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Allergic rhinitis
Making Education Easy 2022

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This education review outlines various treatment strategies recommended for the management of allergic rhinitis (AR), with a focus on the place of combination therapy (intranasal antihistamine and intranasal corticosteroid). This review also outlines how mobile technology, such as the MASK-air® app, can provide insights into how AR is treated and managed in the real world.

Introduction

Allergic rhinitis (AR) is caused by immunoglobulin E (IgE)-mediated reactions to inhaled allergens and it involves mucosal inflammation that is driven by type 2 cells.[1-3]

AR is characterised by various symptoms, including sneezing, nasal itching, sniffing, nasal obstruction/congestion, itchy throat, the frequent need to clear the throat, clear rhinorrhoea (nasal discharge), and allergic conjunctivitis.[1, 2]

Classification

Depending on the timing of the allergen exposure, historically AR has been defined as:[2]

- Perennial, in which the symptoms may appear year around and are often triggered by indoor allergens; or
- Seasonal, in which the symptoms worsen during spring or summer, with pollens or moulds being the trigger(s)

However, epidemiological studies do not support this distinction, as most patients are polysensitsed (i.e., sensitised to more than one allergen).[1] Instead, the organisation Allergic Rhinitis and its Impact on Asthma (ARIA) have suggested replacing seasonality with intermittent and persistent rhinitis.[1, 3] In addition, AR can be classified as mild or moderate/severe depending on the severity of the symptoms (**Figure 1**).[1, 2]

AR can also be defined as occupational, with chemicals, irritants, and allergens in the workplace triggering the development of symptoms.[1, 2]

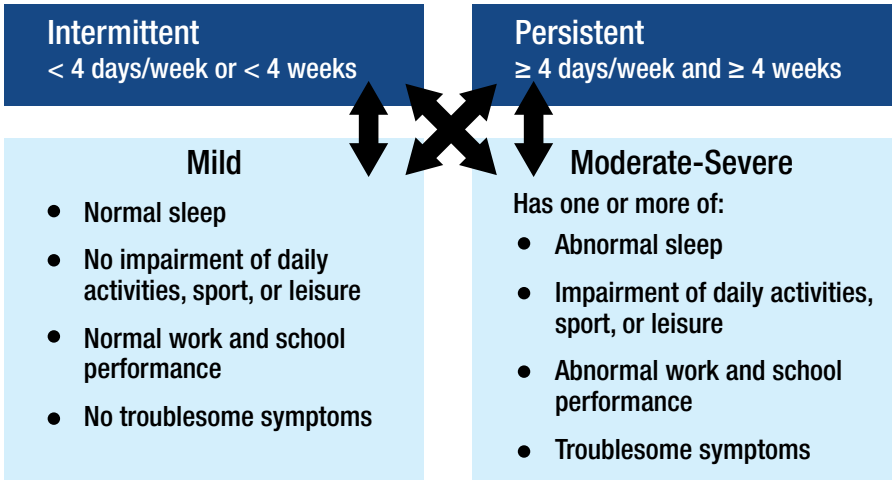

Figure 1. Classification of allergic rhinitis[2]

Allergens and risk factors

AR appears to be the consequence of environmental exposure to allergens acting on a predisposed genetic background.[1]

Allergens present in the environment which are associated with AR include:[1, 2]

- pollens from grasses, weeds (e.g., ragweed), and trees that are wind pollinated;
- moulds;
- house dust mites; and
- pet dander.

Risk factors for AR include antibiotic use, self-reported air pollution, exposure to farm animals, exposure to cats and/or dogs, maternal and paternal smoking, and vigorous physical activity in adolescents.[1]

Diagnosis

The diagnosis of AR is based upon the concordance between a typical history of allergic symptoms, supported by examination findings (physical examination, and, if needed, nasal endoscopy), and diagnostic testing (if necessary).[1-3] Diagnostic testing may involve skin prick testing or serum specific IgE testing for aeroallergens sensitisation.[2] However, pharmacotherapy for AR can be initiated based on symptoms without waiting for diagnostic allergy testing.[2] Diagnostic tests increase the accuracy of the diagnosis and identification of potential allergens.[2]

Epidemiology

AR is one of the most common allergic reactions, affecting nearly 20% of Australians (more than 4.6 million people in 2017-2018), with the Australian Capital Territory having the highest rate (29%).[4] The prevalence of AR increases throughout childhood and into early adulthood,[4, 5] as demonstrated in the longitudinal Perth Infant Asthma Follow-up (PIAF) cohort study.[5] In this study, the prevalence of AR increased rapidly from 7% at age 6 years to 18% at age 11 years and then increasing to 44% at 24 years.[5]

Burden of disease

AR is associated with disability, and it can significantly reduce a patient's quality of life.[1, 6] It affects social life, sleep, school/work, and daily activities.[7-9] The economic impact of AR is often underestimated but the indirect costs are substantial.[10-12] In Tasmania, for example, total costs for AR in 2018 were estimated to be between $AU65.3 million and $AU259.7 million, with the main financial burden being related to productivity losses from presenteeism and absenteeism.[12]

United airway disease

AR and asthma are upper and lower tract manifestations, respectively, of the same inflammatory process known as "united airway disease".[2, 13] AR is a risk factor for subsequent asthma development.[2, 13] Moreover, most people with asthma also have some form of upper airway inflammatory disease such as AR.[14, 15] Poorly controlled AR can also worsen asthma symptom control and increase the risk of exacerbations or flare-ups.[2, 13] In children and adults with asthma, the likelihood of needing hospital treatment is more than doubled by the presence of AR.[16]

AR is also associated with a variety of other comorbidities, such as atopic dermatitis, food allergies, conjunctivitis, sinusitis, otitis media, sleep problems, secondary effects on concentration and behaviour, and turbinate hypertrophy.[17]

Expert comment

Patients with nasal symptoms may present to general practitioners and pharmacists seeking treatment for their condition. However, as with other chronic conditions, patients can become accustomed to their symptoms over time and not bother to seek help with them. It is important that clinicians actively ask about nasal and other allergic symptoms when patients are seen with three other specific conditions that can be caused by or exacerbated by AR. These are chronic cough (upper airway cough syndrome), snoring and obstructive sleep apnoea, and asthma.

Obstructive sleep apnoea and snoring occur when the upper airway muscles relax too much during sleep, so that the negative pressure in the pharynx that is generated during inspiration, causes the upper airway to collapse. When asleep, people preferentially breathe through their noses. If the nose is congested or blocked, there will be more negative pressure generated in the upper airway worsening sleep apnoea and snoring.[18]

Sleep apnoea is twice as common in those with, than those without, AR.[19]

One cause of chronic cough is nasal congestion. The mechanism is not fully understood and may relate to mucus moving from the back of the nose into the pharynx stimulating cough receptors and/or a common inflammatory mechanism in the nose and pharynx.[20]

About 75% of people with asthma may also have AR, and these people tend to have poorer asthma control.[14, 15]

Treatment

AR is often under-diagnosed, under-treated, and sub-optimally self-treated.[2, 21] Patients can consider AR to be a nuisance and may mistakenly think there is no effective treatment.[2] However, AR can be effectively treated.[2]

Treatment for AR includes education, allergen avoidance, allergen immunotherapy, and pharmacotherapy.[1, 22]

Patient education is central at all stages of treatment and should include education about the disease, awareness of symptoms, importance of adherence to treatment, and the correct use of intranasal sprays.[22] Patient participation in the decision-making process and in goal-setting is encouraged, and therapy should be matched to these goals and to patient preference.[22]

Allergen avoidance or minimisation of confirmed allergens may help some individuals reduce the severity of AR symptoms.[1] However, this can be difficult to achieve, especially for outdoor allergens or dust mites.[2] Avoiding exposure to cats and dogs during early life may prevent the development of allergy but results are not conclusive.[23] Interestingly, the wearing of face masks due to the COVID-19 pandemic has reduced AR symptoms in chronically affected individuals with intermittent disease, potentially by reducing the allergic response.[24]

Allergen immunotherapy involves the regular administration of commercially available allergen extracts to promote clinical tolerance to the allergen(s).[2] It is potentially curative in patients with moderate-to-severe symptoms;[25] however, it can take 3 to 5 years to produce durable results.[2, 25]

Pharmacotherapy

Pharmacotherapy options (**Table 1**) for patients with AR include:[1, 2, 21, 22]

- Non-sedating oral and/or intranasal H_1-antihistamines;
- Intranasal corticosteroids (INCSs); and
- Fixed combinations of INCSs and intranasal H_1-antihistamines.

Other possible treatments may include saline treatments, intranasal and ocular chromones, intranasal anticholinergic sprays and oral leukotriene antagonists (**Table 1**).[1, 2] Decongestants and systemic oral corticosteroids may be used as short-term treatment options.[1, 2]

A guide to the main intranasal treatment options for AR available in Australia, as of mid-August 2022, is available here.

Table 1. Treatment options for allergic rhinitis[1]

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	++++	++++	++++	++++	+++	5-10 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.

H_1-antihistamines

Oral and intranasal H_1-antihistamines are recommended as first-line treatments for patients with mild symptoms of AR.[1, 2, 21, 22] However, first-generation oral H_1-antihistamines should be avoided owing to adverse effects, in particular sedation, and are not recommended for AR treatment.[1, 2] Intranasal H_1-antihistamines have a very rapid onset of action (within 30 minutes) and may be used as a rescue medication to provide immediate relief of symptoms.[2] Oral H_1-antihistamines can be administered once or twice daily, and they have a rapid and effective onset of action (1-2 hours).[1, 2, 21, 22] However, they are less effective than INCSs, particularly for nasal congestion (which is a common symptom of AR).[1, 2, 21, 22]

Intranasal corticosteroids

INCSs are first-line therapeutic options for patients with persistent or moderate-to-severe AR symptoms.[1, 2, 21, 22] INCSs effectively control the major symptoms of AR (**Table 1**).[1, 2, 21, 22] INCSs are more effective than H_1-antihistamines and leukotriene receptor antagonists, particularly for nasal congestion, although their efficacy may not be apparent for several hours or days (**Table 1**).[1] The mechanism of action of INCSs is the result of their local anti-inflammatory effect on nasal mucosal cells.[1]

The most common adverse effects associated with INCSs are local, including nasal irritation, stinging, and epistaxis, and these can usually be prevented by aiming the spray slightly away from the nasal septum.[1] The long-term use of INCSs does not damage nasal mucosa or induce glaucoma.[1]

INCS and intranasal H_1-antihistamine fixed combinations

Fixed combinations of an INCS and an intranasal H_1-antihistamine for treatment of AR offer the combined advantages of both medications (**Table 1**). Examples include azelastine hydrochloride-fluticasone propionate (Product information; DYMISTA®)[26] and olopatadine hydrochloride-mometasone (Product information; RYALTRIS®).[27]

The combination of an INCS and an intranasal H_1-antihistamine is more effective than an INCS or H_1-antihistamine administered separately.[1, 21] Fixed combinations are generally well tolerated, and they are rapidly effective against both nasal and ocular symptoms (**Table 1**).[1, 21]

Expert comment

Not only can treating AR improve the symptoms and quality of life specifically related to the AR, but it can also have other benefits.

Reducing nasal congestion with intranasal corticosteroids can reduce the severity of obstructive sleep apnoea.[19, 28] But the main treatment for obstructive sleep apnoea is continuous positive airway pressure (CPAP). Nasal masks are usually preferred by patients, so having the nose clear makes it easier to use CPAP. Ask about nasal congestion and treat it before CPAP is commenced to improve adherence with CPAP.

It is difficult to suppress cough, so the best way to treat chronic cough is to treat the underlying cause. Rhinitis or post-nasal drip, now called upper airway cough syndrome, is a common cause of chronic cough. Specifically ask about nasal symptoms, and if they are present, treat them enthusiastically. If the cough is related to the AR, it should improve and maybe resolve completely.

Patients with asthma and/or AR may confuse the symptoms of each and use inappropriate treatments. Those with asthma should be treated with inhaled corticosteroids possibly combined with a long-acting beta agonist. They should be specifically asked about AR, and if it is present, it should also be treated with intranasal corticosteroids, possibly combined with an antihistamine.

Treatment guidelines and algorithms

This section will outline recent guidelines and algorithms, focusing on recommendations involving fixed-combination treatments.

ASCIA guidelines

The Australian Society of Clinical Immunology and Allergy (ASCIA) guidelines recommend that pharmacotherapy for AR follows a stepwise approach according to the duration and severity of symptoms (**Figure 2**).[2] In particular, ASCIA guidelines recommend the combination of an INCS and an intranasal H_1-antihistamine as first-line therapy for patients with persistent and mild, intermittent and moderate-severe, and persistent and moderate-severe AR.[2]

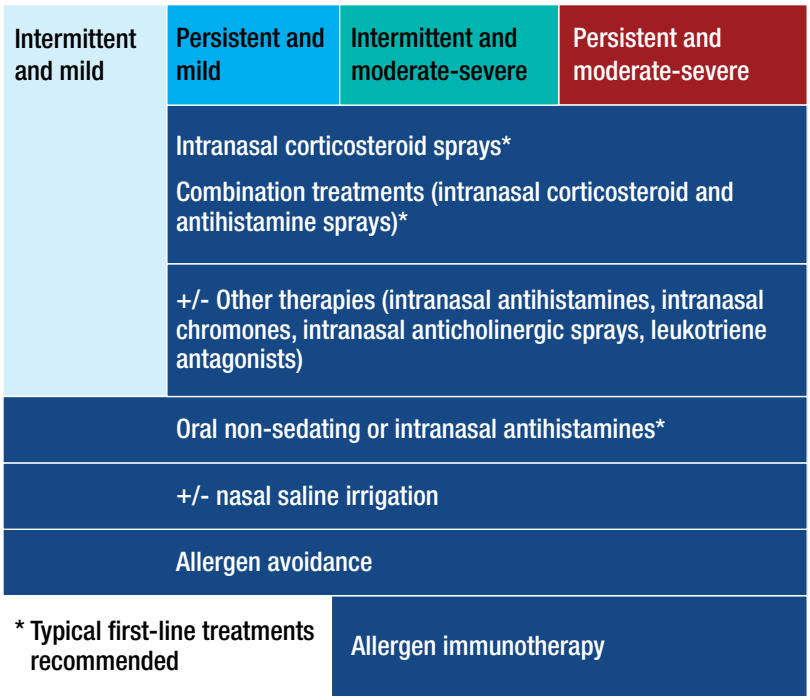

Figure 2. Stepwise treatment of allergic rhinitis, according to Australian Society of Clinical Immunology and Allergy (ASCIA) guidelines[2]

ARIA guidelines

ARIA have developed next-generation guidelines (**Table 2**) for the pharmacologic treatment of AR by using existing GRADE (Grading of Recommendations Assessment, Development and Evaluation)-based guidelines, real-world evidence provided by mobile technology (see section below), and additive studies (allergen chamber studies).[21] The ARIA guidelines recommend the fixed combination of an INCS and intranasal H_1-antihistamine as therapy in patients with AR, noting that this combination is more effective than INCSs and that it is effective within minutes (**Table 2**).[21]

Table 2. Next-generation ARIA guidelines[21]
Oral H_1-antihistamines are less potent than INCSs BUT many patients prefer oral drugs
Intranasal H_1-antihistamines are less effective than INCSs
Intranasal H_1-antihistamines are effective within minutes
INCSs should continue being prescribed as first-line therapy in patients with moderate-to-severe rhinitis
Onset of action of INCSs takes a few hours to a few days (ciclesonide has a faster onset)
The combination of INCSs and oral H_1-antihistamines offers no advantage over INCSs
The combination of INCSs and intranasal H_1-antihistamines is more effective than INCSs
The combination of INCSs and intranasal H_1-antihistamines is effective within minutes
Leukotriene antagonists are less potent than INCSs

INCSs = intranasal corticosteroids.

EUFOREA algorithm

The European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) have developed a treatment algorithm to expedite access to AR treatment and facilitate coordinated care (**Figure 3**).[22] Patient education is central at all stages and patient participation in the decision-making process and in goal-setting is encouraged.[22] Therapy should be matched to these goals and to the patient's preference.[22] In particular, digital technology can be used to support adherence and to evaluate disease control.[22]

AR treatment is selected depending on the type and the history of the patient, disease control (assessed by visual analogue scale [VAS]), and point of care (i.e., pharmacy, general practitioner, or specialist).[22]

In the first treatment step, patients with suspected AR presenting to any care provider should be treated with an INCS, a non-sedating oral H_1-antihistamine, or an intranasal H_1-antihistamine.[22]

The second treatment step includes patients who have tried and failed (i.e., VAS score ≥5/10 cm) the first treatment step at the pharmacy or previously at physician level and patients with difficult to treat AR. At this step, a diagnosis of AR should be confirmed, medication adherence checked, and co-morbidities evaluated. Treatment should be stepped up to a fixed-dose INCS/ intranasal H_1-antihistamine. Add-on therapy to intranasal corticosteroid is not recommended.[22]

The third treatment step involves patients who have tried and failed Step 2 treatment (VAS remains ≥5/10 cm) or those who present with severe symptoms.[22]

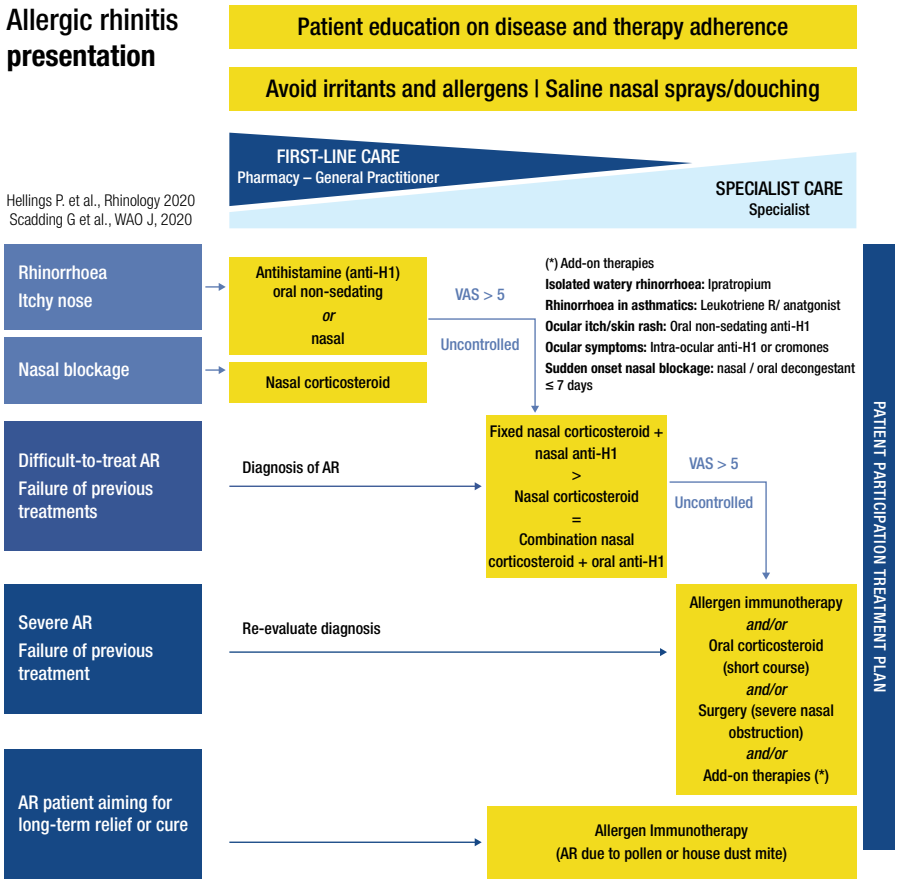

Figure 3. EUFOREA allergic rhinitis pocket guide treatment algorithm[22]
AR = allergic rhinitis; **VAS** = visual analogue scale.

Expert comment

There are now multiple studies showing the effectiveness of intranasal corticosteroids in the treatment of AR, and that when combined with an antihistamine, patients will have a reduction in symptoms, which is quicker and to a greater extent than using a corticosteroid alone. Even though these sprays are easy to use, patients still need to be taught how to use them properly to get maximum benefits.

The left hand should be used to spray in the right nostril and the right hand for the left nostril. The drugs work by acting on the mucosa, not the mucus in the nose. So, the nose should be cleaned of mucus with saline washes before using the AR spray.

Occasionally some people get nose bleeds with intranasal corticosteroid sprays. If this happens, I suggest that they stop the spray until the bleeding stops, then resume the spray at a reduced frequency.

Real-life data and mobile technology

Real-life observational studies involving the use of mobile technology can complement data from randomised, controlled trials.[29] Real-world data obtained by mobile technology are offering new insights into AR phenotypes and their management.[1]

Mobile health (mHealth) apps such as MASK-air® (Mobile Airways Sentinel NetworK) can collect large volumes of direct patient data for patients with AR and/ or asthma.[29, 30] This app can also be used to monitor symptoms and can act as a useful reminder for patients to take medication.[29]

MASK-air® has been available since 2015 and can be downloaded via the Apple App and Google Play Stores in 27 countries (www.mask-air.com). MASK-air® comprises a daily monitoring questionnaire in which patients are requested to quantify the impact of their AR symptoms on that day, as well as to provide information on the medication used.[29]

Cross-sectional studies that have analysed MASK-air®-directed patient data have provided novel information on medication use and disease control in the everyday life of AR patients.[29-35] Data from these studies can, and have been, incorporated into digitally-enabled, patient-centred next-generation guidelines (e.g., the ARIA guidelines).[21, 29]

A recently published study assessed MASK-air® app data (May 2015–December 2020) from users aged 16–90 years with self-reporting AR.[29] As part of the study, the researchers compared different medication schemes on reported VAS of allergy symptoms.[29] The impact of allergen immunotherapy on AR symptoms was also assessed (**Figure 4**).[29]

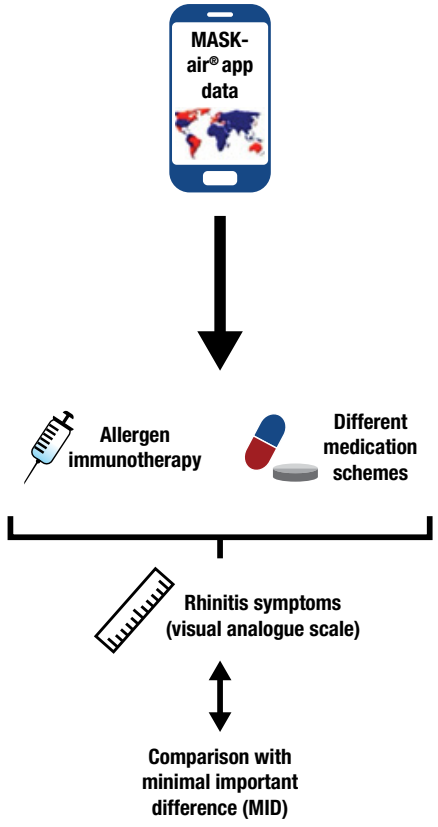

Figure 4. Study design of a MASK-air study comparing treatments used in patients with allergic rhinitis[29]

The study analysed 269,837 days from 10,860 users.[29] Most days (52.7%) involved medication use.[29]

Median VAS scores for global symptoms, nose symptoms, eye symptoms, and impact on work, respectively, are shown in **Figure 5**, with the lowest median global VAS scores being observed with azelastine-fluticasone and INCSs (**Figure 5**).[29]

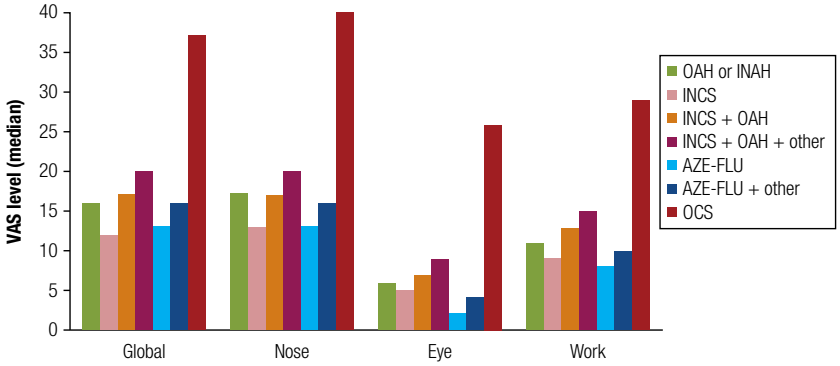

Figure 5. Median visual analogue scale (VAS) levels for global allergy symptoms, nose symptoms, eye symptoms and impact of allergic rhinitis on work[29]
INAH = intranasal antihistamines; **INCS** = intranasal corticosteroids; **AZE-FLU** = azelastine-fluticasone; **OAH** = oral antihistamines; **OCS** = oral corticosteroids.

Multivariable linear mixed-effects models demonstrated that azelastine-fluticasone (fixed combination) was the treatment associated with the lowest adjusted average VAS score for global allergy symptoms when compared with no treatment (i.e., on days when VAS was low), while the contrary was observed for oral corticosteroids (**Table 3**).[29]

Table 3. Difference in visual analogue scale for global allergy symptoms with medication scheme versus no treatment[29]

	Number of days	Average difference in VAS on days of treatment vs VAS on days of no treatment (95% CI)
No treatment	127,565	
Any treatment	142,272	6.2 (6.1; 6.4); p<0.001
OAH or INAH	39,736	7.9 (7.7; 8.1); p<0.001
INCS	22,577	2.2 (1.9; 2.5); p<0.001
Azelastine-fluticasone	12,755	1.5 (1.1; 1.9); p<0.001
Any OCS	2457	15.0 (14.1; 15.9); p<0.001

CI = confidence interval; **INAH** = intranasal antihistamines; **INCS** = intranasal corticosteroids; **OAH** = oral antihistamines; **OCS** = oral corticosteroids; **VAS** = visual analogue scale.

Azelastine-fluticasone was also the least likely to be combined with other medications (adjusted odds ratio 0.75 95% CI 0.71, 0.80).[29]

Expert comment

As with all chronic conditions, adherence with treatment can be a problem in AR. Symptomatic improvement can occur quickly with an intranasal corticosteroid, particularly when combined with an antihistamine. Patients then tend to forget to keep taking their treatment. The AR has been suppressed, not cured, so when treatment has been stopped, the symptoms will recur. Patients need to be educated that persistent AR requires long-term treatment to keep the symptoms under control. Even intermittent AR requires continuous treatment for months, not just a few days. The study by David Price showed that symptoms continued to improve over several months of continuous use, and that the benefits lasted for at least fifty-two weeks.[36]

Using electronic devices and apps as reminders and providing feed-back are becoming a part of everyday life. People commonly monitor their exercise, sleep, and diet, and use electronic diaries and reminders. These are also becoming standard care in conditions such as obstructive sleep apnoea and diabetes. An app has been developed called MASK-air® (Mobile Airways Sentinel NetworK) for use in allergic conditions such as asthma, AR, and allergic conjunctivitis.[37] It is free to download, and provides feedback and reminders to patients about their treatments. When used in clinical practice, it has been shown to improve adherence with AR treatments and reduce symptoms.[30]

Clinicians can also use MASK-air® to check their patients' adherence with medication. This is useful as patient-reported adherence can often be an overestimate. Poor adherence with medication is a common cause of the lack of response to treatment.

Take-home messages

- AR is a local IgE-mediated allergic reaction, involving a response of the nasal airways to inhaled allergens.
- Nearly 20% of Australians (more than 4.6 million people) have reported AR, with this disorder impacting an individual's social life, sleep, school/work, and daily activities and reducing their quality of life.
- AR is often under-diagnosed and under-treated, despite the availability of effective pharmacological treatments.
- Available treatment options for AR include:
  - non-sedating oral and/or intranasal H_1-antihistamines;
  - INCSs; and
  - fixed combinations of an INCS and an intranasal H_1-antihistamine.
- Recent guidelines and algorithms recommend the use of fixed combinations of an INCS/intranasal H_1-antihistamine in the management of AR.
  - The next-generation ARIA guidelines note that a fixed combination of an INCS and an intranasal H_1-antihistamine is more effective than INCSs in patients with AR, and that it is effective within minutes.
- Real-world data obtained by mobile technology are offering new insights into AR phenotypes and their management, with the data increasingly influencing guideline recommendations.
  - In particular, the MASK-air® digital tool can be used to help both patients and their healthcare professionals track AR symptoms and treatment.

Expert's concluding remarks

AR is common in Australia. Some people present to have the symptoms relieved and quality of life improved. In addition, we should ask about AR symptoms in patients with chronic cough, asthma, and snoring and obstructive sleep apnoea. Treating AR in these groups of patients may also help with their other conditions.

AR is an allergic type of inflammation predominantly mediated by eosinophils. As eosinophils are well compressed by corticosteroids, corticosteroids have become the main treatment for AR. Systemic corticosteroids have significant side effects. These adverse effects can be avoided by using corticosteroids topically – that is intranasal corticosteroids.

When intranasal corticosteroids are combined with antihistamines, symptoms will be brought under control more quickly, and more people will have their AR symptoms controlled in the long term.

When using these nasal sprays, patients should clean their noses beforehand, so that the drugs can be deposited on the nasal mucosa.

Clinicians should consider the use of electronic reminders and tracking with an app such as MASK-air®. This can help improve patients' adherence. It can also provide insights for the clinician into the reasons behind a poor response to treatment.

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