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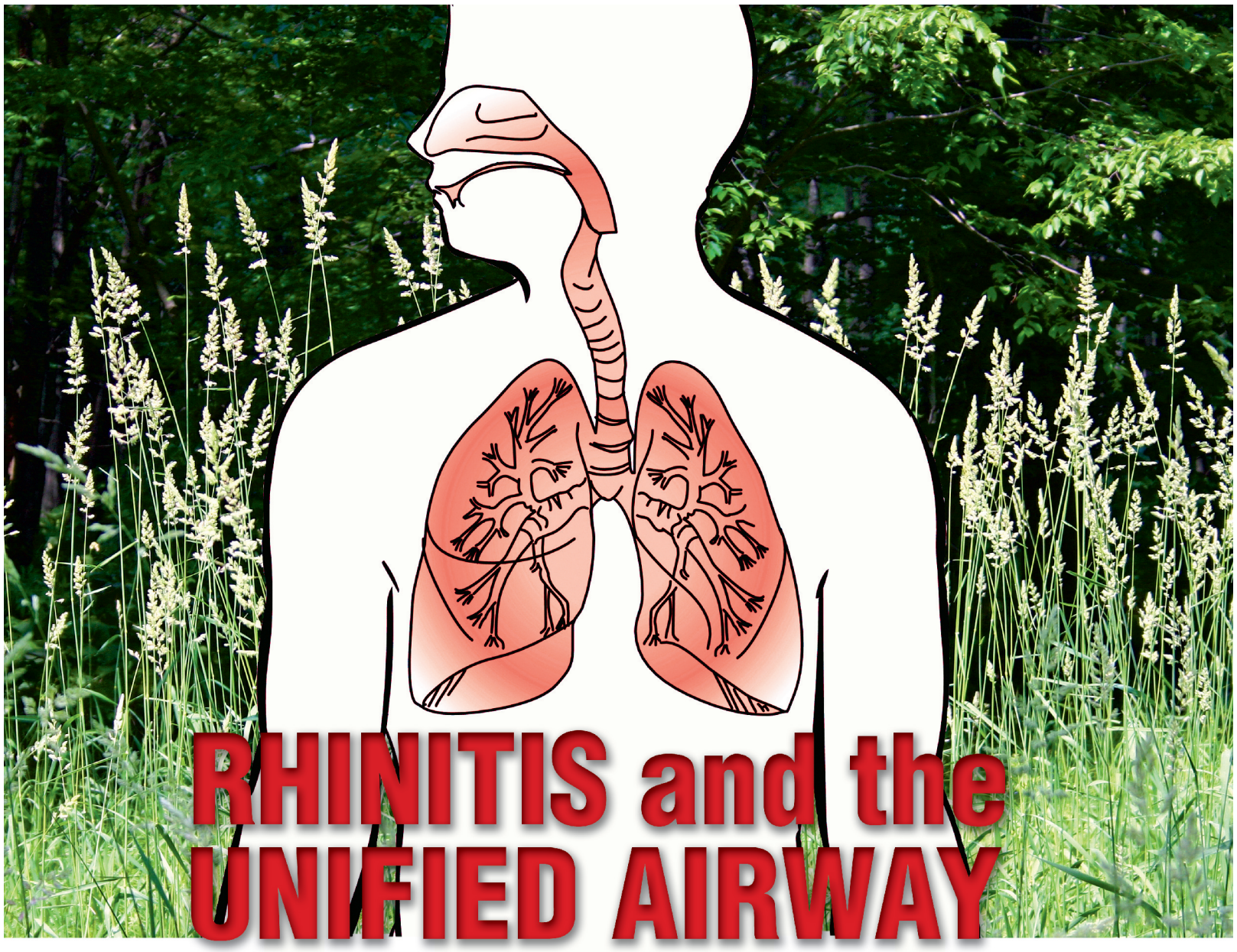

RHINITIS and the UNIFIED AIRWAY

Background

SINCE the 1990s, our pathophysiological understanding of chronic airway conditions has progressed from simple models of obstruction and infection to a more comprehensive understanding of mucosal health, inflammation and the concept of a 'unified airway'.

Recent clinical and pathophysiological research suggests that symptoms in one portion of the respiratory tract are a marker of diffuse airway inflammation, and may indicate the presence of concurrent disease elsewhere in the respiratory tract. Even when concurrent disease is not present, there is an increased likelihood it will develop subsequently over time.

Compartmentalisation of airway inflammation into anatomical areas would appear to be the exception rather than the rule. This unified airway concept represents a shift from the traditional focus on local factors such as focal infection. Patients with chronic airway conditions often initially respond to antimicrobial therapy, but an underlying inflammatory process continues, with recalcitrant symptoms or recurrence of localised infection.

Both epidemiological and pathophysiological data suggest the respiratory tract behaves as an integrated system. This includes the middle-ear mucosa, nose, paranasal sinuses, as well as the entire lower respiratory tract including the larynx. This interdependence has been the focus of clinical studies, which have explored the concept of a common inflammatory process and sought to explain the benefits of airway-wide treatment compared with localised interventions.

This phenomenon of concurrent upper and lower respiratory disease was noted as early as the 1920s, but little formal research was conducted until clinical observations in the 1980s. The model of a unified airway has its foundations in three important observations:

- Epidemiological evidence of a high prevalence of rhinitis and rhinosinusitis in people with asthma and, likewise, an increased prevalence of upper respiratory disease when the lower airway is affected.
- The underlying pathophysiology is common to all airway compartments, explaining the observed inter-relatedness of upper and lower airway disease
- Treatment of one airway compartment results in improvement in a separate portion of the airway, or even the entire airway.

This article aims to:

- Update the reader on current clinical and research concepts of the unified airway.
- Explain the importance of treating both the upper and lower airway concurrently to achieve resolution of symptoms.
- Help the physician manage patients who develop airway-wide inflammatory changes and answer patients' questions regarding causative relationships between the upper and lower airway.

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inside

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The unified airway: evidence

Epidemiological evidence

MOST patients with asthma have rhinitis (figure 1). Multiple studies have shown rhinitis to be present in 50-85% of subjects with asthma, with the differences between studies likely caused by differences in methodology.

Patient self-reported symptoms may be an insensitive measure, considering that many patients with asthma may be more bothered by their asthma than rhinitis symptoms (figure 2). In a retrospective review of 1245 subjects with asthma in the US Midwest, 52% were found to have allergic rhinitis, and 6% had non-allergic rhinitis.[1] However, on prospective assessment with direct questioning and examination of patients with asthma:[2]

- 100% of subjects who had allergic asthma induced by pollen had allergic rhinitis from pollen.
- 89% of subjects who had allergic asthma caused by animals had allergic rhinitis from animals.
- 95% of subjects who had allergic asthma caused by mites had allergic rhinitis from mites.

That the vast majority of patients with asthma also have rhinitis has therapeutic implications.

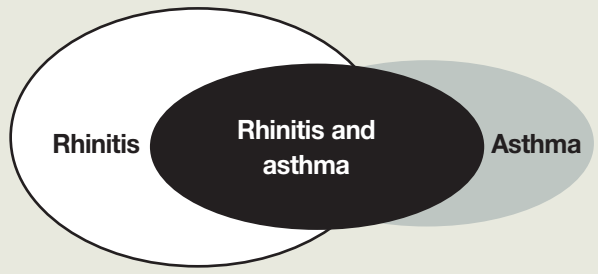
While the presence of rhinitis in patients with asthma is common, the converse association was thought to be less strong. However, recent evidence suggests that patients with rhinitis are also likely to have asthma. Large population studies have shown the incidence of asthma symptoms in rhinitis to be 19-38%.[3] In two early surveys, the prevalence of asthma symptoms in people with rhinitis was reported as 16.2% and 4.7%.[4,5] Both these surveys were based on questionnaire or video questionnaire diagnosis.

The frequency of diagnosis of asthma is much greater when other investigations are used. In a 23-year follow-up of college students using an initial skin-prick test and then questionnaires, the prevalence was 21.3%. When skin-prick testing, spirometry and methacholine challenge were used in a population of almost 3000 Italian subjects, the prevalence of asthma was 67.2% in those with rhinitis.[6]

In a prospective study using a Danish database of more than 8000 patients with one or both of these diseases, rhinitis and asthma developed within the same year in 25% of patients. Additionally, in 75% of patients the two conditions developed within two years.[7]

Similarly, in a Finnish twin cohort of 11,000 patients there was a fourfold increased risk of developing asthma in those with rhinitis.[8]

Figure 1: Proportions of clinically overt rhinitis and asthma. The overlap of symptoms becomes greater when the patient's condition is assessed over time or when more sensitive measures are used to assess the airways.



These correlations have been demonstrated in differing demographic and racial groups including both atopic and non-atopic individuals. Longitudinal studies document that rhinitis is almost always diagnosed before asthma. This trend, when rhinitis precedes the development of asthma, is often referred to as 'the allergic march'.

The prevalence of atopy and allergic diseases has increased both in Australia and worldwide over recent decades. In Australia, asthma prevalence is 10.2%, or two million people, and plateauing over the past 5-10 years.

The proposed explanation for the worldwide increase in allergic disease has been titled the 'hygiene hypothesis', which suggests that a 'cleaner environment' (eg, less exposure to bacteria, use of vaccines, antibiotics, etc.) predisposes to persistence of an allergic phenotype from childhood. This hypothesis is supported by a diverse body of literature and the reader is referred to Romagnani and colleagues (2004) for a comprehensive overview.[9]

Anecdotally, there is a link between rhinitis, allergy and the development of chronic rhinosinutis (CRS). Many 'cause and effect' theories have been the focus of research, but the relationship remains unclear. There are good data to suggest a higher incidence of allergy and rhinitis in CRS and these patients also have worse CT findings along with higher IL-5 levels and more eosinophilic mucus.

However, studies of rhinitis and allergy in CRS seem to indicate that CRS is an inflammatory condition resulting from interacting immunological, microbial and mucociliary factors (figure 3). The pathophysiological interaction of intrinsic mucosal inflammation, microbial flora and mucociliary dysfunction results in ongoing inflammatory changes.

Current topical therapies can affect all three of these processes:

- The ability to substitute for loss of mucociliary clearance and alter mucus rheology (including viscosity) using saline irrigation.
- Delivery of steroids to intrinsic mucosal inflammation.
- Antimicrobial therapies.

Figure 2: 'Cobblestoned' mucosa of rhinitis (right posterior aspect of the middle turbinate) due to seromucinous glandular hypertrophy. Many of these changes are present in people with asthma, but lower respiratory tract symptoms tend to predominate in these patients.

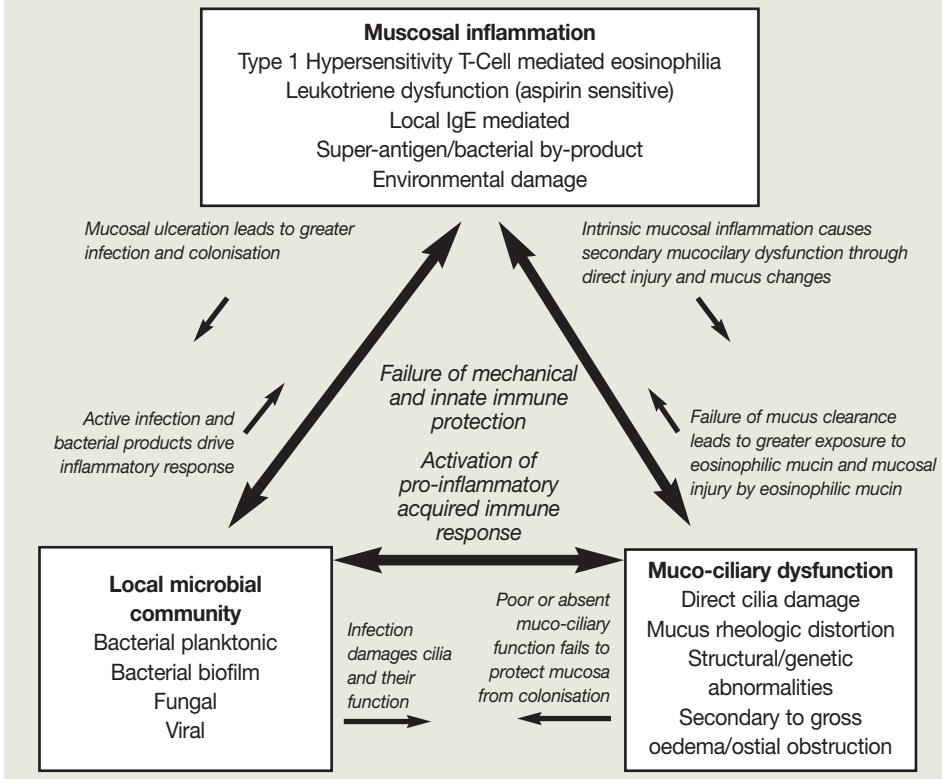
Each patient will have a dominant mechanism, so tailored therapy is required. Many patients with asthma will develop polypoid changes of the sinus mucosa (figure 4, page 30). Polyps develop when a chronic inflammatory infiltrate causes areas of swelling and thickening of the sinus mucosa. Unlike 'colonic polyps', for example, nasal polyps are inflammatory rather than hyperplastic or neoplastic. Although surgery is used to remove them and open the sinus cavity widely, it is the topical postoperative treatment of the mucosa that allows the inflammatory process to be controlled, not the surgery.

These epidemiological data support the concept that inflammation in the upper airway can be a predisposing factor in the development of lower airway disease, and the respiratory tract functions as a unified system.

Pathophysiological evidence

Airway hyper-reactivity to bronchoconstricting agents can occur in people with rhinitis without a clinical diagnosis of asthma. In one study, 48% of patients with rhinitis had airway reactivity in the asthmatic range without a clinical diagnosis of asthma.[10] Self-reported nasal allergies and positive allergy skin tests are also independent predictors of bronchial hyper-reactivity.[11]

Figure 3: The triangle of pathological mechanisms causing the unregulated pro-inflammatory mucosal response.
(Reproduced with permission from the division of rhinology, St Vincent's Hospital, Sydney, NSW.)



While there is substantial evidence to link upper and lower airway inflammation, the underlying mechanisms have only recently been the focus of research. Three proposed mechanisms are under investigation:

- The nasobronchial reflex.
- Sino-nasal protection of the lower airway.
- Shared inflammation within a unified airway.

Nasobronchial reflex

Kaufman initially described a trigeminally mediated nasobronchial reflex wherein nasal irritation provokes bronchoconstriction. The ability of silica particles applied to nasal mucosa to induce increased airway resistance was reported, with the effect blocked by atropine or resection of the trigeminal nerve.

Although other authors have failed to accurately replicate these early studies, some reproducible reflex responses can be demonstrated. In normal individuals, cold nasal (but not oral) air inhalation caused increased lower airway resistance, and this response could be blocked by nasal anaesthesia, nasal anticholinergic, or bronchial anticholinergic. Mechanical or chemical stimulation of the nose can induce bronchoconstriction in animals and people with cold-sensitive asthma.[12]

However, most changes in bronchial responsiveness after nasal challenge take 30 minutes to four hours to occur, suggesting that a direct neural reflex has a limited role. Additionally, reflexes exhibit tachyphylaxis, and cannot account for the chronic symptoms associated with rhinosinusitis and asthma. Overall, the nasobronchial reflex does not provide a comprehensive mechanistic explanation for the link between rhinosinusitis and asthma.

Sino-nasal protection of the lower airway

The concept of mouth breathing and bypass of normal humidification and warming of nasally inspired air has been postulated as a cause of lower airway disease. However, theory is not supported by evidence.

Humidification of inspired air is increased rather than compromised with antigen exposure and rhinitis.[13] Additionally, patients sensitive to cat allergen, with and without nasal occlusion, demonstrate no deterioration in lung function after antigen exposure, whereas a week of pretreatment with a nasal steroid spray reduced allergen-induced lung function changes.[14]

It appears unlikely that rhinitis represents a loss of protection of the lower airways either through filtering or loss of humidification.

Shared inflammation

There is a strong histopathological association between inflammatory upper airway conditions (such as CRS) and asthma. Common findings in these conditions include:

- Basement-membrane thickening.
- Subepithelial remodelling.
- Oedema.
- Goblet cell hyperplasia.
- Persistent inflammation.

These identical features have prompted several research groups to consider a common pathology model. These models of pathogenesis lend support to the notion of a unified airway with similar histopathological changes and immunological mechanisms occurring as a result of inflammatory insult.[15,16]

An interaction occurs between different airway compartments when stimulated separately. Braunstahl and colleagues placed antigen onto bronchial mucosa using a bronchoscope and demonstrated subsequent nasal inflammation.[17] Likewise, nasal stimulation with allergen produced a bronchial response on biopsy. Eosinophilic inflammation is common in asthma and CRS. Increased numbers of eosinophils can even be seen in the nasal mucosa of people with asthma but without nasal symptoms. Similarly people with allergic rhinitis demonstrate lower airway inflammation in bronchial biopsies, even without clinical asthma. There is also good correlation of eosinophil counts in sputum, from the lower airway and in the serum, with sinus disease severity.

It is hypothesised that inflammatory mediators, cytokines and interleukins (ILs) mediate this shared inflammation. Current pathophysiology models view the airway as the organ responsible for both the mediation of, and the end target for, this immunological cascade. The airway is an immunologically unique organ that possesses antigen-presenting cells, T-lymphocytes and secondary lymphoid tissue capable of driving a mature Th2 immune response. It is believed that

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cytokine and IL release from the respiratory mucosal creates the airway-wide responses that are seen. IL-5 has received significant focus as a key mediator, and commercially available antibodies to IL-5 will soon be available for people with severe asthma. Unfortunately, like antihistamines, they target only one of many mediators involved in the disease process.

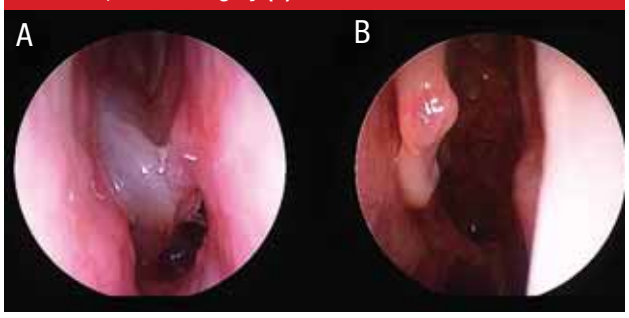
Unsupported theories

Aspiration of infected or inflammatory sinonasal secretions is commonly proposed as a connection between rhinosinusitis and asthma. Although popular with patients trying to understand their disease, this explanation lacks convincing evidence. It is at odds with the multiple physiological mechanisms that effectively protect the airway in a neurologically intact patient, including:

- Strong cough reflexes.
- A powerful mucociliary blanket that clears the tracheobronchial tree.
- Reflex swallowing when there is material in the oropharynx.

Additionally, studies have provided evidence against this hypothesis. Scintigraphy does not demonstrate pulmonary aspiration after placement of radionucleotide tracer in the maxillary sinus in rhinosinusitis. Although there is obvious anatomical continuity between the upper and lower airways, it is unlikely that direct transfer of inflammatory or infected secretions occurs.

Figure 4: Nasal polyps (A) are really chronic inflammatory changes, with sinus mucosa that results in slow distension and swelling of the sinus mucosa due to inflammatory infiltrate. They are not benign neoplastic 'growths', in comparison with most colonic polyps. Although surgery is used to remove them and open the sinus cavity widely, topical postoperative treatment of the mucosa allows the inflammatory process to be controlled, not the surgery (B).



Treatment-based evidence

Double-blind placebo-controlled trials have shown that rhinitis management with intranasal steroid improves asthma. A Cochrane review demonstrated a trend to overall benefit, even with heterogenous studies.[18] Much attention has been placed on managing sino-nasal disease to alter outcomes in patients with asthma.

Nasal and bronchial symptoms, nasal and peripheral blood eosinophilia, and bronchial response to methacholine challenge were reduced in a double-blind, randomised placebo-controlled trial in patients with allergic rhinitis and birch pollen sensitivity but no asthma, using orally inhaled budesonide (600µg twice daily) or placebo. Additionally, reduced ED visits and hospitalisations have been observed in population-based studies looking at the effect of treatment of patients with asthma with nasal steroids.

Diagnosis and investigations

THERE are multiple approaches to the diagnosis of inhalant allergy (see box, opposite).

Skin-prick tests

Skin-prick tests (SPTs) are the most straightforward technique to confirm a clinical history suggestive of inhaled antigen-induced inflammation. The wheal size, not the erythema, is measured for assessing response.

Mast cells are the key effector cells in type I hypersensitivity and reside in the subepithelial layer of nearly all epithelial organs, including the respiratory tract and the skin. The SPT is a rapid and convenient way of accessing the mast cell population to detect specific IgE responses (figure 5). The test should be performed with appropriate positive (histamine) and negative (saline) controls and should include antigens to be used in subsequent immunotherapy.

There is a poor correlation between SPT, specific serum IgE measurements, and direct allergen challenges to the airway; positive SPT reactions with negative responses to direct antigen challenge are common. Therefore a careful clinical history is essential to determine the relevance of positive SPT or IgE results. Indiscriminate SPTs should be avoided.

Figure 5: Epicutaneous antigen testing or skin-prick testing.

Direct end-organ challenge (provocation) tests

Challenge tests for upper and lower airways use both specific allergens and non-specific stimulants. They have been used most extensively to measure lower airway hyper-responsivess in suspected asthma and have a well-established role in most lung function laboratories. Testing can either be a direct agent such as histamine or methacholine, which are smooth muscle agonists, or an indirect challenge that includes exercise, eucapnic hyperventilation, hypertonic saline and, more recently, mannitol.

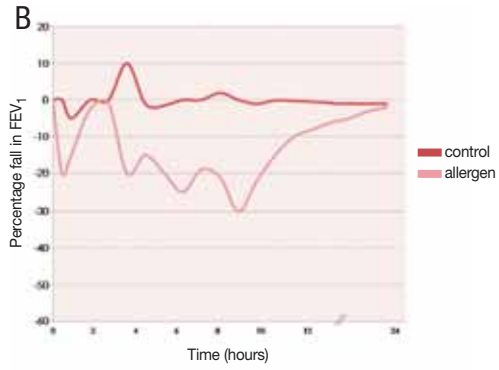
These tests alter airway osmolarity, releasing endogenous mediators that cause airway smooth muscle contraction. The severity of lower airway hyper-responsivess (mild, moderate and severe) can be established and response to treatment can be demonstrated (figure 6). Specific allergen challenge has largely been a research tool but sometimes can be very useful to diagnose occupation-induced asthma.

In the upper airway, nasal challenge can be performed with specific allergens and a variety of non-specific agents such as histamine, cold air, etc. However, there is a greater overlap in results between patients with rhinitis and normal patients than there is with lower airway disease, making the test results harder to interpret. This testing is only available at specialised centres (figure 7).

Intranasal lysine aspirin can be used to define the presence of AERD (aspirin exacerbated respiratory disease) or Samter's triad (asprin sensitivity with nasal polyposis and asthma). This affects 4-11% of patients with asthma. The pathogenesis of aspirin intolerance relates to abnormal metabolism of arachadonic acid involving both the lipoxygenase and cyclo-oxygenase pathways.

This group of patients often presents a difficult clinical management problem, with poor control of upper and lower airway symptoms. Almost 70% of

Figure 6: Lower airway challenge.



C

	Pre-bronch			Post-bronch		
	Actual	Predicted	% Pred	Actual	% Pred	% Change
Spirometry						
FVC (L)	3.13	4.61	68	2.88	63	-8
FEV_1 (L)	1.85	3.52	52	1.92	54	4
FEV_1/FVC (%)	59	76	78	66	87	13
FEF 25% (L/sec)	2.15	8.09	27	2.77	34	29
FEF 75% (L/sec)	0.37	1.62	23	0.40	25	10
FEF 25-75% (L/sec)	0.88	2.99	29	0.91	31	4
FEF Max (L/sec)	5.95	9.10	65	5.60	61	-6
FIVC (L)	2.65			2.48		-7
FIF Max (L/sec)	3.52			2.86		-19

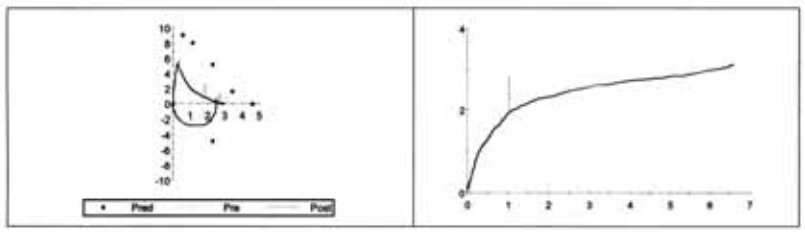
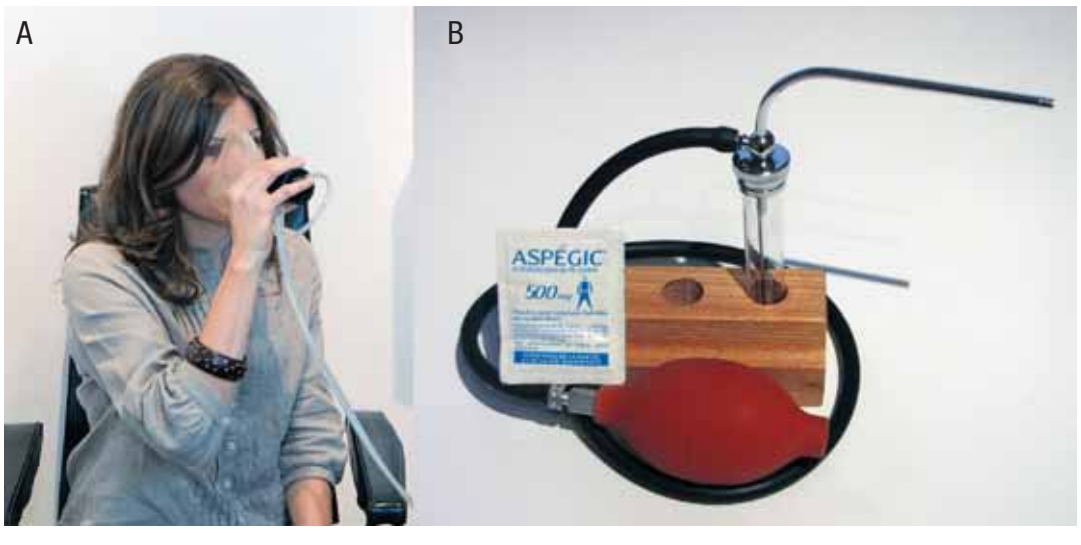
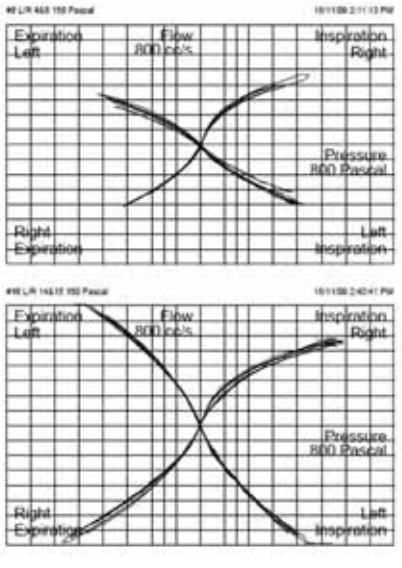


Figure 7: Upper airway challenge testing. A: The use of rhinomanometry and acoustic rhinometry is critical for effective nasal challenge testing. B: Lysine aspirin is atomised into the nasal airway with an insufflator. C: The corresponding resistance and cross-sectional airway measurements, with symptom reporting, determine the response.

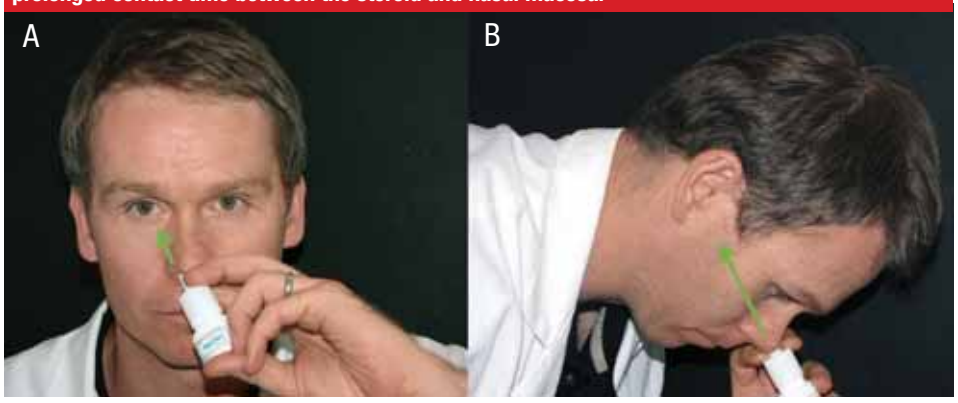




aspirin-intolerant patients have nasal polyps (figure 4) compared with 4% of the general population. Oral aspirin desensitisation can be beneficial, but the existence of aspirin sensitivity makes this form of treatment risky at times due to its potential to trigger asthma. In addition, the doses of aspirin required to control nasal polyp symptoms have often been high and are poorly tolerated due to gastrointestinal side effects. Intranasal lysine aspirin desensitisation maybe beneficial for this group.

Tests for confirming IgE-mediated allergy
Skin tests
Intracutaneous (intradermal)
Intradermal single-dilution test
Intradermal dilutional test
Epicutaneous (prick/puncture) tests:
• Multiple antigen
• Single antigen
End-organ challenge (provocation) tests
Nasal provocation
Bronchial provocation
Conjunctival provocation
Serological/blood tests
Radioisotope labelling (rarely used), eg, RAST
Enzyme-linked labelling, eg, ELISA

Figure 8: Intranasal corticosteroid technique. Sniffing the steroid on initial application should always be avoided, as this will only bring the steroid to the nasopharynx. Angulation is toward the corner of the eye (A) and parallel to the hard palate (B) as the sprays are given. The patient waits for a drop to be felt on the tip of the nose then sniffs back softly. The sniff and waiting for the drop to reform is repeated as long as a drop is felt (usually only 2-3 cycles). This technique ensures prolonged contact time between the steroid and nasal mucosa.



Management of rhinitis

Principles of management

THERE are four broad groups of therapeutic modalities — antigen avoidance, pharmacotherapy, surgery and immunotherapy. Too often these modalities are used sequentially when evidence suggests that a multimodal approach is best for most patients (table 1).

For example, a patient with rhinitis (without CRS) with persistent nasal congestion after trialling intranasal steroid should not be directed to antihistamines or further antigen avoidance. Immunotherapy is long term and not effective for nasal obstruction. However, an endoscopic turbinate reduction will provide immediate relief from the obstruction. Understanding severity scales is useful to ascertain a reasonable starting point for patient treatment (tables 2 and 3). For example, in persistent asthma or rhinitis a topical steroid should always be used as first-line management.

Antigen avoidance

Allergen avoidance has a limited impact on real-life disease course. Although removal of people with allergic rhinitis to places such as high-altitude sanatoria can significantly reduce symptoms, this is of little practical benefit. Significant focus has been placed on altering the indoor environment to improve control. This is a multimillion dollar industry, with special dust covers, foam pillows and air filters commercially available.

However, there is increasing evidence that many of these interventions have little impact on the disease course. A Cochrane meta-analysis concluded that current chemical and physical methods aimed at reducing exposure to mite allergens seemed to have limited clinical effectiveness for people with asthma and mite sensitivity.[19] The evidence supporting these interventions is listed in table 4 (page 32), with several systematic reviews showing no beneficial effect.

Pharmacotherapy

Intranasal steroids (INS), antihistamines and nasal saline form the basis of pharmacotherapy.

The early-phase response is primarily mediated by histamine, and acute symptoms dominated by sneezing and itching, with rhinorrhoea and congestion also present but often more delayed in their presentation.

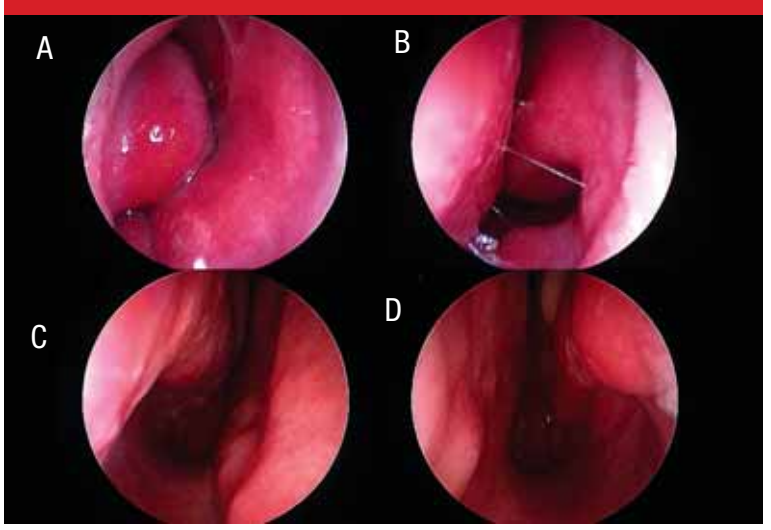
The late-phase response generally occurs more than two hours from antigen exposure and is mediated by T-cell cytokines. These symptoms are more prolonged than those triggered by histamine alone. Nasal congestion and postnasal discharge are common.

Table 1: Targeted strategies for symptoms (evidence levels)*

	Treatment strategies	
Symptoms	**Medical**	**Surgical**
Nasal obstruction	Topical corticosteroids (1a)	Turbinate reduction (2c) Septal surgery (2c)
Rhinorrhoea	Topical corticosteroids (1a) Ipratropium (3) Injected intranasal botox (4) Leukotriene inhibitors (4) Immunotherapy (1a)	Vidian neurectomy (4)
Sneezing	Chromones (1a) Antihistamine (1a) Intranasal capsaicin (4) Leukotriene inhibitors (4 Immunotherapy (1a)	Turbinate reduction/ neurectomy (5)
Postnasal discharge	Saline irrigation (1a) Topical corticosteroids (higher dose) (5) Immunotherapy (1a)	Adenoidectomy (4) Posterior neurectomy (4) Turbinate reduction (4)
Sinusitis	Corticosteroids Culture directed antimicrobial therapy (4)	Endocopic septal surgery with postsurgical topical therapies (1b)

*The benefit of interventions depends on specific symptoms. Most patients benefit from a multi-faceted concurrent therapeutic approach to symptom control.

Figure 9: Turbinate hypertrophy and surgical reduction. Severe preoperative turbinate hypertrophy in a patient with allergic rhinitis (right A and left B). Post formal endoscopic turbinate reduction (not simple diathermy) can significantly increase the patency of the nasal airway (C and D).



Antihistamines

Non-lipophilic second-generation oral antihistamines (eg, loratidine, cetirizine) are the most commonly available medications to manage the early symptoms. They do not cross the blood–brain barrier and have minimal sedative effects.

Not only do these agents compete with histamine in binding to the H_1 receptor, they also change the three-dimensional configuration of the receptor, decreasing its affinity for histamine. This deforming of the receptor has been termed reverse agonism.

Although oral antihistamines are usually prescribed for itching and sneezing, they are less effective than topical steroids. However, when multi-end-organ symptoms occur (pharynx, mouth, conjunctivae and upper or lower airway), they may be more convenient than topical corticosteroids delivered to multiple sites. The topical antihistamine azelastine is currently available for the treatment of allergic rhinitis and conjunctivitis, and an excellent solution for rapid short-term relief in intermittent disease, especially in socially awkward exacerbations.

Table 2: Severity grading for asthma

Grading	Symptoms (daytime)	Symptoms (night)	PEF or FEV_1 %: of normal (variability post vs pre-bronchodilator)
Intermittent	Less than once a week Asymptomatic and normal PEF between attacks	No more than twice a month	≥80% (<20%)
Mild persistent	More than once a week and less than once a day Attacks affect activity	More than twice a month	≥80% (20-30%)
Moderate persistent	Daily Attacks affect activity	More than once a week	60-80% (>30%)
Severe persistent	Continuous Limitation of physical activity	Frequent	″60% (>30%)

PEF = peak expiratory flow

Table 3: Classification and severity grading for rhinitis

Classification	Criteria
Pathology	
Allergic	If clinical history AND Skin prick test (or other IgE evaluation) supports antigen exposure induced symptoms
Non-allergic	A collective group of conditions that involve non-allergic mechanisms, including: vasomotor, intrinsic, neurogenic and occupational rhinitis
Duration	
Intermittent	Fewer than four days a week OR Fewer than four weeks' duration
Persistent	Four or more days a week AND Four or more weeks' duration
Symptoms	
Mild	Normal sleep and minimal impairment of daily activities
Moderate–severe	Abnormal sleep or impairment of sport, leisure, work or troublesome symptoms

Intranasal corticosteroids

Newer INSs, mometasone (Nasonex) and fluticasone furorate (Avamys), generally have bioavailabilities less than 1% (reducing the risk of systemic side effects), and a greater affinity for the glucocorticoid receptor. Corticosteroids affect a large number of cellular and humoral mediators and influence both early and late phases of antigen exposure. Similar to correct inhaler technique, effective use of intranasal sprays are essential for optimal benefit (figure 8).

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Chromones

Chromones, mast-cell-stabilising agents, are available as topical ophthalmic drops, nasal spray and as an aerosol inhaler. They may be useful in selected patients (level 1b evidence). Olopatadine is a newer preparation that has both antihistaminic and mast-cell-stabilising effects. At present it is available in Australia only as an ophthalmic solution.

Anticholinergics

Intranasal anticholinergic (ie, ipratropium) can be very useful for symptoms of watery rhinorrhoea.

Oral and intranasal aspirin therapy

The confirmation of non-allergic aspirin-sensitive airways disease raises the therapeutic option of aspirin desensitisation. The mechanism of therapy is unclear. Desensitisation involves incremental oral dosing, with ongoing, daily high-dose aspirin, indefinitely.

Most studies examining aspirin desensitisation show a clinical benefit, with improvement in asthma, rhinosinusitis, and control of sinonasal polyps (figure 4, page 30). Additionally, therapy may result in a decreased need for oral and topical steroid use. Unfortunately, aspirin-induced gastritis can lead to discontinuation of therapy.

The intranasal administration of lysine–aspirin for both diagnosis and desensitisation is our preferred method (figure 7, page 30). This is an area of current interest and research.

Leukotriene inhibitors

Leukotrienes are potent inflammatory mediators released during the late-phase allergic response. They are synthesised from arachidonic acid by lipoxygenase enzyme activity. While modification of the effect of these mediators with receptor antagonist (ie, montelukast) has been beneficial in asthma, the impact on rhinitis is less so. Several studies have demonstrated a benefit similar to that of oral antihistamine but less effective than intranasal steroid in controlling nasal symptoms.

Table 4: Evidence-based allergen avoidance measures*

Evidence level	Dust mite	Pet allergen
1	Specialised pillows, mattress and quilts (1b for allergen reduction, but 1a for no clinical benefit in adults. 1b for clinical benefit in children) Removal of carpets (1b for allergen reduction)	HEPA filters* (1b for allergen reduction but 1a for no clinical benefit in adults.)
2	Bed linen washing (2b for allergen reduction) HEPA filter for dust mite (2b for allergen reduction)	Removing pet (2b for allergen reduction) Washing pet (2b for allergen reduction)
3	Acaricides/tannic acid (allergen reduction)	
4	Removing or washing toys (allergen reduction) Closed storage of dust-accumulating objects (allergen reduction) All interventions, except bed linen washing (clinical effect)	Removal of carpets (allergen reduction) All interventions, except HEPA filters (clinical effect)

*Evidence for clinical effectiveness is poor (except negative studies for HEPA filters [a high-efficiency particulate absorbing or arrestance filter] and dust mite reduction). Studies on allergen reduction use it as a surrogate endpoint but whether the allergen reduction translates into a clinical benefit is questionable.

Leukotriene inhibitors are considered an ancillary therapy for both upper and lower airway, with little guidance available as to which patients may benefit.

Novel therapies

Neural dysregulation of the nasal mucosa may be important, especially in non-allergic (previously called 'vasomotor') rhinitis. Capsaicin, the pungent agent in chillies, is known for its degenerating/desensitisation effect on peptidergic sensory C-fibres. This may explain its therapeutic effect of reducing the hyper-responsiveness of the nasal mucosa in non-allergic rhinitis.

Capsaicin therapy is limited to non-obstructive symptoms to non-allergic stimuli such as cold air. It is a medical alternative for some patients in whom a vidian neurectomy may be inappropriate. There is little evidence for its use in allergic rhinitis. Multiple treatments (usually five) are given after local nasal anaesthesia and lip/mouth protection. This treatment is not readily available in Australia.

Botulinium toxin has been reported as a therapy for refractory rhinitis. It has to be injected into the nasal mucosa because topical mucosal application using a sponge has only limited efficacy. This makes delivery more problematic and poorly tolerated. The effects are short-lived and efficacy appears to be similar to that of intranasal ipratropium spray. Although beneficial effects have been observed using inferior turbinate injection, endoscopic turbinate reduction is probably a better option.

Surgery

Turbinate reduction

In patients with rhinitis, turbinate hypertrophy results from chronic inflammation. The mucosal layer, mucus glands and venous sinusoidal tissue increases in bulk, and not just from vascular engorgement (figure 9, page 31). This slow increase in size often accounts for the loss of the initial intranasal steroid benefit. There are many techniques that can be used but true surgical reductive procedures appear to have better long term results than ablation with radiofrequency, laser or diathermy.

Vidian neurectomy

Division of the autonomic supply of the pterygopalatine ganglion is an effective therapy, especially in the setting of significant rhinorrhoea. It carries a risk of decreased lacrimal secretions, due to shared innervation of the lacrimal gland. It is more effective than capsaicin in animal models of neuropeptide reduction, and an excellent option for refractory symptoms, in particular, chronic watery discharge.

Posterior neurectomy

Posterior neurectomy is an alternative to vidian neurectomy, to limit the effects of total proximal autonomic block of both nose and eye. This procedure is often combined with a simple turbinate reduction. The terminal nerve branches that supply the turbinate and posterior nose are divided as they exit the lateral nasal wall. Posterior neurectomy is a relatively novel therapy for non-allergic rhinitis and does not preclude a patient proceeding to a formal vidian neurectomy if symptoms persist or if symptom control is sub-optimal.

Endoscopic sinus surgery

Since the 1980s, endoscopic sinus surgery (ESS) has been widely employed to manage CRS refractory to medical management. There are numerous case series, prospective studies and a few randomised controlled trials to support its use. Traditional surgical concepts have centred on relieving ostial obstruction and enhancing ventilation. However, as CRS is increasingly seen as an inflammatory disorder, the role of ESS has changed.

Before surgery, delivery of topical therapies to the sinuses is extremely limited regardless of device. Sprays are the least effective of all delivery devices. ESS improves the delivery of topical medications to the sino-nasal mucosa.[20,21]

Modern endoscopic sinus surgery aims to be a minimally invasive yet effective treatment. Careful wide exposure of the paranasal sinus system with preservation of the mucosal lining of the remaining cavity is the goal of ESS (figure 4B, page 30) This allows easy management of mucosal-based disease with topical therapies.

Immunotherapy

Directed immunotherapy (desensitisation), whether sublingual (SLIT; level 1a) or subcutaneous injection (SCIT; level 1a) has good evidentiary support. Cochrane reviews support the use of both SLIT and SCIT. It is mainly used for the treatment of allergic rhinoconjunctivitis and if carefully selected is very successful. It can also be beneficial for asthma although this is not currently an indication for its use in Australia.

Additionally, it is accepted that some children with allergic rhinitis will develop further sensitisation to new allergens and the potential for wider involvement of the airway (asthma and CRS) over time. There is evidence to suggest that early intervention with immunotherapy can alter the course of these conditions.

An early single-blinded, saline-placebo-controlled study involving 210 children with perennial bronchial asthma with allergies, with 62% followed up to their 16th birthday. Of those treated with immunotherapy, 72% of were symptomatically free from asthma, while only 22% of the placebo children were symptomatically free from asthma.[22]The potential for identifying and altering the Th2 (allergic) response early in these patients and thus the development of widespread airways inflammation is supported by Moller et al., using pollen SCIT immunotherapy and demonstrating reduced asthma rates.[23] At three years, 29 of 69 children (42%) in the control group developed asthma versus 19 of 79 children (24%) in the immunotherapy group. Similar findings occur using SLIT, with the development of asthma after three years at 3.8 times more frequent in the children who did not receive immunotherapy compared with those who did receive immunotherapy.

Conclusion

OUR current understanding of airway disease suggests that both upper and lower airway disease exist concurrently. It is likely that both are manifestations of a single inflammatory process within the respiratory tract and also involves a systemic inflammatory response.

Clinically this means that even if a patient presents with symptoms relating to one site, it is important to elicit symptoms and signs from both upper and lower airway with appropriate supportive investigations.

Treatment of both upper and lower airway at the same time will improve outcomes for the whole airway, and a multifaceted treatment approach is often the most successful, especially in complex cases.

Summary

- Compartmentalisation of chronic inflammation to one part of the respiratory tract is the exception rather than the rule.
- Aspiration of inflammatory secretions, as a causal link between upper airway and lower airway disease, is unlikely in a neurologically intact patient.
- Good evidence suggests the same inflammatory process occurs in both the upper and lower airways.
- Multifaceted concurrent therapy is the key to obtaining rapid symptom control.
- Surgery such as turbinate reduction should be used as an adjunct in therapy, and not as a treatment of last resort.
- Immunotherapy started early may alter the course of rhinitis and asthma, halting the 'allergic march'.

Online resources

Australasian Society of Clinical Immunologists and Allergists (ASCIA)
www.allergy.org.au

References and further reading

Available on request from julian.mcallan@reedbusiness.com.au

Conflict of interest statement

No external funding was received. Professor Harvey has served on an advisory board for Schering Plough and has received grant support from NeilMed. Dr Rimmer has served on Advisory Boards for Novartis and GlaxoSmithKline and has particated in a number of commercial clinical trials (GSK, Schering Plough, Novartis, Novatech, Epigenesis, Medpointe) and received funding from Pharmaxis.

GP's contribution

DR ROSS WHITE
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Case study

COLLEEN, 56, has had upper airway problems since age 11, when recurrent epistaxes were treated with cautery. From age 17 she has had recurrent allergic rhinitis, treated with the older oral antihistamines, then nasally inhaled budesonide for short periods until the epistaxes recurred.

After an episode of anaphylaxis after taking aspirin in 1987, she saw an allergist who found, on SPT, multiple allergies to herbs. The allergist said that desensitisation therapy would not be successful with so many possible allergens. Colleen found

cont'd page 34

from page 32

the Medihaler Epi prescribed at that time very useful in relieving the symptoms.

She has since moved from a rural to an urban area and the frequency of attacks has decreased. However, she can get episodes of facial swelling and severe rhinitis with exposure to tobacco smoke, latex, strong perfumes and basil. Loratidine did help but now it takes 1-2 days to get over an episode.

A recent ENT consultation found no polyps and the cautery to septal nasal mucosa gave only temporary relief to the epistaxes.

Questions for the author

Would there be any advantage in repeating the skin tests with a view to immunotherapy? What of the newer treatments would be most suitable for relieving her symptoms?

If there is a convincing clinical history to accompany some of the positive antigen responses this could be used to direct possible multi-antigen immunotherapy. However, the history has mixed elements of a patient with an inhalant allergy with that of aspirin sensitive airway disease. Newer antileukotrienes (Singulair) may be beneficial with a discussion about aspirin desensitisation if this is the predominant history.

Epistaxis is usually a result of minor mucosal trauma from spray use. Nasal mucosa does not undergo atrophy (neither does the lung) unlike skin. Skin is a stratified keratinised cell bulk with active turnover and protein synthesis that does undergoes reversible atrophy with topical steroid use. There are other local steroid therapies (ie, Flixonase drops) that can be used for a patient with recurrent epistaxis from pump spray use.

Author 2: Yes it would be useful to repeat SPTs. Immunotherapy may have a place, but would not reduce symptoms due to non-specific triggers, for example the perfumes and tobacco smoke.

She needs to be tested for latex allergy and provided with specific avoidance advice if she is allergic.

I would say for this patient there are multiple problems each of which need to be addressed: aspirin sensitivity with anaphylaxis, allergic rhinitis, nonallergic rhinitis, food allergy (basil), and possible asthma as well.

Colleen has friends who had nasal surgery in the 1980s for nasal/sinus problems with no lasting benefit. She would like to know what percentage of patients have significant improvement with endoscopic nasal surgery.

There are different types of nasal surgical interventions: for nasal breathing (turbinate reduction), uncontrolled rhinorhhoea (vidian neurectomy) and for chronic sinus dysfunction/inflammation (endoscopic sinus surgery). Patients with severe persistent rhinitis will often have completely normal sinus function. There is no role for sinus surgery in these patients.

Unfortunately, poor selection for sinus surgery has led to sub-optimal outcomes (despite a short-lived result due to the suppression of rhinitis by the recovering mucosa). Patients with severe persistent rhinitis do extremely well from turbinate reduction for nasal obstruction. Immunotherapy has limited effect on nasal obstruction as a symptom and thus is not recommended for obstruction (although excellent for itch, sneeze, discharge and conjunctival symptoms).

For true chronic inflammatory rhinosinusitis, endoscopic sinus surgery (with appropriate postoperative therapy) offers a significant improvement of the condition in 70-80% of patients based on recent patient centered outcome studies.[1]

General questions for the author

Can topical azelastine cause rhinitis medicamentosa?

Azelastine is a potent, second-generation, selective, histamine antagonist (histamine H_1 receptor antagonist). As a spray it is useful to assist in severe intermittent rhinitis and in situations where a predictable nasal reaction might be anticipated.

It is not intended for long-term use where symptoms are sufficiently intermittent so as not to warrant routine oral antihistamine. Despite this, histamine receptors do not undergo tachyphylaxis and the rebound phenomenon. This patient's Medihaler Epi is a topical decongestant for the lower airways and so a rebound effect is possible of her lower airway. It is unclear if it was used for anaphylaxis or for asthma.

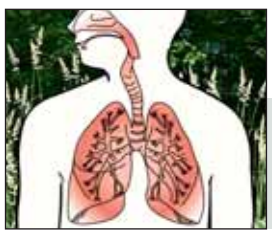
Infants with asthma often have their inhaled steroids and bronchodilators administered by a mask and spacer. When they get older they change to a spacer alone. If an older child has asthma and nasal disease both requiring inhaled steroids, would it be effective to use a mask with the spacer, or use nebulised budesonide with eye protection?

It is very common for children with asthma to have concomitant rhinitis. Suppressing the inflammatory reaction in both upper and lower airway is important for overall control.

Unfortunately, inhalers and nasal sprays differ in particle size of their medication. Generally, nasal sprays atomise the solution to >20µm, which will preferentially distribute to upper airway. Inhalers produce fine particles or <5µm with general distribution better for lower airway delivery. Single delivery technique is unlikely to provide an efficient delivery mechanism.

Reference

1. *Otolaryngology — Head & Neck Surgery* 2010; 142:55-63.



How to Treat Quiz

Rhinitis and the unified airway — 2 July 2010

INSTRUCTIONS

Complete this quiz online and fill in the GP evaluation form to earn 2 CPD or PDP points. We no longer accept quizzes by post or fax.

The mark required to obtain points is 80%. Please note that some questions have more than one correct answer.

ONLINE ONLY

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1. Which THREE statements are correct?

a) Epidemiological and pathophysiological data suggest that the upper and lower respiratory tracts behave as an integrated system

b) Most patients with allergic asthma induced by pollen, animals or mites also have allergic rhinitis from these causes

c) While the presence of rhinitis in people with asthma is very common, the converse association is not supported by the evidence

d) The 'allergic march' refers to the observation that rhinitis is nearly always diagnosed before asthma

2. Which TWO statements are correct?

a) The 'hygiene hypothesis' for the worldwide increase in allergic disease is that a greater exposure to bacteria in early life predisposes to the persistence of an allergic phenotype from early childhood

b) Chronic rhinosinusitis (CRS) is due to the interaction of intrinsic mucosal inflammation, microbial flora, and mucociliary dysfunction

c) The key medical therapies for CRS are saline irrigation, topical corticosteroids, and antibiotics

d) Nasal polyps have a neoplastic aetiology

3. Which TWO statements are correct?

a) Patients with rhinitis can have increased airway reactivity in the asthmatic range, without a clinical diagnosis of asthma

b) The nasobronchial reflex, whereby nasal irritation provokes bronchoconstriction, provides a likely comprehensive explanation for the link between CRS and asthma

c) Mouth breathing and the bypass of normal humidification and warming of nasally inspired air is a likely cause for the development of lower airway disease in those with rhinosinusitis

d) There is a strong association between the histopathological findings in the upper and lower airways in CRS and asthma, including oedema, goblet cell hyperplasia, and persistent inflammation

4. Which THREE statements are correct?

a) Antigen placed onto the bronchial mucosa using a bronchoscope results in subsequent nasal inflammation

b) Nasal stimulation with allergen produces an inflammatory bronchial response on biopsy

c) There are good correlations between sinus disease and severity eosinophil numbers in sputum from the lower airway and in the serum, with

d) Aspiration of infected or inflammatory sinonasal secretions is a likely explanation of the association between rhinosinusitis and asthma

5. Which TWO statements are correct?

a) In a neurologically intact patient the lower airway is protected by a strong cough reflex, an effective muco-ciliary blanket, and reflex swallowing of material in the naso/oropharynx

b) Rhinitis management with intranasal steroids does not improve asthma

c) In patients with allergic rhinitis and birch pollen sensitivity, but no asthma, orally inhaled budesonide reduces both nasal and bronchial symptoms

d) There is a good correlation between skin-prick testing (SPT) and direct allergen challenges to the upper or lower airway

6. Which THREE statements are correct?

a) Mast cells are the key effector cells in type I hypersensitivity and reside in the subepithelial layer of the respiratory tract and the skin

b) SPT is a rapid and convenient way of accessing the mast cell population to detect specific IgE responses

c) Challenge tests for the lower airways use direct agents (histamine or methacholine) or indirect stimulants (exercise, hypertonic saline or mannitol)

d) Specific allergen challenge of the airway is a routine part of lung function tests

7. Which THREE statements are correct?

a) Nasal challenge tests have a greater overlap in results between normal patients and those with rhinitis, compared with lower airway disease

b) Testing with intranasal lysine aspirin can be used to diagnose Samter's triad (aspirin sensitivity with nasal polyposis and asthma)

c) Oral aspirin desensitisation in CRS may trigger asthma and cause GI side effects

d) Intranasal lysine aspirin desensitisation is ineffective in people with aspirin-related CRS

8. Which TWO statements are correct?

a) Antigen avoidance, pharmacotherapy, surgery and immunotherapy are best used sequentially

b) Many antigen-avoidance interventions have little impact on the disease course of CRS or asthma

c) Specialised pillows, mattresses and quilts reduce dust mite allergen exposure, and result in clinical benefit in adults

d) The early-phase allergic response is primarily mediated by histamine and characterised by sneezing and itching

9. Which THREE statements are correct?

a) The late-phase allergic response generally occurs more than two hours from antigen exposure, is mediated by T-cell cytokines and characterised by nasal congestion and postnasal discharge

b) Oral antihistamines are more effective than topical corticosteroids for the treatment of itching and sneezing

c) When allergic symptoms involve the conjunctivae and upper and lower airway, oral antihistamines may be more convenient than topical corticosteroids delivered to multiple sites

d) Corticosteroids affect a large number of cellular and humoral mediators and influence both early and late phases of antigen exposure

10. Which THREE statements are correct?

a) Intranasal ipratropium is ineffective in treating watery rhinorrhoea

b) Formal surgical reduction for inferior turbinate hypertrophy has better long-term results than ablation with laser or diathermy

c) Either posterior neurectomy or vidian neurectomy are indicated for uncontrollable chronic watery rhinorrhoea

d) Subcutaneous immunotherapy early in the course of allergic disease may prevent the development of widespread airways inflammation

CPD QUIZ UPDATE

The RACGP requires that a brief GP evaluation form be completed with every quiz to obtain category 2 CPD or PDP points for the 2008-10 triennium. You can complete this online along with the quiz at **www.australiandoctor.com.au.** Because this is a requirement, we are no longer able to accept the quiz by post or fax. However, we have included the quiz questions here for those who like to prepare the answers before completing the quiz online.

Australian Doctor Education

HOW TO TREAT Editor: **Dr Giovanna Zingarelli**
Co-ordinator: **Julian McAllan**
Quiz: **Dr Giovanna Zingarelli**

NEXT WEEK The next How to Treat reviews the latest in managing lipid disorders. The author is **Professor Ian Hamilton-Craig**, professor of preventive cardiology and internal medicine, school of medicine, Griffith University, Southport, Queensland.