One airway, one disease

This article provides a summary of a detailed review of the implications of the 'one airway, one disease' view for healthcare professionals (HCPs) caring for patient with rhinitis. Our intention is for the upper airways to be considered in tandem with the lower airways to avoid misdiagnosis and undermanagement. Implications for diagnosis and treatment are discussed and an algorithm offered. Both the original document and this summary have been produced as a consensus document based on a working group comprising PCRS members Dr Katherine Hickman, Dr Steve Holmes, Thushy Kailayanathan and Vikki Knowles. You can read the full review online https://www.pcrs-uk.org/resource/one-airway

Introduction

Allergic rhinitis (AR) is often under recognised and poorly managed.[1,2] AR and chronic rhinosinusitis (CRS) impact quality of life (QoL) not only because of the physical discomfort, but also because of the associated detrimental effects on the psychological and social aspects of patients' lives.[3,4] Indeed, even when accurately diagnosed and well-managed, patients tend to be poorly adherent to treatment, generally self-medicate and use on-demand treatment when symptomatic.[5] AR is not a discreet disease. The respiratory tract runs continuously from the nasal vestibule to the alveoli[6] and considerable epidemiological, pathophysiological and clinical evidence now suggests that the upper and lower airways are a single functional and morphological unit.[7–9] This understanding prompted Interasma (Global Asthma Association) to publish a manifesto stressing that patients with 'United Airways Diseases', such as AR, nasal polyposis and asthma, need "timely and adequate diagnosis, treatment, and, when recommended, referral for management in a specialized center".[10] According to the so-called 'one airway, one disease' view, asthma, polyposis, AR are on "a continuum of inflammation" and inter-related with other respiratory diseases within one airway.[11]

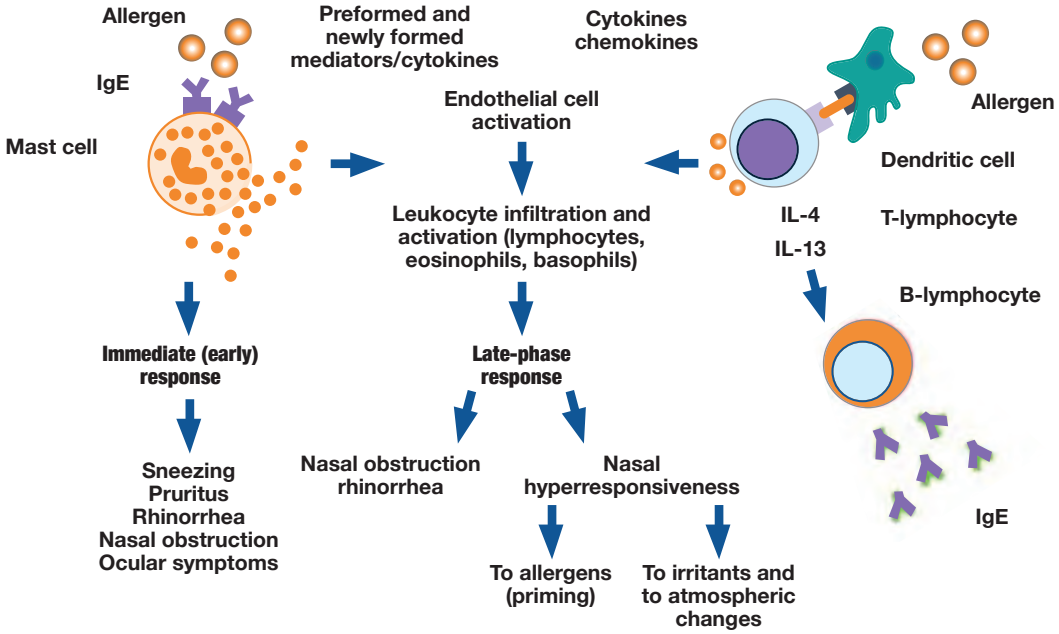
The complexity of rhinitis

Rhinitis refers to inflammation of the nasal mucosa.[1] Clinically, patients experience nasal discharge, itching, sneezing and blockage or congestion of varying severity and frequency (Table 1).[1,12] There are several types of rhinitis including AR, non-allergic rhinitis (NAR), infective and mixed.[1]

Table 1: The ARIA classification of AR[12]

Characteristic	Definition
Intermittent	Symptoms are present <4 days a week or <4 consecutive weeks
Persistent	Symptoms are present >4 days a week and >4 consecutive weeks
Mild	Patient does not experience any of the following: • Sleep disturbance • Impairment of daily activities, leisure and/or sport • Impairment of school or work • Symptoms present but not troublesome
Moderate/ severe	Patient experiences one or more of the following • Sleep disturbance • Impairment of daily activities, leisure and/or sport • Impairment of school or work • Troublesome symptoms

Figure 1. A cascade of inflammatory mediators causes allergic reactions[23]



Reproduced by permission from Independent Nurse magazine/Mark Allen Healthcare. Image adapted from Dhruve *et al* 2013[23].

Numerous lines of evidence support the "one airway, one disease" concept. Common inflammatory mediators, some disease susceptibility genes and pathophysiological profiles seem to underlie asthma, AR and CRS.[7,9] The same factors (e.g. house dust mite faeces, fungi, saliva and urine of domestic animals and pollen) can trigger AR and asthma.[3] In addition, common immunological pathways seem to link asthma with CRS with nasal polyps (CRSwNP), including those involving interleukin (IL)-4 and IL-13.[7] Eosinophilia in peripheral blood, which indicates systemic inflammation (Figure 1), is often identified in AR and asthma.[13] Asthma patients with AR tend to show worse disease control and more intense airway inflammation than those with asthma alone.[7] Indeed, untreated or poorly managed rhinitis can increase the risk of an asthma exacerbation.[3]

Differential diagnosis

History, examination and, when necessary, specific allergy tests are the foundation of AR diagnosis. Table 2 summarises some red flags that should alert clinicians to potentially important other causes that could warrant specialist referral. Figure 2 offers an algorithm summarising the diagnosis and management of AR in people with asthma.

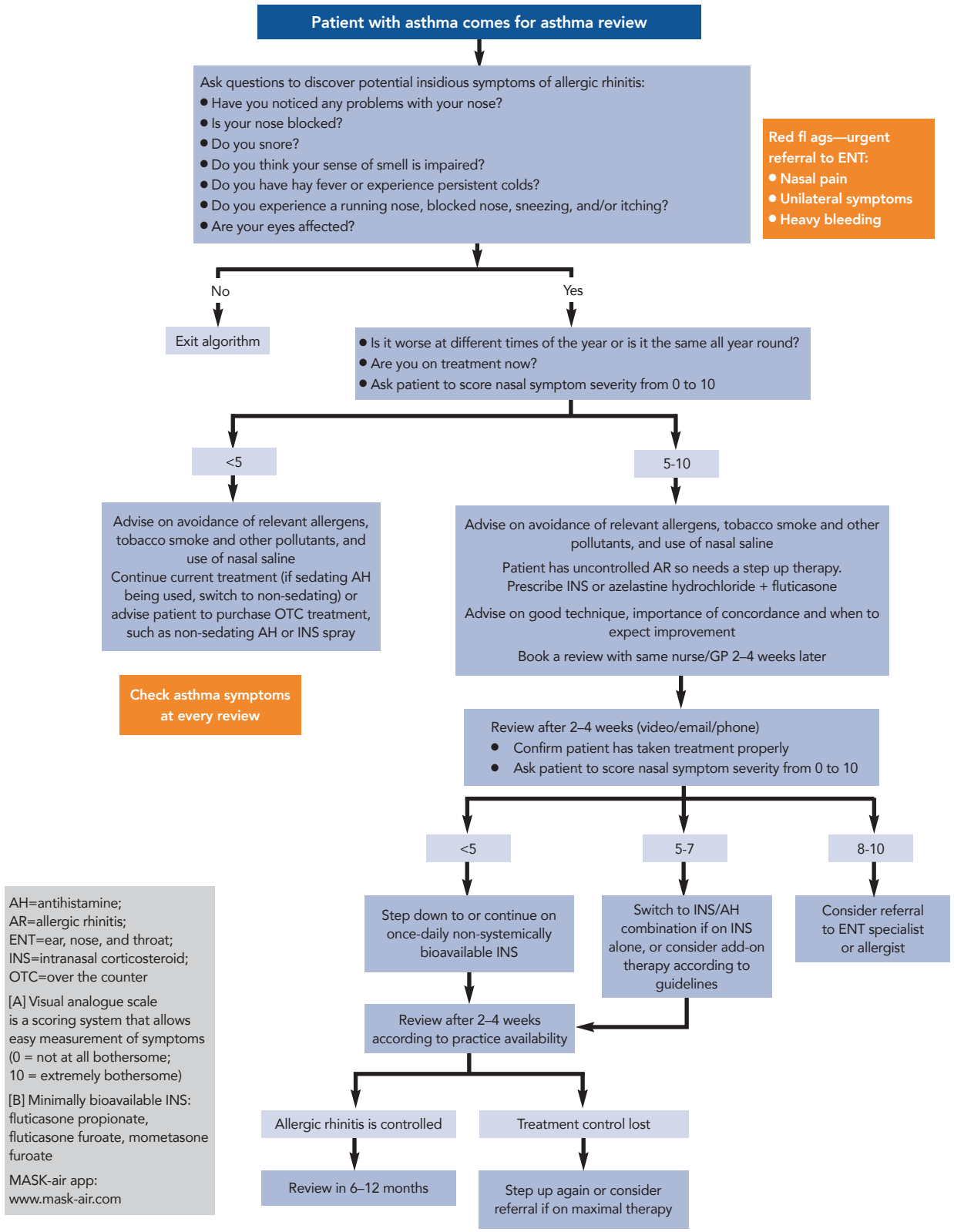
Allergic rhinoconjunctivitis

Unilateral rhinorrhoea (Table 3) is uncommon and, because of the risk of cerebrospinal fluid (CSF) leak, is a red flag.[1] Visual inspection and anterior rhinoscopy can aid the differential diagnosis (Tables 4 and 5).[1] AR patients often develop lower respiratory tract symptoms, including cough, wheeze and

Table 2: "Red flags" and other indications for ENT referral[1,35]

Speciality	Indication for referral
Red flags	Heavily blood-stained nasal discharge
	Nasal pain
	Recurrent epistaxis
	Unilateral symptoms
Other indications	Nasal blockage inadequately relived by drug treatment
	Structural deviations (eg septal deviation) that make drug treatment difficult

Figure 2. Identifying and managing AR in the asthma population[24]



The suggestions in this algorithm are informed by evidence-based guidance.

Table 3: Interpreting rhinorrhoea[1]

Colour	Interpretation
Continuously clear	Infection unlikely; secretions are clear in early viral rhinitis
Unilateral and clear	Exclude CSF leak
Yellow	Allergy or infection
Green	Usually infection; secretions may show small amounts of blood
Unilateral and coloured	Tumour, foreign body, nose picking or nasal spray misapplication
Bilateral and coloured	Nasal spray misapplication, granulomatous disorder, bleeding diathesis, infection, nose picking

CSF, cerebrospinal fluid.

Table 4: Interpreting visual assessment

Observation	Interpretation
Allergic salute	Supports AR diagnosis
Horizontal nasal crease across nasal dorsum	Supports AR diagnosis
Conjunctivitis and other eye involvement	Bilateral, non-sticky conjunctivitis that is associated with other symptoms supports AR diagnosis; Unilateral conjunctivitis, sticky eyes or reduced visual acuity should warrant further assessment
Chronic mouth breathing	Several causes need consideration, especially in children, including enlarged tonsils, habitual mouth breaking and, mainly, causes of blocked nose
Allergic shiners	Supports AR diagnosis, but a non-specific appearance may indicate other causes of oedema
Assessment of nasal airflow (eg metal spatula misting)	Supports a diagnosis of nasal blockage with many potential causes (e.g. allergic and non-allergic AR; foreign body, tumour)
Depressed nasal bridge	Post-surgery, granulomatous polyangiitis, cocaine misuse, infections (e.g. syphilis, leishmaniosis, leprosy), racial background
Widened nasal bridge	Polyps and nasal polyposis
Changes to nasal appearance	Sarcoidosis (purple nasal tip); seborrhoeic dermatitis (nasal crease); rosacea (phymatous changes)

AR, allergic rhinitis.
Based on Scadding *et al* 2017,[1] Andrade *et al* 1999,[19] Park *et al* 2015,[20] Zhang *et al* 2021[21] and the authors' clinical experience and expertise.

dysponea.[1] AR is also associated with co-morbidities, such as asthma and other allergic diseases, loss of smell, middle ear, throat and laryngeal problems, chronic obstructive pulmonary disease (COPD), obstructive sleep apnoea and sleep-related breathing disorder and ocular involvement.[1,2,10] Consider exposure to pets and other animals, and whether certain medicines (e.g. alpha and beta-blockers, other anti-hypertensives, aspirin and other non-steroidal anti-inflammatory drugs) could cause or aggravate rhinitis.[1] Consider referral for skin prick tests (SPTs), measurement of specific IgE or both. FeNO testing may also aid the differential diagnosis of AR and asthma.[14,15]

Non-allergic and occupational rhinitis

NAR is a diagnosis of exclusion which HCPs should consider in patients with nasal symptoms and negative SPT.[1] Occupational rhinitis is 2 to 3 times more common than, and often precedes, occupational asthma, which often co-exist.[1] The diagnosis of occupational rhinitis depends on a detailed history, which a symptom diary facilitates helping to determine sea-

Table 5: Interpreting anterior rhinoscopy

Finding	Interpretation
Hypertrophic, pale and boggy inferior or middle turbinates	Inflammation (nasal appearance may be normal in AR); Nasal polyps are usually described as boggy and non-tender; middle turbinates are very sensitive if touched
Presence or absence of clear, coloured or purulent secretions	See table 1
Deviated septum	Unlikely cause of rhinitis, although deviated nasal septum and AR are both common
Presence or absence of nasal polyps	Polyps and nasal polyposis
"Cobblestone" yellow submucosal nodules	Sarcoidosis (Rare presentation)
Crusting and granulations	May suggest infection and, possibly vasculitis
Septal perforation	Septal surgery, chronic vasoconstriction (cocaine, alpha agonists), granulomatous polyangiitis, anti-phospholipid antibody syndrome and nose picking

AR, allergic rhinitis.
Based on Scadding *et al* 2017[1] and the authors' clinical experience and expertise.

sonality and whether the symptoms occur indoors, outdoors or both.[1] The symptom pattern may also indicate possible triggers.[1] Removing a possible allergen from the individual's environment or vice versa can help confirm the diagnosis.[3]

Rhinitis in children

In general, the approach to diagnosis is similar to that in adults: history, SPT and anterior rhinoscopy. HCPs should refer children with entopy (local allergic rhinitis) for nasal allergen challenge.[1] Acute viral rhinitis is common in children, particularly during the winter. Most children experience up to 10 episodes per year. The number of cases peaks between 6 months and 6 years of age. After this age, children typically experience 1–2 episodes a year, mainly during the winter.[1] Chronic infective rhinitis (rhinosinusitis) persists for more than 3 months and, particularly if severe, can be a manifestation of underlining pathologies such as primary ciliary dyskinesia, cystic fibrosis or antibody deficiency, requiring referral to clarify the diagnosis.[1] AR may also be associated with otitis media with effusion, adenoidal hypertrophy or both. AR often presents alongside other atopic disorders, especially asthma, eczema and food allergy.

Treatment

Allergen and irritant avoidance

Advise rhinitis patients to avoid, where possible, irritants, including smoke and traffic pollution.[1] Suggest that people with allergies to animals limit their exposure as far as possible.[1] People with allergies to house dust mite could consider allergen-impermeable bedding and using acaricides on carpets and soft furnishing.[1]

Drug treatments

Medication is appropriate if patients experience persistent symptoms despite making best efforts to avoid allergens and irritants.[1]

Antihistamines: The BSACI guidelines suggest oral antihistamines as first-line therapy for mild-to-moderate intermittent and mild persistent rhinitis (Table 1).[1] Second-generation oral antihistamines (Table 6) are long acting, generally non-sedating and have no clinically significant anti-cholinergic activity.[1] Nasal antihistamines are more effective than oral formulations at reducing rhinitis symptoms and nasal obstruction, and act more rapidly (within 15 minutes) allowing use as rescue therapy, although continuous use is more effective than on-demand treatment. The BSACI guidelines suggest mast cell stabilisers (e.g. sodium cromoglycate, nedocromil sodium and lodoxamide) as the first-line treatment for ocular symptoms.[1]

Oral corticosteroids: Oral steroids are rarely indicated in AR but may be useful in specific circumstances, such as short-courses before a wedding.[1] Consider a short-course (0.5 mg/kg in the morning for 5–10 days) for adults with severe, uncontrolled symptoms that significantly affect QoL.[16]

Nasal corticosteroids: Intranasal corticosteroids (INS) are the main anti-inflammatory for AR and are the treatment of choice for moderate to severe persistent AR.[1] If monotherapy fails to adequately control symptoms, INS plus intranasal antihis-

Table 6: Examples of first and second generation anti-histamines[22]

Generation	Example
First-generation (should not be used in allergic rhinitis because of risk of drowsiness)	Brompheniramine
	Chlorpheniramine
	Dexchlorpheniramine
	Hydroxyzine
	Ketotifen
	Promethazine
Second-generation	Cetirizine
	Desloratadine
	Ebastine
	Fexofenadine
	Levocetirizine
	Loratadine

AR, allergic rhinitis.

tamine is more effective than either alone.[1] Advise patients that the onset of action of INS is 6–8 hours after the first dose and maximal effect may not be apparent for several weeks.[1] Consider combining an INS plus intranasal antihistamine during the first two weeks of treatment.[17]

Intranasal decongestants: Intranasal decongestants cause vasoconstriction which relieves severe nasal congestion within minutes and can address eustachian tube dysfunction when flying and increase nasal patency before douching or INS administration allowing delivery beyond the inferior turbinates.[1] The BSACI guidelines recommend using intranasal decongestants for <10 days.[1]

Leukotriene receptor antagonists: In general, LTRAs are as effective as loratadine in seasonal AR, but are less effective than INS.[1] In addition, the response to LTRAs is less consistent than to antihistamines.[1] Nevertheless, LTRAs may have a place in some asthma patients (especially those with exercise-induced or aspirin-exacerbated symptoms) with seasonal AR.[1,17]

Topical anti-cholinergics: Ipratropium bromide can be used three times daily to reduce rhinorrhoea, but does not improve other nasal symptoms. Add-on topical anti-cholinergics may be effective when INS and antihistamines fail to adequately control watery rhinorrhoea but can cause dry nose and epistaxis.

Biologics: Dupilumab, a monoclonal antibody against IL-4Ra, is approved for severe asthma with type 2 inflammation and CRS with nasal polyps (CRSwNP). Omalizumab, an antibody targeting IgE is approved for asthma mediated by this immunoglobulin and CRSwNP. Benralizumab and mepolizumab, which block IL-5, are indicated for severe refractory eosinophilic asthma. Biologics are currently prescribed in secondary care, have very specific criteria for initiation and monitoring, and are expensive.

Immunotherapy

Immunotherapy is the only treatment that can modify the course of AR and induce long-term tolerance to allergens.[18] There are two approaches: subcutaneous injection immunotherapy (SCIT) and sublingual Immunotherapy (SLIT). The choice depends on patient preference.

Subcutaneous injection immunotherapy: SCIT is effective for seasonal rhinitis due to pollens and perennial rhinitis due to house dust mite and cat allergens.[1] SCIT requires weekly treatment with increasing doses followed by 4–6 weekly maintenance injections for 3–5 years. Because of the risk of anaphylaxis, SCIT should be given only in specialist clinics by trained personnel with immediate access to adrenaline and resuscitation facilities.[1]

Sublingual Immunotherapy: SLIT is effective and safe for treatment of AR with and without seasonal asthma caused by grass pollen, ragweed and house dust mite.[1] In children with seasonal AR, SLIT reduces progression to asthma and prevents the development of new allergen sensitisation.[1] A physician supervises the first dose followed by a one-hour observation. SLIT is then administered daily at home.[1] The most common side-effects are local itching and mouth and throat swelling.[1] Oral antihistamines before starting SLIT and for the first two weeks can reduce local oral irritation.[1]

Pregnancy and breastfeeding

At least 20% of pregnant women experience rhinitis, which can arise at any time during gestation and may be due to nasal vascular engorgement and placental growth hormone.[1] Women with pre-existing AR tend to be the more severely affected during pregnancy.[1] Most medications cross the placenta so, medicines should only be prescribed when the apparent benefit is greater than the risk to the foetus.[1] Clinical studies have not established the safety of INS during in pregnancy.[1] The BSACI guidelines note, however, that beclomethasone, fluticasone propionate and budesonide have good safety records and are widely used in pregnant women with asthma.[1] Among the antihistamines, there is considerable clinical experience with chlorphenamine, loratadine and cetirizine in pregnancy. Nasal lavage is safe and effective in pregnant women, reducing the need for antihistamines. The guidelines suggest avoiding decongestants.[1] Patients on immunotherapy may continue if they have already reached the maintenance phase, but HCPs need to consider the risks and benefits in

each case. Immunotherapy should neither be started nor the dose increased during pregnancy. Similar recommendations can be made about treating AR during lactation.[1]

Children

Treatment of children follows the same principles as adults, including encompassing the 'one airway, one disease' concept. Nasal saline irrigation is effective for AR in children.[1] A 3-day course of topical decongestants can be helpful in children with significant nasal blockage to aid INS introduction. Monitor growth in children, especially those who receive steroids by multiple routes.[1] Consider a short-course of oral steroids (10–15 mg in the morning for 3–7 days) for children with severe, uncontrolled symptoms that significantly affect QoL.[16] The BSACI guidelines recommend immunotherapy if children do not adequately respond to maximal pharmacotherapy. SCIT or SLIT may be appropriate for children with seasonal pollen induced rhinoconjunctivitis whose symptoms persist despite INS and antihistamines taken regularly and perennial allergic rhinoconjunctivitis in patients with an allergy to house dust mite who respond inadequately to anti-allergic drug.[1]

Summary and conclusion

AR the most common immunological disease, remains under recognised and poorly managed, with an under-appreciated socioeconomic impact. Diagnosing and treating AR can prove challenging. Clinicians need to be vigilant that AR does not mask an underlying serious conditions and seek red flags at each review. Considerable epidemiological, pathophysiological and clinical evidence now suggests that the upper and lower airways are a single functional and morphological unit. Therefore, considering the upper airways in tandem with the lower airways avoids misdiagnosis and undermanagement. The overlap is not total and HCPs need to use their clinical acumen to individualise treatment to the patient.

The production of this resource has been funded by an educational grant from Viatris UK Healthcare Ltd. The sponsor has had no input to the content of this article and editorial control rests exclusively with PCRS.

References

1. Scadding GK, Kariyawasam HH, Scadding G, et al. BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis (Revised Edition 2017; First edition 2007). Clin Exp Allergy 2017;47:856–89.
2. Bjermer L, Westman M, Holmström M, et al. The complex pathophysiology of allergic rhinitis: scientific rationale for the development of an alternative treatment option. Allergy Asthma Clinical Immunol 2019;15:24.
3. Paiva Ferreira LKD, Paiva Ferreira LAM, Monteiro TM, et al. Combined allergic rhinitis and asthma syndrome (CARAS). Int Immunopharmacol 2019;74:105718.
4. Blaiss MS. Cognitive, social, and economic costs of allergic rhinitis. Allergy Asthma Proc 2000;21:7–13.
5. Bousquet J, Schünemann HJ, Togias A, et al. Next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for allergic rhinitis based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and real-world evidence. J Allergy Clin Immunol 2020;145:70-80.e3.
6. Kariyawasam HH, Rotiroti G. Allergic rhinitis, chronic rhinosinusitis and asthma: unravelling a complex relationship. Curr Opin Otolaryngol Head Neck Surg 2013;21:79–86.
7. Niimi A. Redefining "one airway, one disease": broader classification considering specific pathophysiology and treatment. Respir Invest 2021;59:573–5.
8. Samitas K, Carter A, Kariyawasam HH, et al. Upper and lower airway remodelling mechanisms in asthma, allergic rhinitis and chronic rhinosinusitis: The one airway concept revisited. Allergy 2018;73:993–1002.
9. Haccuria A, Van Muylem A, Malinovschi A, et al. Small airways dysfunction: the link between allergic rhinitis and allergic asthma. Eur Respir J 2018;51:1701749.
10. Tiotiu A, Novakova P, Baiardini I, et al. Manifesto on united airways diseases (UAD): an Interasma (global asthma association - GAA) document. J Asthma 2021;1–16.
11. Grossman J. One airway, one disease. Chest 1997;111:11s-16s.
12. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008. Allergy 2008;63:8–160.
13. Jeffery PK, Haahtela T. Allergic rhinitis and asthma: inflammation in a one-airway condition. BMC Pulm Med 2006;6 Suppl 1:S5–S5.
14. Stonham C, Baxter N. FeNO Testing For Asthma Diagnosis - A PCRS Consensus. Primary Care Respiratory Update 2019. Available at https://www.pcrs-uk.org/sites/pcrs-uk.org/files/pcru/articles/2019-Autumn-Issue-18-FeNo-testing-asthma-diagnosis.pdf. Accessed April 2022.
15. Busse WW, Wenzel SE, Casale TB, et al. Baseline FeNO as a prognostic biomarker for subsequent severe asthma exacerbations in patients with uncontrolled, moderate-to-severe asthma receiving placebo in the LIBERTY ASTHMA QUEST study: a post-hoc analysis. Lancet Respir Med 2021;9:1165–73.
16. NICE. Clinical Knowledge Summary Allergic rhinitis: Scenario: Management. Available at https://cks.nice.org.uk/topics/allergic-rhinitis/management/management/. Accessed April 2022.
17. Brożek JL, Bousquet J, Agache I, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. J Allergy Clin Immunol 2017;140:950–58.
18. Alvaro-Lozano M, Akdis CA, Akdis M, et al. EAACI allergen immunotherapy user's guide. Pediatr Allergy Immunol 2020;31(Suppl 25):1–101.
19. Andrade M, Fernandes VS, Boléo-Tomé JP. Saddle nose: our approach to the problem. Aesthetic Plast Surg 1999;23:403–6.
20. Park J, Suhk J, Nguyen AH. Nasal analysis and anatomy: anthropometric proportional assessment in Asians-aesthetic balance from forehead to chin, Part II. Sem Plastic Surg 2015;29:226–31.
21. Zhang H, Tang K, Wang Y, et al. Rosacea Treatment: Review and Update. Dermatol Ther 2021;11:13–24.
22. Dávila I, del Cuvillo A, Mullol J, et al. Use of second generation H1 antihistamines in special situations. J Investig Allergol Clin Immunol 2013;23 Suppl 1:1–16.
23. Dhruve H. Allergic rhinitis: assessing the triggers and treatments. Independent Nurse 2018; Available at https://www.independentnurse.co.uk/clinical-article/allergic-rhinitis-assessing-the-triggers-and-treatments/172766/. Accessed April 2022.
24. Scadding G. If they are wheezing, are they sneezing too? Presented at the Primary Care Respiratory Society Respiratory Conference 25th and 26th September 2020.