	+++	+ to ++	6–48 hours
Intranasal corticosteroid plus intranasal H_1-antihistamine	++++	++++	++++	++++	+++	10–60 minutes
Nasal decongestant	0	0	0	+++	0	15 minutes
Intranasal chromone	+	+	+	+	0	15 minutes
Ocular chromone	0	0	0	0	++	15 minutes
Leukotriene receptor antagonist	+	+	+	+	0	1 hour
Intranasal anti-cholinergic agent	++	0	0	0	0	1 hour

0, no evidence of efficacy;+ to ++++, increasing levels of evidence of efficacy.

In general, the advantages of oral H_1-antihistamines are once-a-day administration, rapid and effective action and low cost. However, they are less effective than INCS, particularly for nasal congestion (which is a common symptom of AR). Oral H_1-antihistamines are often sufficient for the treatment of mild AR, and many patients prefer oral drugs to other formulations. Some oral H_1-antihistamines may, with caution, be used in pregnancy or in women who are breastfeeding (for example, cetirizine, levocetirizine and loratadine[107]).

Topically administered H_1-antihistamines (alcaftadine, azelastine, bepotastine, cetirizine, epinastine, ketotifen, and olopatadine (as eye drops) and azelastine and olopatadine (as nasal sprays)) are suitable for patients with mild AR or ocular symptoms. These medicines may have a bitter taste in 15–20% of patients. The effect begins 1–3 hours after administration[104,108]. Mild uncommon adverse effects include dry mouth, drug-induced rash and swelling of the salivary glands. As previously mentioned, patients should be educated on the correct way to administer intranasal H_1-antihistamines.

Intranasal corticosteroids. INCS such as beclomethasone, budesonide, ciclesonide, fluticasone propionate, fluticasone furoate, mometasone furoate and triamcinolone acetonide are first-line therapeutic options for patients with persistent or moderate to severe symptoms. INCS effectively control the four major symptoms of AR (TABLE 1), and some INCS (such as intranasally administered fluticasone furoate) can reduce ocular symptoms[109]. INCS are more effective than H_1-antihistamines and leukotriene receptor antagonists, particularly for nasal congestion, although their efficacy requires several hours or days[104,110] (TABLE 1). The mechanism of action of INCS is related to the local anti-inflammatory effect on nasal mucosal cells. As with intranasal formulations of other drugs, all patients should be educated on the correct way to administer intranasal products.

INCS are not systemically absorbed; therefore, there are no systemic adverse effects. The most common INCS adverse effects are local, including nasal irritation, stinging and epistaxis[111], and can usually be prevented by aiming the spray slightly away from the nasal septum. Long-term INCS use does not damage nasal mucosa or induce glaucoma[112], and growth effects in children seem to be minimal[78]. Some INCS, such as budesonide, can be safely used during pregnancy at the recommended therapeutic dose after a thorough medical evaluation[113].

INCS and intranasal H_1-antihistamine fixed combination. Fixed-dose combinations of INCS and intranasal H_1-antihistamine for treatment of AR and rhinoconjunctivitis include fluticasone propionate–azelastine[114] and mometasone–olopatadine, which was approved in Australia in 2019 (REF.[115]). These medications are more effective than the individual compounds administered separately, are well tolerated (except for some bitter taste in a few patients) and are effective within minutes (fluticasone propionate–azelastine)[116] or within 1 hour (mometasone–olopatadine)[117] (TABLE 1). These therapies are typically used in patients who failed to benefit from INCS treatment alone and have been suggested for use in non-adherent patients who treat their symptoms intermittently. Combining oral H_1-antihistamines and INCS does not seem to increase the efficacy of INCS[118,119].

Other drugs. Leukotriene receptor antagonists, montelukast and zafirlukast, are used in the treatment of AR. Their effect is close to that of oral H_1-antihistamines[104]. In Europe, leukotriene receptor antagonists have been approved by the EMA only for patients with co-morbid asthma and AR. Other AR therapies, such as chromones and ipratropium bromide, are effective for only some symptoms. For example, chromones (disodium cromoglycate) can mostly be self-administered and tried in patients with mild local ocular symptoms[104]. Chromones are safe, but their effectiveness is usually quite modest. The ipratropium bromide nasal spray is well tolerated but is effective only for nasal secretion[104]. Decongestants include intranasal sprays (for up to 7 days), such as oxymetazoline or phenylephrine sprays, and H1-antihistamines combined with decongestant

sympathomimetic tablets or capsules (for up to 10 days), such as acrivastine, cetirizine hydrochloride or desloratadine plus pseudoephedrine[104], and are indicated only in those with severe nasal obstruction and should not be used long term to avoid rhinitis medicamentosa (for intranasal preparations). Saline irrigation may reduce patient-reported disease severity in adults and children with AR, with no reported adverse effects[120,121]. Herbal products, homeopathy and acupuncture are still largely used for treatment of AR but lack clear evidence, and herbal medicine can cause adverse effects such as contact dermatitis, headache, itchy eyes and gastrointestinal symptoms[122].

AR pharmacotherapy and children. Few studies have evaluated AR pharmacotherapy in preschool children[99]. The therapies with demonstrated efficacy are rupatadine[123] and, in school-aged children, cetirizine[124], azelastine hydrochloride and the fluticasone propionate–azelastine fixed combination[125]. Cetirizine is approved at 6 months of age in some countries. In addition, INCS can be prescribed in preschool children, H_1-antihistamines are suitable for persons older than 1 year, and cromoglycate or antihistamine eye drops are suitable for patients older than 3 years.

AR pharmacotherapy in elderly patients. In most elderly patients, rhinitis symptoms, diagnosis and treatment are the same as for other adult age groups. However, elderly patients often have mixed AR and non-allergic rhinitis with multiple triggers and have higher levels of mucosal dryness than younger patients[126]. Rhinitis symptoms in elderly patients may include profuse rhinorrhoea without itching, isolated nasal obstruction usually when lying down, and nasal crusting in winter or in patients treated with diuretics.

INCS, oral H_1-antihistamines, intranasal H_1-antihistamines and the azelastine hydrochloride–fluticasone propionate fixed combination are first-line therapeutic options in elderly patients[127]. Of note, ageing can affect the nasal mucosa by increasing cholinergic activity and atrophy[126]; thus, the dose of topically administered therapies may need to be reduced in elderly patients. In addition, some therapies can cause specific adverse effects in elderly individuals. Indeed, oral decongestants or systemic glucocorticosteroids are not recommended in elderly patients owing to adverse effects[127]. Oral decongestants can cause, for example, palpitations, insomnia, nervousness, irritability, trouble with urination and reduced appetite, whereas glucocorticosteroids can induce glaucoma, cataract, osteoporosis and diabetes mellitus. Moreover, first-generation H_1-antihistamines are strongly discouraged in elderly individuals owing to sedation and anticholinergic effects[128,129]. Caution should be exercised in patients with co-existing diseases, polymedication and organ (such as renal or liver) dysfunctions[127].

Real-life data and next-generation guidelines. Real-life observational studies using mobile health have found that most patients with AR self-medicate or use over-the-counter medications, placing the pharmacist at the forefront of treatment[130]. Patients consulting primary care physicians usually have uncontrolled symptoms despite use of multiple medications. Adherence to treatment is a major issue[131], as many patients do not seek advice from physicians, do not follow the physician's prescriptions and self-medicate to control their symptoms often using over-the-counter medications[130]. Surprisingly, the use of multiple medications is associated with poor rhinitis control[132].

Some recommendations for AR treatment are based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guidelines[104,118,119,133]. Next-generation guidelines[134] were subsequently developed using existing GRADE-based guidelines and real-world evidence including data from randomized controlled trials, real-world data provided by mobile technology[131,132] and data from additive studies, such as allergen chamber studies assessing the speed of onset of medications[116,117] (TABLE 2). Real-life data

Table 2 | **Next-generation ARIA guidelines**

Guideline	GRADE evidence (RCT)	Real-world evidence
Oral H_1-antihistamines are less potent than INCS	V	RCT and RWD
Many patients prefer oral drugs	None	None
Intranasal H_1-antihistamines are less effective than INCS	V	RCT and RWD
Intranasal H_1-antihistamines are effective within minutes	None	Chamber studies
INCS are potent medications, first-line therapy in moderate to severe AR	V	RCT and RWD
INCS need a few hours to 1–2 days to be effective (except ciclesonide)	V	Chamber studies
The combination of INCS and oral H_1-antihistamines does not offer advantage over INCS	V	RCT and RWD
INCS and intranasal H_1-antihistamines are more potent than INCS in moderate to severe AR	With restriction	RCT and RWD
INCS and intranasal H_1-antihistamines are effective between 10 and 60 minutes	None	Chamber studies

Adapted with permission from REF.[134], Elsevier. AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; INCS, intranasal corticosteroids; RCT, randomized controlled trial; RWD, real-world data using mobile technology.

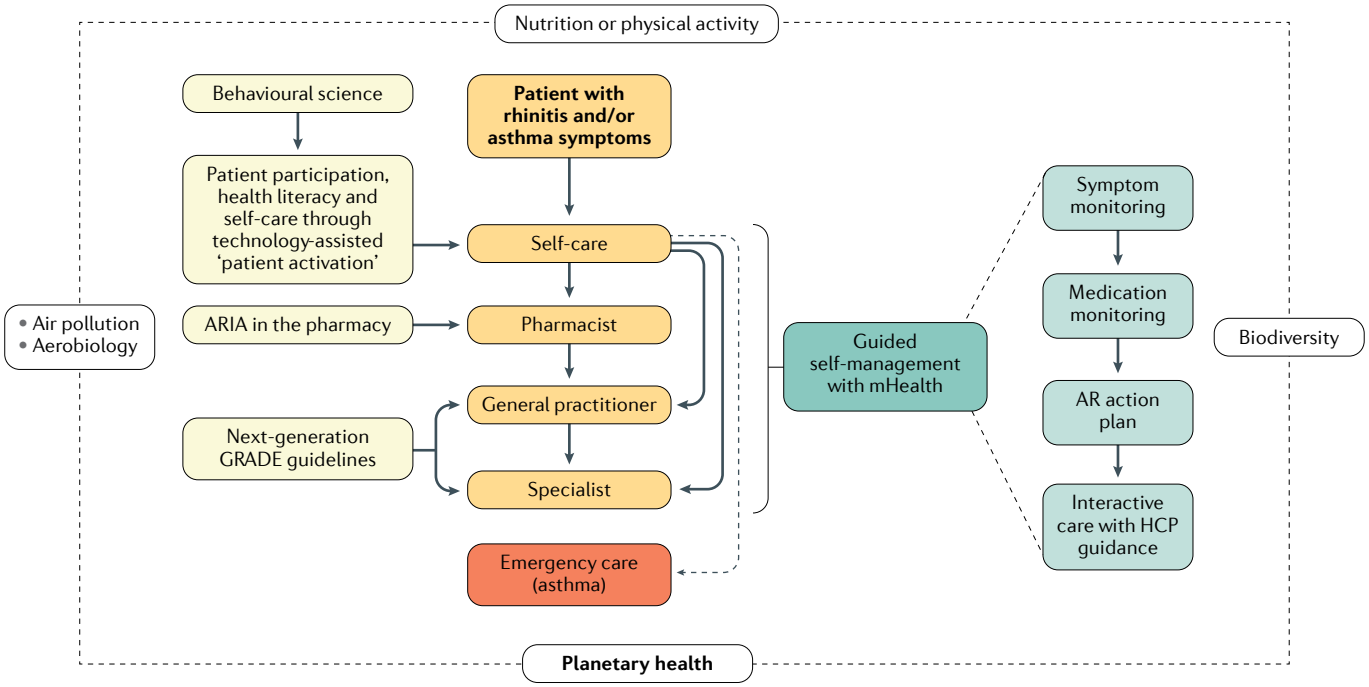

Fig. 2 | **Care pathways for allergic rhinitis.** The MASK-air study is conducted in 27 countries across the world. The MASK-air good practice was recognized by the Directorate-General for Health and Food Safety of the European Commission as a digital tool for citizen empowerment and for person-centred care. It proposes a stepwise care pathway for allergic rhinitis (AR). Patients with rhinitis symptoms typically use self-care. Patients typically then consult a pharmacist (in many but not all countries), then their general practitioner and then, if needed, specialists. Patients attend emergency care facilities in cases of severe asthma exacerbation. The next-generation care pathway approach for AR management proposes strategies to improve the stepwise approach using guided self-management with mobile health technology (mHealth). Non-pharmacological treatment (allergen and environmental pollutant avoidance, nasal saline douching exercise, nutrition and increasing biodiversity) needs to be included in the care pathway to sustain both patient and planetary health. ARIA, Allergic Rhinitis and its Impact on Asthma; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HCP, health-care professional. Adapted from REF.[135], CC BY 4.0.

clearly indicate that patients prefer as-needed treatment to continuous treatment, and this should be reflected in future guidelines.

Care pathways for a digitally enabled, patient-centred approach. AR treatment should be individualized according to the symptom profile, severity and duration, the patient's preference of oral versus intranasal administration, and the availability and affordability of medications. Mobile technology can improve shared decision-making, and one example has been recognized as a Good Practice by the Directorate-General for Health and Food Safety of the European Commission for digital health in AR[135] and for change management[136] (FIG. 2).

Multistakeholder care pathways should be established in each country or region as health-care systems differ[135,137]. As many patients with AR self-medicate and have poor symptomatic control, there is a great need to improve self-management for patients with AR, which can be aided by mobile health. In this scenario, patient counselling is first done by pharmacists with the help of allergy guides and websites (FIG. 3), following which patients should be referred to physicians. Mobile technology could reduce the time between the first symptoms and referral of patients with uncontrolled symptoms to specialists, as primary care physicians can have an objective assessment after the first allergy season (pollen or indoor allergens), including adherence to treatment and control of rhinitis and asthma.

Allergen-specific immunotherapy

AIT is indicated for AR, allergic rhinoconjunctivitis and/or asthma when symptoms remain uncontrolled with avoidance measures and appropriate pharmacotherapy in adherent patients[138].

The aim of AIT is to induce tolerance to the allergens and, therefore, to reduce the symptoms of allergic diseases. For a sustained effect, AIT should be applied for a minimum of 3 years, either continuously or preseasonally[139]. The induction of tolerance by AIT leads to changes in allergen-specific memory T cell and B cell responses and in the allergen-specific IgE and IgG antibody levels, and modifies the activation thresholds for mast cells, basophils and dendritic cells[140]. Of note, the levels of allergen-specific nasal and serum IgG4 antibodies correlate closely with the clinical response to AIT in patients with AR[141].

Selecting allergens that have a clinical effect on the patient is paramount to the success of AIT. These causative allergens can be identified through clinical history taking, component-resolved diagnosis and, if indicated and necessary, nasal provocation testing. The use of

prescription databases has indicated that the product-specific efficacy demonstrated in double-blind, placebo-controlled, randomized trials translates into real life[142]. Evidence of efficacy of AIT has been demonstrated for grass, birch (covering the homologous group of Betulaceae tree pollen), ragweed and *Cryptomeria japonica* pollen[143,144], as well as house dust mites[145], whereas less evidence is available for other types of pollen, animal dander or moulds. Only regulated, standardized allergen extracts that have demonstrated efficacy and safety should be used for AIT[138,146,147]. However, efficacy can be assumed for allergens within homologous groups, including several pollen and house dust mite extracts as defined by respective EMA guidelines for allergen products[138]. There is no evidence that mixing different allergens is effective in AIT, as this may result in underdosing and a potential degradation of specific allergens.

AIT can be applied via the subcutaneous or the sublingual routes, as tablets or drops, following the same indications and contraindications[148]. Natural allergens or chemically modified allergens (known as allergoids) may be used, with the aim of reducing the risk of adverse events but maintaining efficacy or enabling an increased dosage[138,149]. International and national guidelines are available[104,150–152] and are updated on a regular basis.

Owing to the need for long-term use and the cost in most countries, only selected patients should receive AIT, which should be prescribed by allergists (FIG. 4). However, no validated biomarkers for predicting or monitoring the efficacy of AIT at an individual patient level are available in clinical practice[153], although mobile health may be of great interest. The symptom–medication score, grading symptoms and medication use on a daily basis, still remains the most reliable parameter of success in daily practice.

Adverse effects of AIT are relatively common but are rarely severe[138]. Local reactions include redness and swelling at the injection site that occurs immediately or several hours after injection. Other adverse effects, such as sneezing, nasal congestion or hives, indicate systemic reactions. Serious reactions such as swelling of lips and tongue, laryngeal oedema, shortness of breath and chest tightness (asthma) in response to injections are very rare but require immediate medical attention and upfront preparations, such as availability of equipment and medications, and training of the personnel. Symptoms of an anaphylactic reaction typically include swelling in the throat, wheezing or tightness in the chest, nausea and dizziness and should be immediately treated with adrenaline (auto-injector) and preparation of an intravenous access. As most serious reactions develop within 30 minutes after injection, it is recommended that patients are supervised in the physician's office for at least 30 minutes before leaving. Allergen drops or tablets have a more favourable safety profile than injections. The first sublingual therapy dose should be administered under the supervision of a physician, but subsequent doses can be administered at home. Most adverse events are local (mouth itching, lip swelling and nausea) and spontaneously subside with further administration.

Quality of life

Health-related QOL (HRQOL) is the most frequently patient-reported outcome in AR (TABLE 3). The ARIA recommendations[73] have proposed grading AR severity by taking into account the effect of AR on HRQOL. Moreover, regulatory authorities such as the FDA[154] and the EMA[155] have provided guidance to the industry on how to use patient-reported outcomes to support labelling claims and routinely consider patient-reported outcomes as a tool used for data collection. In addition,

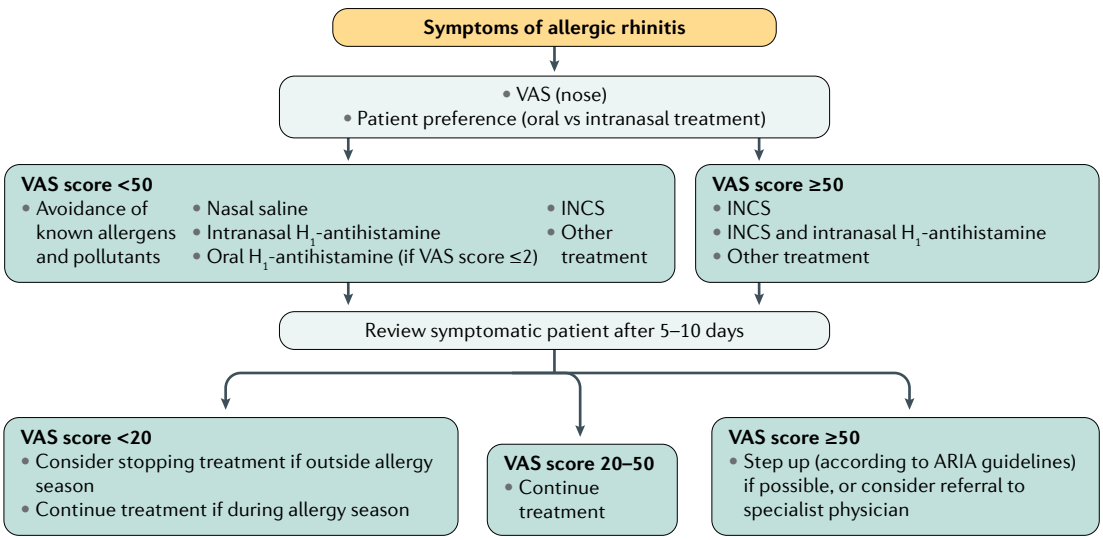

Fig. 3 | **Care pathway for the management of allergic rhinitis in the pharmacy.** A simple algorithm to help the pharmacist diagnose allergic rhinitis and dispense over-the-counter medications is required. Use of a visual analogue scale (VAS) to determine symptom severity is simple and accurate. The patient's symptoms need to be reassessed regularly if not daily to propose stopping the treatment, to continue use of over-the-counter medications or to send the patient to a physician. ARIA, Allergic Rhinitis and its Impact on Asthma; INCS, intranasal corticosteroids. Adapted with permission from REF.[130], Wiley.

patient preferences and values are introduced as cornerstones in GRADE, which is the best option for grading clinical evidence and developing recommendations for diagnostic and therapeutic interventions[156]. Although patient-reported outcomes are not explicitly included in the definition of personalized medicine, they represent a real opportunity for involving patients in each step of disease management[157].

The availability of validated questionnaires for AR has permitted the evaluation of the effect of this disease in adults, children and adolescents. The use of generic tools, which are applicable to all health conditions, has underlined that adults with AR who have HRQOL scores significantly lower than those of the general population have HRQOL scores that are lower than those of patients with asthma[158]. In addition, children and adolescents with AR had lower HRQOL scores than healthy peers[159]. The effect of AR on the physical domain of QOL was comparable in teenagers with AR and in those with asthma[160].

The aspects of HRQOL that are relevant for patients with AR have been identified by disease-specific questionnaires[161,162]. A rich literature shows how the presence and severity of symptoms negatively affect daily activities, performance, sleep, physical and emotional status and social functioning at all ages[163]; the effect of AR and multimorbid asthma[164–166]; the possibility to minimize or delete AR impact[164]; and the effect of symptomatic treatments[167] or specific immunotherapy. Of note, AR impairs QOL to a greater extent than moderate asthma[158] and significantly impairs work productivity[4].

Interest in the patients' perspective is continuously growing in AR research. Nonetheless, the routine use of HRQOL in clinical practice, which is encouraged owing to the potential to optimize disease management[168,169], remains limited. In the next few years, the questionnaires for assessing and monitoring AR HRQOL in individual patients need to be validated[170] and introduced into routine care.

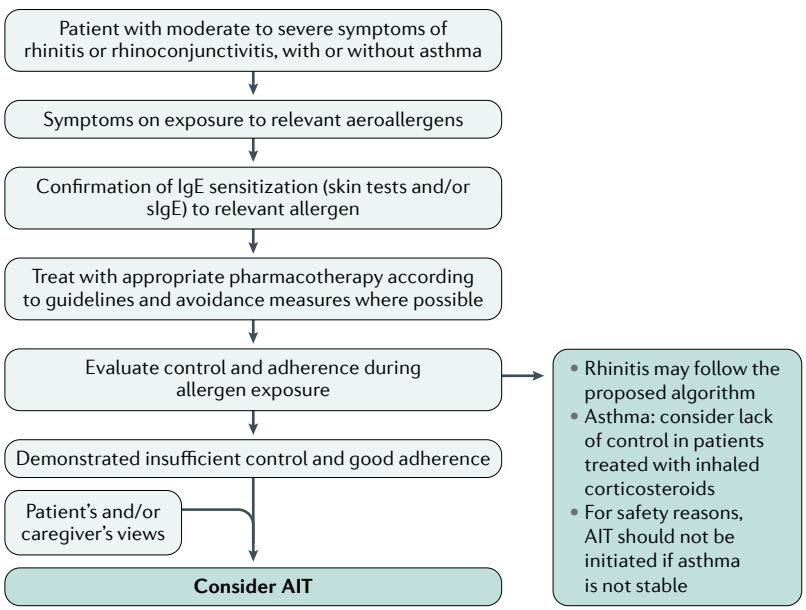

Fig. 4 | **Stratification of patients for AIT.** Only some patients with allergic rhinitis need allergen immunotherapy (AIT), such as patients who respond poorly to optimal treatment. Several steps are required before AIT can be performed, including a correct allergy diagnosis, the assessment of adherence to medications and the demonstration of an uncontrolled disease during the allergen exposure despite optimal medications. IgE, immunoglobulin E; sIgE, serum-specific immunoglobulin E. Adapted with permission from REF.[138], Wiley.

Outlook

Mobile health

Multimorbidity in allergic airway diseases is well known[76], but a mobile application (MASK-air) created to assess how multimorbidity affects symptoms and severity has provided further findings[32]. Indeed, data from this mobile application have revealed that AR and rhinoconjunctivitis do not seem to be the same disease and have identified a pattern of uncontrolled multimorbidity in some patients (uncontrolled rhinitis, conjunctivitis and asthma on the same day)[32]. Data from such mobile applications are generating hypotheses that need confirmation in epidemiological studies. In this regard, differences between AR alone and AR associated with conjunctivitis were previously known[29] but epidemiological studies using data from mobile applications demonstrated that ocular symptoms are more common in patients with polysensitization[30], are associated with nasal symptom severity[33] and are important to consider in severe asthma[33]. Moreover, the severity of allergic diseases increases with the number of allergic multimorbidities[34]. This is the first example of a discovery of novel allergic phenotypes using a mobile health application confirmed by classic epidemiological studies. Other mobile tools have been proposed[171] but few have been tested[172]. There is an urgent need to replicate existing data and to optimize mobile health for AR management in the digital transformation of health and care[173]. An interesting approach will be to propose alerts for pollen[174], pollution or asthma exacerbations[175].

Mechanisms and multimorbidity

As previously mentioned, allergic diseases are heterogeneous; some patients have AR alone, whereas others have AR and asthma (with or without other allergic manifestations), although few patients have asthma alone. In addition, there are probably common genes associated with asthma and AR and specific genes associated with AR alone. Combining big data analyses (such as from the MASK-air application[135]), classical epidemiological studies, in silico analysis, transcriptomics using microarray data (as exemplified in MeDALL[22,24,35]) or RNA sequencing[176] has led to the reclassification of the mechanisms of allergic diseases. For example, polysensitization and multimorbidity represent the extreme allergic phenotype, starting early in life, and are associated with *IL5* and *IL33* activation. Notably, several of these and other genes associated with allergic multimorbidity point towards type 2 inflammation[177] and eosinophil activation[24]. By contrast, rhinitis alone is associated with Toll-like receptor pathways, which have a key role in the innate immune system. Assessing these mechanisms in more detail may allow better understanding of the mechanisms of allergy and provide novel insights for prevention and treatment. Although it is well established that

Table 3 | **Questionnaires for the assessment of HRQOL in patients with rhinitis**

Questionnaire	Number of items	Population	Ref.
Rhinoconjuctivitis Quality of Life Questionnaire (RQLQ)	28	Adults	196
raciborskiMini Rhinoconjunctivitis Quality of Life Questionnaire (Mini-RQLQ)	14	Adults	197
Nocturnal Rhinoconjunctivitis Quality of Life questionnaire (NRQLQ)	16	Adults	198
RHINASTHMA	30	Adults	199
RhinAsthma Patient Perspective (RAPP)	10	Adults	170
Adolescent Rhinoconjunctivitis Quality of Life Questionnaire	25	Adolescents	200
RHINASTHMA Adolescents	20	Adolescents	166
Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ)	23	6–12 years	201
RHINASTHMA children	17	6–11 years	165
RhinAsthma Patient Perspective children (RAPP)	5	6–11 years	202

HRQOL, health-related quality of life.

rhinitis can lead to asthma, the exact phenotype of AR prone to developing asthma is still unclear. It is possible that polysensitized individuals can more commonly develop asthma.

New treatments

As many patients do not experience full relief from AR symptoms with available treatments, knowledge gaps undermine the development of new pharmacological and biological interventions to improve management. One important area of research is the identification of novel reliable biomarkers to phenotype or endotype patients with AR to predict treatment response and management strategies. Other areas of research include the elucidation of novel molecular mechanisms involved in allergen-specific response perpetuation in the nasal mucosa and translational integration of genomics, transcriptomics, proteomics and metabolomics into health care.

Novel cost-effective pharmacological treatments

Despite AR being one of the most prevalent diseases in the world with a high economic burden, no big pharmaceutical companies are developing novel treatments. The reasons for this paradox are complex but can be summarized as follows: overall, low-cost medications are effective in most patients if they are used appropriately, and, in many countries, they are given over the counter with no cost for the payers; AR is not a life-threatening disease and payers prioritize life-saving medications, for example, for cancer, rare diseases and COVID-19; developing medications with an efficacy substantially higher than that of those currently on the market may be difficult; and, owing to the number of patients with AR, only low-cost medications may eventually be reimbursed if patients with AR are not stratified, and therefore the cost of the development of an AR treatment largely surpasses potential revenues and very few trials are ongoing[178].

In addition, although monoclonal anti-IgE or anti-IL-4/IL-13 is effective in AR[179,180] and some of the available biologics (or those in the pipeline) for asthma may be suitable for patients with severe, multimorbid allergic conditions or stratified patients with very severe AR, there are only a few repurposing attempts for asthma medications. One example is montelukast, which, in Europe, is indicated only for asthma with AR multimorbidity as there was a request from the payers to lower the price of the asthma drug if the medication was also approved for AR alone. In addition, monoclonal antibodies to allergens may be of interest in those with AR caused by a single major allergen driving the allergic reaction.

Patient stratification is needed to find a group of patients that are unresponsive to the current medications and to obtain indirect costs incurred by these patients. The estimated cost of AR in Europe owing to presenteeism ranges from €25 billion to €50 billion[6]. A novel model of reimbursement of medications should be developed with, for example, enterprises paying for a potential new treatment with a precise cost-effectiveness analysis showing potential benefits. Mobile health can have a role in the cost-effectiveness analysis.

Improved treatment

Increasing safety while maintaining or even increasing efficacy are the main goals of research for novel vaccine development and improvement of treatment schemes in AIT. Perspectives in AIT are well established[181], and many new products are in development[182–185]. However, the vast majority of previous attempts failed because safety issues or lack of efficacy was observed. Future directions for conventional AIT include use of adjuvants, including vitamin D, Toll-like receptor ligand agonists, biologics[186] or probiotics[187]. Several attempts have been made to increase tolerance and efficacy using molecular allergy vaccines acting on B cells or T cells but none has produced convincing results[188].

Treatment of AR could also be improved by the use of shared decision-making, a process whereby both the patient and the physician contribute to the medical decision-making process. In AR, data from mobile technology have revealed that patients are not adherent to treatment and self-medicate using as many medications possible to control their disease. Accordingly, there is an urgent need to propose shared decision-making using mobile health tools to optimize AR treatment. In addition, drug repurposing could be useful for treatment

of AR and could be aided by mobile health[135,189,190]. Value-added medicine can help address unmet patient needs and could improve treatment-associated QOL.

The global allergy solution

The delivery of cost-effective modern health care is challenging for the management of chronic diseases and in particular for allergic diseases[191], as management, which is often dependent on specialist and supporting services, is becoming unaffordable. Accordingly, innovative solutions often based on mobile health are required[192,193]. Authorities should be supported for the transformation of health and care towards integrated care with organizational health literacy for allergic diseases[135,173,194] A global allergy simple solution should provide the framework to digitally transform the prevention and control of allergic diseases in a cost-effective manner. Mobile health could be used optimize an accessible and affordable treatment in stratified and participatory patients with allergic diseases to provide change management[195].

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Author contributions

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