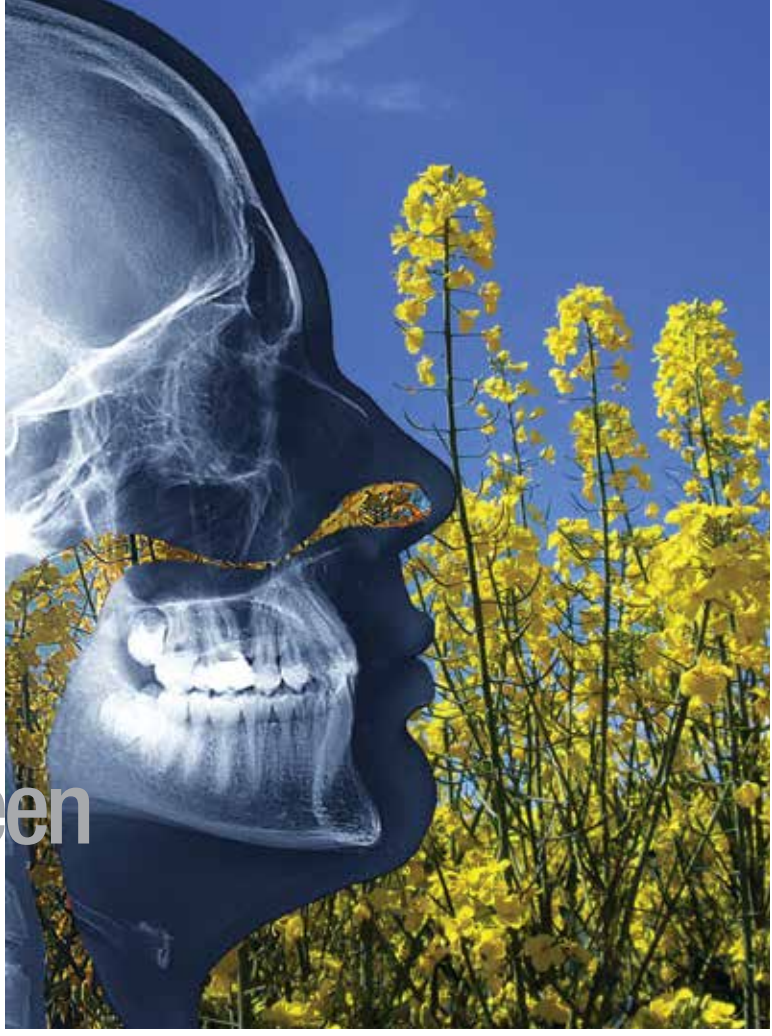
# Continuous airways

## Allergic and nonallergic associations between the nose and lungs



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**This article illustrates the continuous airway, focusing on allergic and nonallergic associations between the nose and lungs, studying firstly the link between allergic rhinitis and asthma and secondly aspirin-exacerbated respiratory disease.**

### Key points

- **Rhinitis is a common chronic illness with a lifetime annual incidence of at least 7 per 1000 people.**
- **Over 80% of patients with asthma have rhinitis, and 10 to 40% of patients with rhinitis have asthma.**
- **Both allergic and nonallergic rhinitis are independent risk factors for the development of asthma.**
- **Treatment of rhinitis can influence asthma outcomes.**
- **Aspirin-exacerbated respiratory disease occurs in more than 14% of patients with severe asthma.**

The mucosa of the respiratory tract is covered with the same epithelium from the nasal cavity to the intrapulmonary terminal bronchioles and shows similar patterns of cellular inflammation after exposure to allergen.[1] Functionally, the nose is essential in protecting the lower airways from inhaled particles and maintaining lung homeostasis. Mouth breathing can directly provoke a reaction in the lower airways because air that is unfiltered by the nose can contain allergens, particles, smoke, and turbulent and dry air.[2] Asthma is often induced by inspiration of particles into the lower airways.

### Rhinitis and asthma

Rhinitis can be defined as inflammation of the nasal mucosa leading to anterior or posterior rhinorrhoea, sneezing, nasal blockage and/or itching of the nose, with symptoms occurring for at least two consecutive days.[3] It can be further classified into intermittent or persistent if present for more than four days a week for more than four consecutive weeks, and mild or moderate-to-severe, depending on the presence of any of sleep disturbance, troublesome symptoms or interference with daily activities.[3]

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Rhinitis can be allergic or nonallergic and may be associated with polyps (Figure).[3] Allergic rhinitis is a symptomatic disorder of the nose resulting from IgE-mediated inflammation of the mucosa in response to allergen exposure in an atopic patient. It can be persistent or intermittent, and mild or moderate-to-severe.[3]

Asthma is due to chronic airway inflammation, with respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity. The diagnosis is based on symptoms and evidence of variable airflow limitation, demonstrated by bronchodilator reversibility or other testing.

Asthma is a heterogeneous disease with different phenotypes. One of the most common types is allergic asthma, defined as asthma associated with positive allergy test results (i.e. by skin prick test or serum-specific IgE testing).

### Allergy

The hallmark cellular mechanism that drives allergic disease is an increase in circulating allergen-specific IgE antibodies and the development of an allergen-specific T-helper 2 response, characterised by production of interleukins 4, 5 and 13 (IL-4, IL-5 and IL-13). A diagnosis of allergic rhinitis or asthma relies on identifying characteristic symptoms and clinical history, as well as supportive findings on physical examination. Allergy testing can then confirm the presence of sensitisation to aeroallergens by skin testing or serum-specific IgE testing (sometimes called a radioallergosorbent test [RAST]), but the sensitivity of serum-specific IgE testing is inferior to skin testing.

## Allergic rhinitis and allergic asthma: one syndrome

Allergic rhinitis and asthma are a global health problem with high morbidity. Epidemiology reveals that more than 80% of patients with asthma have rhinitis, and 10 to 40% of patients with rhinitis have asthma. Accordingly, the Allergic Rhinitis and its Impact on Asthma (ARIA) WHO workshop has produced guidelines intended to demonstrate the links between the upper and lower airways and their implications for care.[3]

In Australia, the prevalence of rhinitis in adults aged 25 to 50 years is 28%, and globally the crude lifelong incidence of rhinitis each year is 7 per 1000 men and 7.95 per 1000 women.[4] Although the prevalence of asthma varies worldwide, more than 5% of any investigated population suffers from asthma, most often associated with allergies, making asthma one of the most common chronic diseases.[5] This also shows that the prevalence of allergic rhinitis appears to be at least triple the prevalence of asthma.

The European Community Respiratory Health Study (ECRHS II), followed 6461 adults who did not have asthma at outset over 8.8 years, and showed an adjusted relative risk of developing asthma of 2.71 (95% confidence interval [CI], 1.64 to 4.46) and 3.53 (95% CI, 2.11 to 5.91) for people with nonallergic and allergic rhinitis, respectively.[6] This study showed that many patients with asthma also have rhinitis and, whether allergic or not, rhinitis is a major independent risk factor for the development of asthma.

Local or systemic mechanisms might be responsible for the close interaction between the nose and lungs. These include loss of protective functions of the nose, aspiration of nasal secretions into the lung, neural mediators leading to the nasobronchial reflex, alteration of nasal nitric oxide production and the systemic propagation of inflammation from the nasal mucosa to the bronchial mucosa.[5]

## Managing allergic rhinitis and allergic asthma

The management of allergic rhinitis and asthma involves patient education about the avoidance of allergens and other triggers, pharmacotherapy and possibly allergen immunotherapy (Table).[7-9] There is a therapeutic relationship between the upper and lower airways, whereby treating rhinitis with nasal corticosteroids may improve asthma control by reducing the risk of exacerbations.[10,11] This suggests a key role for nasal inflammation modulating airway responsiveness associated with rhinitis and points to the importance of anti-inflammatory treatments for rhinitis in patients with asthma.[12]

### Immunotherapy

Immunotherapy using aeroallergens (administered subcutaneously or sublingually) is an effective treatment in patients with allergic rhinitis, conjunctivitis or asthma who have a clear link between symptoms and the presence of allergen-specific IgE.[13] Rhinitis due to an inhaled allergen is a relative indication for allergen immunotherapy when allergen avoidance and medical treatments have not achieved adequate control or are burdensome or not tolerated by the patient.[13,14] Allergen immunotherapy is prescribed by specialists but often administered by GPs and should be continued for at least three years. Absolute and relative contraindications are listed in the Box.[15]

Both subcutaneous and sublingual allergen immunotherapy have been shown to induce long-term remission of allergic disease with clinical benefits persisting after stopping therapy.[16] Intriguingly, some data suggest that allergen immunotherapy may prevent the onset of new allergen sensitisations and reduce the risk of developing allergic asthma in patients with allergic rhinitis. This was clearly evident in patients with allergic rhinitis due to pollens treated by three years of subcutaneous allergen immunotherapy, in whom the incidence of asthma in a 10-year follow up was reduced fourfold.[17,18] Retrospective data, including both subcutaneous and sublingual allergen immunotherapy, also suggest a significant reduction in the risk of asthma development following three years of allergen immunotherapy.[19]

The increasing availability of sublingual tablets for specific allergen immunotherapy offers significant promise in treating both allergic

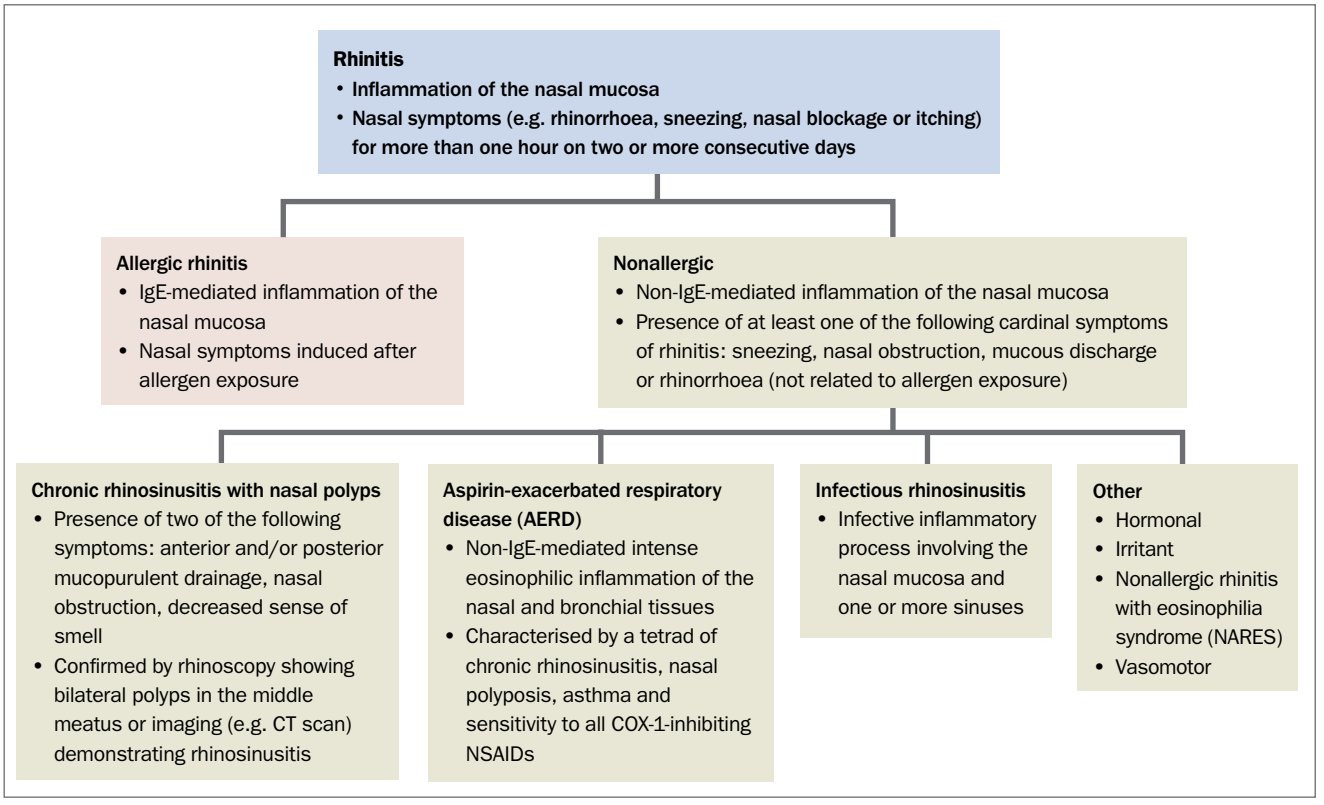


Figure. Classifying rhinitis.[3]

rhinitis and asthma. Although current indications for aeroallergen immunotherapy are dominantly for allergic rhinitis, accumulating evidence from trials of sublingual immunotherapy in allergic asthma suggest that use of effective allergen immunotherapy is associated with a reduction in maintenance asthma therapy as well as exacerbation frequency.[20,21] Taken together, these data suggest an evolving role for allergen immunotherapy in modifying asthma outcomes as well as those of rhinitis. The results of current trials in the area of immunotherapy and asthma are awaited to inform the role of allergen immunotherapy in asthma treatment guidelines.

## Biologics

Newer biological therapies can also help people with severe allergic disease, treating both the nose and lungs,[15,22] although current availability and PBS listings limit their prescribing to specialist physicians. They are currently indicated in the management of severe asthma, although evidence exists for their role in upper airway disease as well.

### *Omalizumab*

Omalizumab, a monoclonal antibody against IgE, is approved by the TGA for use in patients aged 6 years and over with allergic asthma who have documented exacerbations despite the use of high-dose inhaled corticosteroid plus a long-acting beta agonist (LABA). Biologically, omalizumab leads to reduction of the IgE receptor expression on basophils, masts cells and cutaneous dendritic cells. Its efficacy in asthma has been shown in multiple randomised controlled trials, especially in reducing the frequency of exacerbations, emergency visits, hospitalisations and improving asthma-related quality of life.[23] Omalizumab use in patients with severe asthma is also associated with reduced oral corticosteroid use.[24]

There is some evidence to support the use of omalizumab in seasonal allergic rhinitis, with trials showing reduced nasal symptoms and antihistamine use, and improved quality of life. However, the expense of omalizumab renders it unlikely that it will be used to treat allergic rhinitis in the absence of asthma. Several studies are in progress regarding the use of omalizumab in combination with desensitisation, which seem to show a positive effect on seasonal allergic rhinitis symptoms and immunotherapy-related adverse events although the additional basis for the use of omalizumab in immunotherapy trials is not yet clear.[25]

### *Other agents*

Agents targeting IL-5, a cytokine stimulating eosinophil growth and activation, are in the advanced stages of clinical development and one of these, mepolizumab, is TGA approved as an add-on treatment for severe refractory eosinophilic asthma in patients aged 12 years and over. It has been shown effective in reducing asthma exacerbation rates.[26]

Dupilumab is a monoclonal antibody targeting the IL-4 alpha receptor subunit, which inhibits both the IL-4 and IL-13 signalling, and is likely to also be effective in allergic disease. Recent studies have shown its use to be of benefit in reducing nasal polyp

**Table. Recommended therapy for allergic rhinitis* in patients aged over 2 years (not pregnant or breastfeeding)[8,9]**

| Therapy | Symptoms | | | | |
|---|---|---|---|---|---|
| | **Mild, episodic nasal symptoms** | **Persistent nasal symptoms** | **Nasal symptoms associated with allergic conjunctivitis** | **Persistent or severe nasal symptoms resistant to treatment** | **Persistent or severe nasal symptoms resistant to treatment, and immunotherapy ineffective or contraindicated** |
| **General** | Allergen avoidance and treatment of concomitant asthma* | | | | |
| **Preferred** | Oral second generation H1-antihistamine (2 to 5 hours before exposure) | Intranasal corticosteroid spray<br>AND<br>Oral second generation H1-antihistamine, if primary complaint is sneezing or itching | Intranasal corticosteroid spray<br>AND<br>Oral second generation H1-antihistamine, if primary complaint is sneezing or itching<br>AND<br>Topical antihistamine or cromolyn eye drops | Intranasal corticosteroid spray<br>AND<br>Oral second generation H1-antihistamine, if primary complaint is sneezing or itching<br>AND<br>Subcutaneous or sublingual immunotherapy for 3 years depending on specific allergen sensitivity† | Intranasal corticosteroid spray<br>AND<br>Oral second generation H1-antihistamine, if primary complaint is sneezing or itching<br>AND<br>Add-on off-label treatment (e.g. anti-IgE such as omalizumab), NOT if aged under 6 years |
| **Other options** | Intranasal H1-antihistamine spray<br>OR<br>Intranasal corticosteroid spray (more effective than oral anti-histamines) | If failure to respond: Combined intranasal corticosteroid with anticholinergic<br>OR<br>Intranasal decongestant (very short course [5 days maximum] ) in severe nasal obstruction, NOT if aged under 6 years)<br>OR<br>Subcutaneous or sublingual immunotherapy may be appropriate | If failure to respond: Combined intranasal corticosteroid with anticholinergic<br>OR<br>Oral montelukast (add-on treatment, private prescription)<br>OR<br>Intranasal decongestant (very short course [5 days maximum] ) in severe nasal obstruction, NOT if aged under 6 years)<br>OR<br>Subcutaneous or sublingual immunotherapy may be appropriate | | Oral glucocorticoid (short course) in patients resistant to treatment with difficulty functioning, e.g. unable to sleep or work |

* Use a stepped approach as recommended in the *Australian Asthma Handbook* (www.asthmahandbook.org.au/figure/show/31 for adults and www.asthmahandbook.org.au/figure/show/18 for children).

† Depending on patient preference and medication acceptability for allergen immunotherapy, either subcutaneous or sublingual therapy may be appropriate.

burden in rhinitis and medication requirements in asthma.[27,28]

## Aspirin-exacerbated respiratory disease

Aspirin-exacerbated respiratory disease (AERD), or Samter's triad, also illustrates the continuous airways hypothesis in that this non-IgE-mediated disease associates the nose, sinuses and bronchi. Indeed, the upper and lower airways in a patient with AERD share similar pathogenic manifestations, including intense eosinophilic infiltration. A hallmark of AERD is the dysregulated function of the lipo-oxygenase synthase pathway, leading to increased levels of arachidonic acid.[29,30]

AERD affects 0.3 to 0.9% of the general population, with a higher prevalence in females, and typically begins in the third or fourth decades of life. The prevalence of AERD is probably fewer than 5% of all asthma patients but it is present in more than 14% of those with severe asthma.[20] Among patients with asthma, chronic rhinosinusitis and nasal polyps, NSAID sensitivity might affect up to 70% of individuals.[31]

### Contraindications to allergen immunotherapy[15]

**Absolute contraindications**

- Uncontrolled asthma
- Malignant neoplasia
- AIDS
- Age under 2 years
- Should not be initiated during pregnancy

**Relative contraindications**

- Partially-controlled asthma
- Use of β-blockers and ACE inhibitors
- Cardiovascular disease
- HIV infection
- Immunodeficiency or use of immunosuppressive drugs
- Conditions leading to poor adherence to treatment program

## Diagnosing AERD

AERD is characterised by a tetrad of chronic rhinosinusitis, nasal polyps, asthma and sensitivity to all COX-1-inhibiting NSAIDs. It frequently develops after an upper respiratory tract infection and is progressive, with NSAID sensitivity developing at any stage in the process. Although acute reactions triggered by NSAIDs is the central characteristic of this disease, the underlying inflammatory disease begins and continues independently of NSAID exposure.

Reactions to NSAIDs occur from 30 minutes to three hours after ingestion and include rhinorrhoea, nasal congestion, ocular tearing and injection, periorbital swelling and variable degrees of bronchoconstriction. Additional symptoms can include severe abdominal cramping, epigastric pain, urticaria and hypotension.[31,32] Challenge with aspirin or another NSAID can confirm the diagnosis, and although as many as 16% of patients with suspected AERD have negative oral aspirin challenge results, challenge must be conducted under specialist supervision.[33,34]

## Managing AERD

To manage AERD, patients need to be educated to avoid all COX-1 inhibitors including aspirin. Patients often require high-dose asthma medications. Chronic rhinosinusitis must be managed medically with topical corticosteroid treatment and surgically when medical treatment has failed. However, the polyps in patients with AERD recur up to 10-fold more frequently than in patients with other forms of nasal polyposis.[33]

### *Aspirin desensitisation*

Some authors advocate the effectiveness of aspirin desensitisation followed by daily aspirin (or NSAID) use in patients with AERD. This is based on results suggesting improvement in overall symptoms and quality of life, decreased formation of nasal polyps, fewer sinus infections and a reduced need for oral corticosteroids and sinus surgery.[32-34] Aspirin desensitisation needs to be performed in a specialist centre with close observation and monitoring for adverse events, including asthma exacerbation and hypotension. Improvement in nasal and asthma scores and sense of smell can be seen by four weeks.[32-34] The optimal timing of desensitisation is two to four weeks after sinus surgery because long-term aspirin therapy may help prevent regrowth of polyps. Aspirin desensitisation may be an option for patients with AERD who require multiple sinus procedures and for patients who require NSAIDs for antiplatelet therapy.[33] Patients with unstable asthma, gastric ulcers, pregnancy or bleeding disorders are not suitable for aspirin desensitisation.

This mode of treatment is not suitable for all patients however, because the maintenance dose of aspirin required for effective desensitisation in AERD is high (650 mg twice a day) and side effects of this dose can be a barrier to long-term therapy in many. Lower doses of 325 mg of aspirin daily might not adequately treat the airways disease. Furthermore, if there are periods between doses of even as little as 24 hours, there are risks of recurrence of acute symptoms with inherent risks.[34]

### *Other treatments*

Despite all therapeutic measures, there is a subgroup of patients with recurrent eosinophilic asthma (indicated by a blood eosinophil count greater than 0.3 x $10^9$/L in asthma patients). and rhinitis who require further innovative treatment approaches.[22]

In an eosinophil-mediated disease, IL-5 is a key cytokine known to induce the maturation, activation, and recruitment of eosinophils. The anti-IL-5 monoclonal antibody mepolizumab is TGA approved for severe eosinophilic asthma and its use in patients with severe chronic rhinosinusitis with nasal polyps also looks promising in early studies.[31] Similarly, a recent randomised placebo-controlled trial has shown that dupilumab compared with placebo, during 16 weeks in patients with chronic rhinosinusitis and nasal polyps refractory to intranasal corticosteroids, is associated with significant improvements in endoscopic, clinical and radiographic end points.[26]

## Conclusion

The upper and lower respiratory tracts are closely related entities. Investigating for asthma in patients with allergic rhinitis and asking about rhinitis when confronted with resistant or severe asthma is essential to the delivery of good clinical care. Many patients will need treatment of these two entities in parallel. Allergy specialists can assist with correct identification of triggering allergens and prescription of immunotherapy. Similarly, AERD should be considered in patients with chronic rhinosinusitis with nasal polyps and eosinophilic asthma.

The rapid progress in biological therapies is leading to more personalised management of patients and offers the promise of treating both upper and lower airway diseases. **RMT**


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A list of references is included in the website version of this article (www.medicinetoday.com.au).


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