**ALLERGIC RHINITIS AND THE UNITED AIRWAY IN ASTHMA**

**Introduction**

Allergic rhinitis (AR) is an IgE-mediated condition characterised by inflammation of the nasal mucosa with nasal hyperreactivity, nasal congestion, anterior and posterior rhinorrhea, sneezing and/or nasal itching. Symptoms have traditionally been classified as seasonal or perennial, depending on the temporal exposure to allergens, such as seasonal pollens or year-round exposure to dust mites, or episodic when exposure is incidental and not normally encountered in the patient’s environment.

However, this classification has limitations in that the length of the aeroallergen pollen season is variable, depending on geographic location and climate, and may even persist over several months, as in the case of grass pollen on the South African Highveld. Furthermore, it may be difficult to distinguish between AR consequent on seasonal allergens and that associated with exposure to perennial allergens, such as dust mites, where perennial AR may be exacerbated by seasonal pollen exposure.1-3 The Allergic Rhinitis and its Impact on Asthma (ARIA) group has therefore proposed an alternative AR classification that recognises persistence of symptoms and their effect on quality of life, sleep and daily activities (Figure 1).3

**AR symptoms**

In addition to the classic nasal symptoms listed in Figure 1, AR may also be associated with reduced sense of smell, facial congestion/pain/pressure, fatigue, headache, cough, ocular symptoms (itching, hyperaemia, lacrimation) and itching of the palate and ear canals. Common comorbidities include conjunctivitis, sinusitis, otitis media, cough (commonly arising from postnasal drip), nasal polyps (in adults) and asthma, which may complicate treatment and be associated with failure of standard AR management.3,5 Nonallergic (non-IgE-mediated) conditions that can manifest as chronic rhinitis and affect the differential diagnosis of AR are listed in Table 1.
Table 1. Classification of rhinitis and differential diagnosis^2,3

<table>
<thead>
<tr>
<th>Classification of rhinitis</th>
<th>Differential diagnosis of AR</th>
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<tr>
<td>• Infectious (viral, bacterial, other infectious agents)</td>
<td>• Rhinosinusitis with or without nasal polyps</td>
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<td>• Allergic</td>
<td>• Mechanical factors (deviated septum, hypertrophic turbinates, adenoidal hypertrophy, foreign bodies, choanal atresia)</td>
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<td>• Occupational</td>
<td>• Tumours</td>
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<td>• Drug induced (rhinitis medicamentosa caused by topical decongestants or other drugs (beta-blockers, ACE inhibitors, reserpine, calcium channel blockers, methyldopa, alpha-receptor antagonists, phosphodiesterase-5 inhibitors, aspirin, NSAIDs, oral contraceptives))</td>
<td>• Granulomas (Wegener’s granulomatosis, sarcoid, infectious, malignant)</td>
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<td>• Hormonal</td>
<td>• Ciliary defects</td>
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<tr>
<td>• Of other causes: Nonallergic rhinitis with eosinophilia syndrome (NARES), food, irritants, emotional, atrophic, rhinitis of the elderly</td>
<td>• Cerebrospinal rhinorrhoea</td>
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<tr>
<td>• Idiopathic</td>
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Figure 1. Classification of AR^3

MILD
- Normal sleep
- No impairment of daily leisure or sport activities
- Normal work or school functioning
- No troublesome symptoms

Symptoms
≥2 consecutive days for >1 hour on most days
Rhinorrhoea
Blocked nose
Itchy nose
Sneezing
Itchy eyes

Intermittent AR
≤4 days/week or ≤4 consecutive weeks

Mild

Persistent AR
>4 days/week and >4 consecutive weeks

Moderate-Severe
One or more of the following:
- Abnormal sleep
- Impairment of daily leisure or sport activities
- Abnormal work or school functioning
- Troublesome symptoms

Symptoms
>4 days/week and >4 consecutive weeks

Persistent AR
Impact of AR on daily life

Despite AR often being viewed as a somewhat trivial condition, its financial impact may be considerable, with costs arising predominantly from absenteeism, outpatient treatment and medication. Symptoms are extremely bothersome, with almost two-thirds of patients complaining that their illness moderately or severely impacts on daily life, sleep, work, school and/or social life. Daytime fatigue and sleepiness, mood changes, impairment of cognitive function, depression and anxiety may occur, especially if symptoms are moderate to severe. In schoolchildren with uncontrolled AR, nocturnal sleep loss and secondary daytime fatigue may be a cause of learning disability.

Pathophysiology

In susceptible individuals, exposure to allergenic proteins causes sensitisation and production of specific IgE that is present on the surface of mast cells and basophils in the nasal mucosa. Important allergens include house-dust mites, grass, tree and weed pollens, pet dander, cockroaches and moulds.

During subsequent exposure, binding of the allergen to IgE causes immediate secretion of chemical mediators including histamine, prostaglandins and leukotrienes (type I hypersensitivity). This early reaction is associated with activation of mucous glands, increased vascular permeability, vasodilation, stimulation of sensory nerves and rapid onset of symptoms within 30 minutes, including sneezing, rhinorrhea, itching, ocular redness and tearing.

Over the following 4-8 hours, the mediators lead to recruitment of other inflammatory cells and development of an inflammatory infiltrate in the nasal mucosa consisting of mast cells, neutrophils, eosinophils, lymphocytes, fibroblasts and macrophages (late-phase response). Symptoms associated with the late phase are similar to those of the early phase, but congestion and mucus production predominate and may last for hours to days. In contrast to the changes that are observed in the airways of asthmatic patients, epithelial damage is minimal in the nasal mucosa of patients with AR. 3,5

Diagnosis

Although many patients with mild AR receive advice and over-the-counter (OTC) treatments at the pharmacy, those with moderate-to-severe illness require referral to a doctor. They should be carefully assessed for the presence of associated conditions, including asthma, atopic dermatitis, sleep-disordered breathing, conjunctivitis, rhinosinusitis and otitis media. The vast majority of patients with asthma have AR and 10-40% of patients with AR have asthma. In children, comorbid asthma is more likely with increased duration or severity of AR. 3,5

Diagnosis of AR is based on clinical history of typical symptoms and careful examination. Diagnostic tests based on the demonstration of allergen-specific IgE in the skin (skin tests) or blood (specific IgE) may be recommended for patients with a clinical diagnosis of AR who do not respond to empirical treatment, when the diagnosis is uncertain, or when knowledge of the specific causative allergen is required to target therapy. Measurement of total IgE is not helpful. 3,5

In addition to typical symptoms, younger children may develop noisy breathing, repeated throat clearing and snoring. Symptoms that are not associated with AR and that should prompt further assessment are listed in Table 2. Detailed questioning about sleep and daily activities will help to characterise the severity of AR (Figure 1).
### Table 2. Symptoms not associated with AR or allergic conjunctivitis

<table>
<thead>
<tr>
<th>Nasal symptoms</th>
<th>Eye symptoms</th>
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<tr>
<td>• Nasal obstruction without other symptoms</td>
<td>• Unilateral eye symptoms</td>
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<tr>
<td>• Mucopurulent rhinorrhea</td>
<td>• Eye burning, but not itching</td>
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<tr>
<td>• Posterior rhinorrhea (post-nasal drip) with thick mucus and/or no anterior rhinorrhea</td>
<td>• Dry eyes</td>
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<td>• Pain</td>
<td>• Photophobia</td>
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<tr>
<td>• Recurrent epistaxis</td>
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<td>• Anosmia</td>
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Physical examination is usually relatively normal. There may be clear rhinorrhea and ocular symptoms (watery discharge, swollen conjunctivae and erythema). Especially in those with chronic or more severe AR, dark circles may be present around the eyes (allergic shiners) caused by accumulation of blood and other fluid in the infraorbital groove consequent on venous stasis. In children, obstructed breathing may be associated with visible features, such as gaping mouth, chapped lips, hypertrophied gingival mucosa, long face and dental malocclusion. There may be a nasal crease.

Intranasal examination (anterior rhinoscopy) may reveal pale, boggy turbinates, but is often normal. Nasal polyps are uncommon in children and if they are present they should prompt further evaluation for cystic fibrosis. Cobblestoning of the back of the throat indicates postnasal drip.

Nasal endoscopy may be considered in patients with treatment failure.

### Management

#### Allergen avoidance

Although avoidance of aeroallergens is often recommended, it is extremely difficult. Even when an allergen has been identified, most avoidance strategies are ineffective, not cost-effective and insufficient to result in clinical improvement. However, for sensitive individuals guidelines still recommend strategies at home to avoid indoor moulds and animal dander (removal of pets). There is some evidence that using appropriate acaricides sprayed on furniture, rugs and bedding to kill dust mites may help to reduce symptoms.

#### Pharmacotherapy

1. **Antihistamines**

Oral second-generation antihistamines are recommended for the treatment of intermittent AR where the primary complaints are itching and sneezing. Intranasal antihistamines are as effective as oral antihistamines and may help patients when oral antihistamines are ineffective. Topical H1 antihistamines may be effective for allergic conjunctivitis. Because of their sedative effects and other safety concerns, oral first-generation antihistamines are not recommended. Symptoms that do not resolve with one antihistamine are unlikely to respond to another. Patients who require daily medication should be treated with an intranasal corticosteroid (INCS).
2. INCSs

INCSs are the most effective medication for AR. All are equally effective and they are generally well tolerated. Occasional epistaxis does occur, but responds well to temporary discontinuation or lowering or dividing the dose. For patients with severe nasal blockage a decongestant nasal spray may be administered shortly before the ICNS for the first few days of therapy, but must not be used for longer than 10 days.

3. Oral leukotriene receptor antagonists (LTRAs)

Because they are less effective than INCSs, the oral leukotriene receptor antagonists (LTRAs) are not routinely recommended as primary therapy for patients with AR. They may be helpful in patients with AR and comorbid asthma.1

4. Combination therapy

Combination therapy is recommended in patients with an inadequate response to monotherapy.

The most effective addition to an INCS is an intranasal antihistamine. Oral antihistamines and LTRAs confer no additional benefit with an ICNS and these combinations are not recommended. Some patients may benefit from the combination of an oral antihistamine and oral decongestant.1

5. Immunotherapy

Immunotherapy may be helpful in patients with AR whose symptoms respond inadequately to pharmacotherapy, with or without environmental controls.1 Immunotherapy is not a substitute for allergen avoidance.

The united airway: AR and asthma

AR and asthma are often associated. The majority of asthmatics (up to 80% or more) experience symptoms of AR and approximately one-third to half of all patients with AR have concomitant asthma. Epidemiological studies show that AR usually precedes asthma and people with AR are approximately 3-8 times more likely to develop asthma than people without. However, it is possible that AR and asthma are not necessarily two distinct and separate diseases. Rather, AR may represent an early stage of united airways disease (UAD) that can progress to full-blown asthma.

There are numerous similarities between the upper and lower airways that might explain the association between AR and asthma (Table 3).

Nasal obstruction may affect bronchial airflow through various mechanisms. These include oral respiration, systemic absorption of mediators and cytokines, postnasal drip and nervous reflex. Bronchial hyperreactivity can be demonstrated in a substantial proportion of patients with AR and no symptoms of asthma (>80% with persistent AR and >50% of those with intermittent AR), and may be an important risk factor for development of asthma. There is a significant correlation between nasal inflammation, nasal airflow and bronchial function. Studies demonstrate a significant relationship between nasal eosinophil counts, bronchial hyperresponsiveness and abnormal spirometric findings (including compromised FEF25-75 and FEV1). In patients with asthma, comorbid AR is associated with increased disease severity, more frequent asthma exacerbations, increased use and costs of asthma medications and physician visits, and greater likelihood of admission to the emergency room or hospital for asthma.8-10

<table>
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<th>Table 3. Similarities between upper and lower airways, supporting a united airway10</th>
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<tr>
<td>1. Respiratory epithelium is similar from nasal cavities to bronchioles.</td>
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<td>2. Nose and bronchi share the same adrenergic and vagal innervation.</td>
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<tr>
<td>3. IgE-mediated immunopathology of AR and asthma is similar: mast cell/basophil activation and transepithelial migration, Th2 T lymphocyte activation and eosinophil recruitment in both upper and lower airways.</td>
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</table>
Numerous studies have shown that AR treatment with INCSs, antihistamines and montelukast, an oral LTRA, may also improve symptoms of asthma and pulmonary function tests, while reducing admissions for asthma exacerbations and the use of bronchodilators.8-11

Conclusions

AR and asthma are linked disorders. Recent studies indicate that there is immunological cross-talk uniting the upper and lower airways and that AR and asthma are two manifestations of a chronic respiratory inflammatory syndrome. Patients with AR should be evaluated for asthma and those with asthma should be evaluated for AR. The relationship is supported by epidemiological and pathophysiological data and both diseases respond to common anti-inflammatory modalities. Consequently, just as asthma is aggressively and proactively treated to prevent associated morbidity and mortality, so AR needs to be taken seriously, prompting careful assessment and effective management of both upper and lower airways. Treating the nose is an important step to managing patients with AR and asthma.1,10

References


This article is based on a presentation by Dr Todd Marr at the Cipla Respiratory Symposium, Cape Town, 2016. The article was written for deNovo Medica by Dr David Webb.