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John D. Firth
Christopher P. Conlon
Timothy M. Cox

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18.6

Allergic rhinitis

Stephen R. Durham and Hesham A. Saleh

ESSENTIALS

Allergic rhinitis affects more than 20% of the population of Westernized countries and has a significant impact on quality of life and school/work performance.

Aetiology and clinical features—important environmental factors include tree and grass pollens (seasonal allergic rhinitis); house dust mite and domestic pets, most often cats (perennial allergic rhinitis); and a variety of occupational exposures (occupational rhinitis). Pathogenesis involves activation of type 2 (Th2) lymphocytes resulting in IgE antibody production and tissue eosinophilia. Immediate symptoms (itching, sneezing, and watery nasal discharge) result from allergen cross-linking adjacent IgE molecules on the surface of mast cells in the nasal mucosa, resulting in the release of histamine and tryptase, and generation of bradykinin.

Diagnosis and classification—diagnosis is usually straightforward and based on the history, examination, and (when indicated) the results of skin prick tests and/or serum allergen-specific IgE levels. Classification is according to the severity and duration of symptoms as defined by ARIA (allergic rhinitis and its impact on asthma) guidelines, which describe four categories of disease: (1) mild intermittent; (2) moderate/severe intermittent; (3) mild persistent; and (4) moderate/severe persistent.

Management—allergen avoidance, topical intranasal corticosteroids, and nonsedating oral antihistamines are the mainstays of treatment. Combination intranasal sprays containing a corticosteroid and an antihistamine are recently available. Treatment failure often results from poor compliance or inadequate technique in use of nasal sprays. Allergen injection immunotherapy or sublingual immunotherapy is indicated in patients with severe seasonal allergic rhinitis who fail to respond to usual measures: both have been shown to induce long-term disease remission. The repertoire for immunotherapy has recently been extended to include patients with perennial rhinitis and mild asthma due to house dust mite allergy. Rhinitis is often accompanied by significant comorbidities that include conjunctivitis, sinusitis, otitis media, and bronchial asthma: these require separate recognition and treatment.

Introduction

Rhinitis refers to inflammation of the nasal mucosa: in clinical terms it may be defined as symptoms of nasal itching, sneezing, watery discharge, or blockage, that occur for more than 1 h on most days. The lining of the nose and paranasal sinuses is in continuity with the lower respiratory tract such that diseases of the upper and lower airways frequently coexist. The World Health Organization position paper 'Allergic Rhinitis and its Impact on Asthma' (ARIA) recognized this association and provided a classification of the disease based on the severity and duration of symptoms, and a recent update provides the basis for the modern management. In this section a historical perspective and the aetiology, epidemiology, and pathogenesis of allergic rhinitis are described, followed by practical guidelines for diagnosis and management. Finally, immunotherapy (desensitization), including novel approaches are discussed.

Historical perspective

The term 'hay fever' was originally coined by John Bostock in 1819. It is a misnomer, since the disease is not caused by hay and there is no fever. Nonetheless, the term highlighted the seasonality of the disease 'being associated with the effluvium of hay' and the association of severe hay fever with constitutional upset. William Gordon in 1829 referred to 'the aroma emitted by the flowers of grass …', whereas Elliotson in 1831 considered '… it [hay fever] to depend upon the flower of grass and probably the pollen'. Charles Blackley, a physician in Manchester, referred in 1873 to hay fever (*Catarrhus Aestivus*) as 'an aristocratic disease … rarely, if ever, met with but among the educated', and measured pollen counts in the air and related them to the intensity of hay fever symptoms. He also reproduced the disease in himself by experimental challenge with grass pollen, a technique still widely used today to investigate pathogenesis and to test novel treatment approaches. In 1911 Noon and Freeman published their classic paper on desensitization for hay fever. William Frankland, who was a student of Freeman at St Mary's

Hospital, London, published the first randomized controlled trial of desensitization for hay fever in the same journal in 1958.

Aetiology

Both environmental and genetic factors are important in the aetiology of allergic rhinitis. Major causes include seasonal pollens, mould spores, and perennial allergens such as house dust mite and domestic pets. Potential occupational causes should not be missed. Climate change has altered the geographic distribution and timing of pollen exposures. Exposures to a farm lifestyle in early childhood has been shown to be protective against development of allergic rhinitis, asthma, and eczema. Environmental irritants such as tobacco smoke, exhaust fumes, and cold air may exacerbate allergic symptoms.

Environmental allergens

Seasonal allergic rhinitis

The pollens of temperate grasses (including perennial rye, timothy, and cocksfoot) are major causes of seasonal rhinitis during summertime. Grass pollen counts above 50/m^3 are considered high and are the threshold level at which most hay fever sufferers experience symptoms. Tree pollens (including from birch, alder, ash, and plane trees) cause symptoms during springtime. Weed pollens (*Artemisia, Parietaria*) and mould spores (*Alternaria, Cladosporium*, and *Aspergillus* species) predominate in the latter part of the summer and autumn (Fig. 18.6.1).

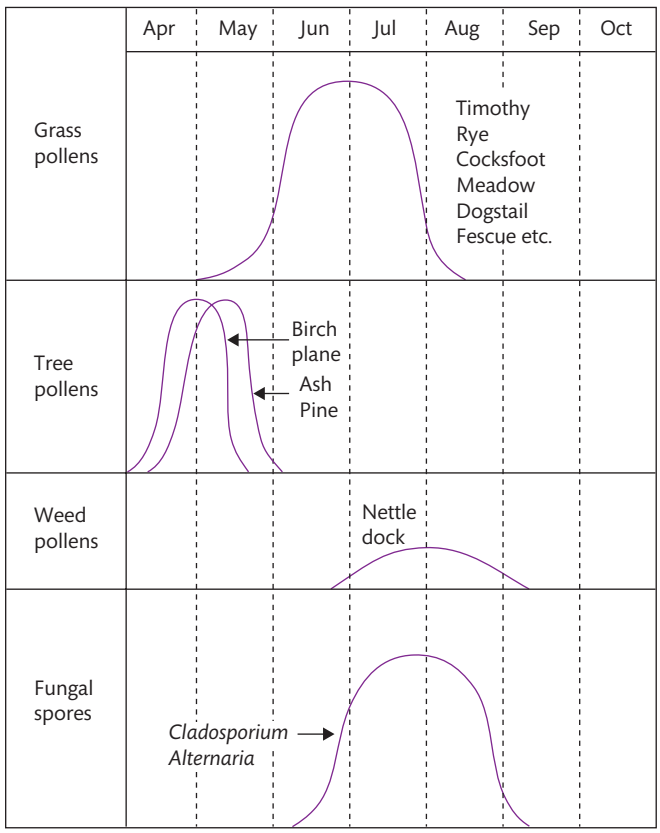

Fig. 18.6.1 Calendar of common seasonal aeroallergens.
By courtesy of Professor A B Kay, Imperial College London.

Pollen allergy (particularly birch) is commonly associated with pollen-food syndrome where sufferers experience immediate itching and swelling in the lips and mouth on eating apples, hazelnuts, and stone-containing fruits such as plums, nectarines, peaches, and (occasionally) root vegetables (carrots, potatoes). Symptoms are generally mild, throat oedema may rarely occur, but anaphylaxis is not a feature. The syndrome results from cross-reactivity between the major birch pollen allergen (Bet v 1) and proteins (PR-10 proteins) contained within the peel of offending fruits and vegetables. The allergens are heat labile such that the cooked foods are well-tolerated.

Perennial allergic rhinitis

By far the commonest cause of perennial allergic symptoms are house dust mites (*Dermatophagoides pteronyssinus, D. farinae*, and *Euroglyphus maynei*). These are found in almost every home, where they live in the dust that accumulates in carpets, bedding, fabrics, and furniture. They live on shed human skin scales and thrive in temperatures of between 15 and 20°C and a relative humidity of 45–65%, conditions which are typical of many modern centrally heated homes. The major allergen of the house dust mite (Der p 1) is a digestive enzyme (a cysteine protease) present in the gut and excreted in high concentrations in the mite faeces.

Domestic pets are the second important cause of perennial allergy, relevant in up to 40% of children with asthma and/or rhinitis. The major allergen (Fel d 1) is a salivary protein that is preened on to the fur and released on very small particles (<2.5 μm diameter) which remain airborne for many hours, explaining why a sensitized person can experience symptoms almost immediately upon entering a home containing a cat, without being directly exposed to the animal. Dog allergens are less well characterized (Can f 1). Cockroaches have been described as a cause of perennial allergic rhinitis and asthma, particularly in inner-city areas.

Food allergy is unusual as a primary cause of rhinitis in the absence of other organ involvement. However, rhinitis may be one component of IgE-mediated food-induced symptoms commonly due to egg, milk, and nuts in children, and to nuts, fish, shellfish, and fruit in adults. Preservatives such as tartrazine, benzoates, and sulphites may provoke symptoms of rhinitis. Important drugs that can trigger rhinitis include β-blockers, aspirin, and (occasionally) angiotensin converting enzyme (ACE) inhibitors.

Occupational rhinitis

Occupational rhinitis refers to rhinitis caused by an agent inhaled in the workplace. Like other causes of seasonal and perennial rhinitis, occupational rhinitis may also be associated with bronchial asthma. Occupations at risk include laboratory animal workers (rats, guinea pigs, mice), bakers (flour, grain mites), agricultural workers (cows, pollens, fungal spores), electronic solderers (colophony), paint sprayers (toluene di-isocyanate, acid anhydrides), and health workers and other users of rubber gloves (latex).

Genetic influences

Atopy (the predisposition to develop allergic disorders as defined by a positive skin prick test or raised IgE antibody level to one or more common allergens) and allergic diseases such as hay fever and asthma occur as a complex interaction between genetic and environmental factors. Twin studies in which a higher concordance rate

of atopy and allergic diseases is found in monozygotic twins compared to dizygotic twins provides unequivocal evidence of genetic influences.

Candidate gene approaches (which study a narrow region of the genome around a suspected gene with highly polymorphic markers) have been difficult to interpret because of variability in the definition of clinical phenotypes within atopy and allergy. Nonetheless, multiple genetic loci have been identified, including the high-affinity IgE receptor β-chain (localized on chromosome 11q), and the interleukins IL-4, IL-3, IL-5, IL-9, IL-13, the β-glucocorticoid receptor, and leukotriene C4 (LTC4) synthase (all co-localized to chromosome 5q). All of these genes have biological functions consistent with a role in pathogenesis of allergic disorders.

A genome-wide association study identified strong linkage between asthma and bronchial hyper-responsiveness with the gene for ADAM33, a cell surface protease that is part of the matrix metalloproteinase family, considered important in remodelling responses in the basement membrane to damaged epithelium and airway smooth muscle. Another study identified novel susceptibility loci for allergic rhinitis that included genes associated with T lymphocytes, B lymphocytes, and epithelial cells. Epigenetic changes such as altered DNA-methylation status of CD4 + T lymphocytes may also result in altered genetic susceptibility to developing allergic rhinitis.

Epidemiology

Recent estimates based on community surveys in Western Europe have suggested that approximately 20% of the population have perennial and/or seasonal allergic rhinitis. Peak prevalence occurs between the second and the fourth decade, with some evidence of remission during adult life. The prevalence has increased over the past 4–5 decades, placing an increased burden on medical services: for example, in the United Kingdom in 1955–56 there were 5.1 consultations with general practitioners for hay fever per 1000 population per year; in 1981–82 this had increased to 19.8. Some studies suggest that a plateau has now been reached.

The increased prevalence of hay fever in countries with a 'Westernized' lifestyle, together with the known increased prevalence associated with small sibships, has given rise to the 'hygiene hypothesis' which suggests that reduced exposure to bacterial pathogens may be the basis of the modern epidemic of allergic disorders. Further support comes from studies that have shown a strong protective effect of a farm lifestyle in early childhood against developing allergic disorders, likely due to an associated altered gut microbiome. These observations tie in with Blackley's recognition of hay fever as a disease more common in the privileged classes over 140 years ago.

Pathogenesis

The cardinal features of allergic rhinitis are IgE production and tissue eosinophilia that are driven by an underlying Th2-type T lymphocyte response.

Immediate symptoms of allergic rhinitis occur as a consequence of allergen cross-linking adjacent IgE molecules on the surface of mast cells in the nasal mucosa (in Coombs' classification, type I, immediate hypersensitivity). This results in the release of granule-derived mediators, including histamine and tryptase, and the generation of bradykinin. IgE-dependent activation of mast cells also results in the release of newly formed membrane-associated mediators derived from arachidonic acid associated with the membrane lipid, including LTC4, LTD4, LTE4, and prostaglandin D_2.

Other characteristic features of allergic rhinitis include tissue eosinophilia and the epithelial migration of inflammatory cells, including mast cells and basophils, during natural allergen exposure. These events occur under the regulation of a distinct population of T lymphocytes, Th2 CD4 + T cells. Th 2 cytokines released include interleukin 4 (IL-4) and IL-13 that induce B-cell switching in favour of IgE production, and IL-5 and granulocyte macrophage-colony stimulating factor (GM-CSF) that result in production and release of eosinophils from the bone marrow and their prolonged survival in tissues due to inhibition of apoptosis. The localization of a population of innate lymphoid cells (innate lymphoid type 2 cells (ILC2s) that do not express the T-cell receptor (CD3-negative) and therefore are unable to respond directly to allergen, whilst remaining capable of producing large amounts of type 2 cytokines, particularly IL-5 and IL-13, is likely to augment and sustain type 2 inflammation in allergic rhinitis. These features are similar to events occurring in the bronchial mucosa in allergic asthma. In contrast, there are no associated features of airway remodelling such as basement membrane zone thickening, mucus gland hypertrophy, nor of the epithelial disruption that characterizes asthma.

The mechanism of selective localization of Th2 lymphocytes, eosinophils, and basophils to the nasal mucosa is likely due to their surface expression of the chemokine receptors (CCR3 and CCR4) and the selective release of their ligands—eotaxin, monocyte-derived chemokine, and thymocyte-associated and released chemokine during allergic reactions. Experimental nasal allergen provocation in humans with grass pollen extract in allergic subjects results in release of tryptase within minutes and increases in Th2 cytokines and eosinophil-derived protein eosinophil cationic protein during the late-phase at 4–12 hours following challenge.

Influence of treatment on T-cell and antibody responses in allergic rhinitis

Whereas intranasal corticosteroids act by inhibiting the production of Th2 cytokines within the nasal mucosa, allergen immunotherapy has been shown to induce long-lived changes in the mucosal Th2/Th1 balance in favour of interferon-γ-producing Th1 cells. In addition, immunotherapy induces antigen-specific T regulatory cells that express the transcription factor FOXP 3. Distinct T regulatory cell subsets have been shown to downregulate Th2 responses directly by mechanisms involving cell–cell contact and by the production of the inhibitory cytokines IL-10 and TGFβ (**Fig. 18.6.2**). In addition to their effects on Th2 cells, these cytokines induce B-cell switching, respectively, in favour of allergen-specific IgG4 and IgA. These 'protective' antibodies are noninflammatory and compete with IgE for allergen and inhibit the formation of allergen-IgE complexes, thereby preventing mast cell IgE-cross-linking and IgE-facilitated activation of T cells. These long-lived changes in memory T cells and B cells underpin the induction of long-term antigen-specific tolerance following immunotherapy.

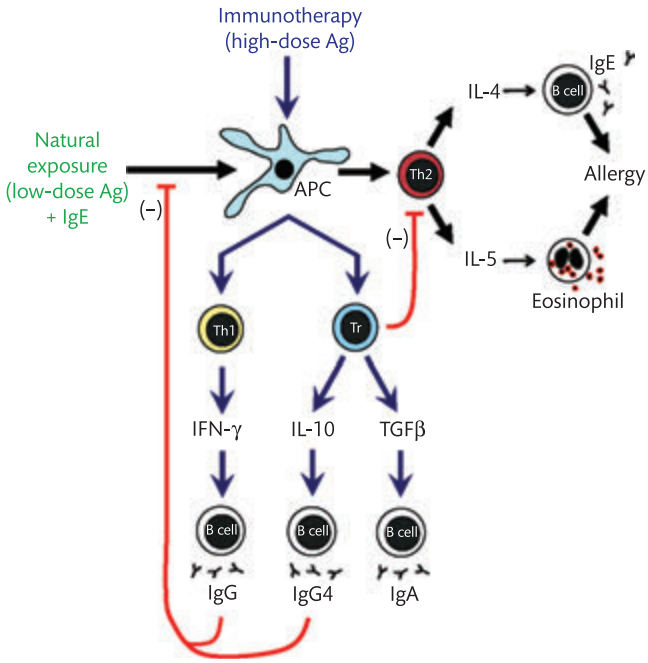

Fig. 18.6.2 Pathogenesis of allergic rhinitis and influence of treatment. Th2 cells are predominantly T lymphocytes, although mast cells, basophils, and eosinophils represent alternative sources of Th2-type cytokines. Topical corticosteroids down-regulate the production of Th2-type cytokines from T lymphocytes and other cells. Allergen immunotherapy acts by immune-deviation of Th2 responses in favour of Th1 responses and/or by inducing a population of antigen-specific T regulatory cells. Both mechanisms may act directly to downregulate Th2 responses and indirectly by inducing 'protective' antibody responses. APC, antigen presenting cell; IFN, interferon; Ig, immunoglobulin; IL, interleukin; TGF, transforming growth factor; T_r, regulatory T cell.

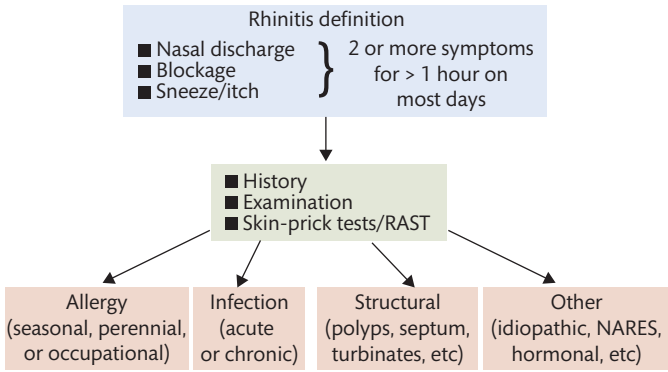

Fig. 18.6.3 Diagnostic approach to patients presenting with nasal symptoms. A careful history, clinical examination, and skin prick tests and/or measurement of serum allergen-specific IgE (RAST or ELISA) should be performed in every case. More than one cause may be present. 'Other' causes include hormonal (pregnancy, premenstrual), drugs (aspirin, β-blockers, ACE inhibitors, cocaine abuse, and atrophic, postsurgical, and ageing). Idiopathic rhinitis refers to nasal hyperreactivity of unknown cause, manifest as an exaggerated response to nonspecific stimuli such as changes in temperature, tobacco smoke, domestic sprays, and other possible factors. The differential diagnosis includes vasculitis (Churg–Strauss syndrome), granulomatous conditions (Wegener's, sarcoidosis), atrophy (old age, surgical), and—rarely—tumours of the nose and paranasal sinuses.

Clinical diagnosis

The diagnosis of allergic rhinitis is usually straightforward (Fig. 18.6.3), but the differential diagnosis should be considered in every case: frequently more than one cause coexists.

History

A careful history is essential both to establish the diagnosis of rhinitis and to assess the severity of symptoms. An allergic aetiology is suggested by dominant itching, sneezing, and watery nasal discharge. Associated eye or chest symptoms (asthma) also point to an allergic cause, and a history of potential allergic triggers should always be sought. However, in addition to provoking immediate nasal symptoms, allergen may also cause late symptoms several hours after exposure, and these may not be recognized as being related.

A history of potential allergic triggers includes enquiry into the seasonality of symptoms and whether symptoms are work related (i.e. do they occur at work or in the evening following work, with improvement at weekends and during holiday periods). The home environment, including the presence of domestic pets, birds, fitted carpets, central heating, and the use of blankets on beds should be established. A personal or family history of atopy is extremely common in patients with allergic rhinitis.

There are many alternative causes of rhinitis symptoms. It is common for there to be more than one cause, and important to consider the differential diagnosis (Box 18.6.1). The presence of facial pain, fever, systemic upset, and mucopurulent discharge suggests infection. Nasal obstruction, which alternates with the nasal cycle, is common to both allergic and infective causes. Nasal crusting and/or bleeding may occur in granulomatous disorders, atrophic rhinitis, or (rarely) tumours (particularly if associated with persistent unilateral symptoms). Impaired taste and/or smell may occur with many forms of rhinitis, but is particularly common with nasal polyposis and may occasionally follow trauma (olfactory nerve damage).

Box 18.6.1 Causes of rhinitis

- Allergic
  - Seasonal (tree or grass pollens)
  - Perennial (house dust mite, domestic pets)
  - Occupational (latex, laboratory animals, antibiotics, and so on)
- Nonallergic
  - Infective (acute, chronic)
  - Autonomic
  - Hormonal (premenstrual, pregnancy, hypothyroidism)
  - Drugs (aspirin, β-blockers)
  - Mucociliary abnormalities (Kartagener's, Young's syndromes)
  - Immunodeficiency syndromes (congenital and acquired, including HIV)
  - Atrophic
  - Idiopathic
- Differential diagnosis
  - Structural (polyps, deflected nasal septum, etc)
  - Connective tissue disorders
  - Granulomatous disorders (sarcoid, granulomatosis with polyangiitis)
  - Tumours (benign, malignant)
  - Cerebrospinal fluid rhinorrhoea (secondary to trauma or surgery)

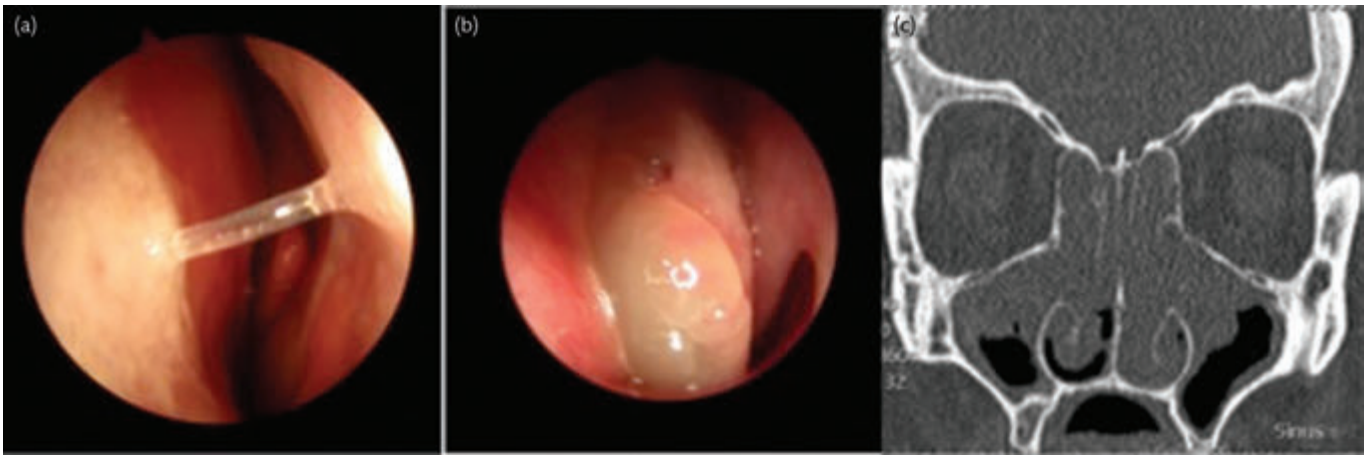

Fig. 18.6.4 (a) An endoscopic view of the left nasal cavity in a patient with allergic rhinitis. Note the pale colour of the nasal septum and turbinate in addition to the clear secretions. (b) An endoscopic view of nasal polyps in the left nasal cavity. Polyps have glistening greyish colour in contrast to the red colour of the turbinate and rest of the nasal mucosa. (c) A coronal CT section of the nasal cavity and sinuses showing extensive opacification in a patient with severe chronic rhinosinusitis.

The presence of infertility and recurrent respiratory infections (including bronchiectasis) should raise the possibility of mucus abnormalities (Young's syndrome or cystic fibrosis) or ciliary dysfunction (primary ciliary dyskinesia, Kartagener's syndrome). Recurrent respiratory infections or a history of chronic rhinosinusitis should also raise the possibility of immune deficiency disorders including hypogammaglobulinaemia and AIDS.

Hormonal imbalance (premenstrual symptoms, pregnancy, hypothyroidism, or acromegaly) may be associated with rhinitis. A history of trauma or previous nasal surgery should be sought.

Enquiry regarding associated chest disease is important. Rhinitis and asthma frequently coexist and recognition and appropriate treatment of rhinitis may potentially also improve the control of asthma. Similarly, allergic conjunctivitis may be particularly bothersome in patients with seasonal disease and requires recognition and treatment.

A very common cause of treatment failure is poor adherence with treatment. The efficacy, frequency, and regularity of previous treatments should be carefully documented. The patient's perception of possible side effects of treatment, particularly corticosteroids including steroid nasal sprays, is a frequently missed cause of poor compliance. Nasal spray technique should be checked as poor technique is another potential cause of treatment failure.

Examination

Local examination may be performed with a head mirror/headlamp and speculum or an auriscope. Allergic rhinitis is accompanied by a pale 'boggy' appearance of the nasal mucosa only if the patient has current symptoms. A red inflamed appearance with pus suggests an infective cause. A granular appearance with fine pale nodules is diagnostic of sarcoidosis. Enlarged turbinates may be confused with polyps by the unwary. If doubt exists, further examination with a rigid and/or flexible endoscope should be performed (Fig 18.6.4). The identification of structural abnormalities such as polyps, deflected nasal septum, or enlarged turbinates is important: surgical treatment may be indicated (a major advance being the development of minimally invasive endoscopic sinus surgery).

Examination of the nose should also include tests of smell and examination of the ears, eyes, mouth, and throat. Examination of the chest, skin and general examination should be performed, and peak expiratory flow and/or spirometry measured when indicated in view of the common association of nasal disease with lower respiratory tract and systemic conditions.

Investigations

Skin prick tests

In the presence of a clear history, particularly of seasonal hay fever symptoms, skin prick testing is not essential. However, skin prick tests are useful for several reasons (Box 18.6.2). They should only be interpreted in conjunction with the clinical history, and not performed when the patient is taking antihistamines. In these circumstances, measurement of serum IgE antibodies by enzyme-linked immunosorbent assay (ELISA) is indicated.

Skin prick tests should employ standardized commercially available allergen extracts in aqueous solution that are in-date and have been stored at –4°C. Prick tests are performed with a sterile 23-gauge needle or lancet, which is lightly inserted through the epidermis without inducing bleeding. Responses are recorded as the mean weal diameter at 15 minutes, a positive test being defined as a weal diameter 3 mm greater than that of the negative control (allergen diluent). In pollen-food syndrome, where the offending allergens are heat labile and unstable with storage, then prick–prick testing may be performed by pricking through the surface of the fruit before pricking the skin with the same needle.

Allergen-specific IgE

To obtain objective confirmation of IgE sensitivity in the context of a relevant clinical history, measurement of serum allergen-specific IgE is an alternative to skin prick testing, particularly in patients with severe eczema, dermographism, or if antihistamines have been taken in the preceding 1–3 days. In general, IgE-testing is less

Box 18.6.2 Advantages of skin prick tests

- They diagnose atopy—the underlying predisposition to develop allergic disorders
- They provide helpful supportive evidence (positive or negative) for the clinical history
- They are essential when potentially expensive and time-consuming environmental control measures, the removal of a family pet, or a change of occupation are involved
- They have educational value, providing a clear illustration to the patient and reinforcing verbal advice

A useful basic skin prick testing kit should include the following:

- a positive control (histamine 10 mg/ml)
- a negative control (allergen diluent solution)
- house dust mite (*D. pteronyssinus*)
- grass pollen
- cat fur
- *Aspergillus fumigatus*

sensitive than skin prick testing although there is access to testing with a wider panel of potential allergens.

Advances in molecular cloning have led to the characterization of many major allergen components of common inhalant and food allergens (a 'major' allergen component is one that is recognized by more than 50% of allergic individuals). By use of allergen microchip technology it is now possible to obtain component-resolved diagnosis, which may allow more accurate allergy diagnosis and resolve irrelevant allergen cross-reactivities. For example, there are 13 known grass pollen allergens, whereas Phleum p 1 (Phl p 1) and Phl p 5 are the dominant major allergens responsible for summer hay fever. In the context of symptoms during the summer months, the detection of IgE to Phl p 1 and Ph p 5 therefore confirms clinically relevant IgE sensitivity to grass pollen. In contrast, the detection of IgE to Phl p 12 is likely due to cross-reactivity with the birch-derived profilin Bet v 2. In the absence of a history of springtime symptoms associated with a positive IgE to the major birch allergen Bet v 1, the patient may exhibit a false-positive skin test to birch pollen extract due to presence of IgE to the irrelevant cross-reacting profilin Ph p12. Such considerations are helpful in selecting suitable patients and the relevant allergen extract for allergen immunotherapy.

Component-resolved diagnosis may also be valuable for risk assessment in patients with pollen-food syndrome. For example, cross-reactivity between Bet v 1 and the hazel nut allergen Cor a 1 results in pollen-food syndrome with symptoms confined to local itching and swelling in the mouth, whereas Cor a 14 reactivity is associated with true food allergy with an increased risk of anaphylaxis on eating hazelnut.

Treatment

Treatment for allergic rhinitis involves the avoidance of provoking allergens where possible and the use of topical corticosteroids and H_1 selective antihistamines. Allergen immunotherapy has a place in patients who do not respond to these measures. The approach is summarized in Box 18.6.3 and in relation to the ARIA classification (Fig. 18.6.5), which emphasizes that rhinitis and asthma are commonly associated and that patients with one condition often also have the other.

Box 18.6.3 Treatment of allergic rhinitis

- Allergen avoidance (house dust mite, animal dander, occupational causes)
- Oral nonsedating antihistamines, or intranasal antihistamines
- Topical corticosteroids; check technique and place emphasis on regular use
- Intranasal spray containing combined corticosteroid and antihistamine
- Topical sodium cromoglycate, nedocromil, or antihistamine for eye symptoms
- Immunotherapy in pollen-sensitive patients unresponsive to the aforementioned measures
- If the patient fails to respond, review the diagnosis and treat any associated conditions (e.g. antibiotics for infection, surgery for structural problems)

Allergen avoidance

It is impossible to avoid pollens, although sensible advice includes wearing sunglasses and keeping car windows tightly shut. All windows should be kept closed, particularly in high buildings. Walking in parks and wide open spaces should be avoided, particularly during the late afternoon or evening when pollen counts are highest. A holiday by the sea or abroad during the peak pollen season may be helpful.

House dust mite control and avoidance measures should be considered in sensitive individuals with disease. Although some success has been achieved in children, the value of mite avoidance measures in adults, such as a single intervention with mite-proof bedding, has been questioned. Further studies involving more effective and multiple interventions are needed, including—in addition to covers for the pillow, duvet, and mattress—restriction of soft toys, which should be washable, changing to hardwood, vinyl, or cork flooring, and thorough vacuum cleaning and damp-dusting at least once weekly. There is no firm evidence to recommend the additional use of air conditioners, air ionizers, or acaracides.

Saline irrigation

Isotonic saline irrigation in adults and children with allergic rhinitis is well tolerated, inexpensive, and may be used regularly with no

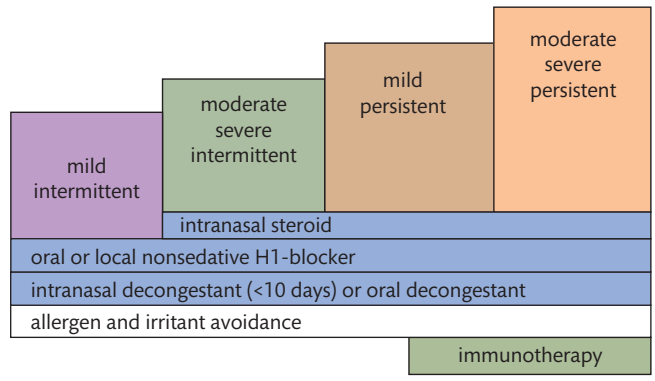

Fig. 18.6.5 A stepwise approach to management of allergic rhinitis. Classification of rhinitis according to ARIA guidelines.

evidence of adverse effects on health. Isotonic saline is available on prescription as a pressurized aerosol nasal spray and commercially as a high-volume, low-pressure irrigation device.

Where animal exposure is relevant, there is frequent resistance to advice to remove a family pet. However, patients can be advised to not replace animals, to confine them to the kitchen or outdoors where possible, and to avoid contact with animals or with individuals with clothing contaminated with animal dander.

Pharmacotherapy

The availability of potent specific histamine H_1 receptor antagonists with a low potential for anticholinergic side effects and a low sedative profile has been a major advance. Antihistamines are particularly effective for sneezing, itching, and watery nasal discharge, but unlike topical corticosteroids they have less effect on nasal blockage. They are also effective for eye and throat symptoms.

A rare but important complication of older antihistamines, including terfenadine and astemizole, is prolongation of the QT interval on the ECG. This only occurs when doses in excess of those recommended are employed, or in the presence of hepatic impairment or concomitant use of ketoconazole or erythromycin, both of which modify the hepatic metabolism of terfenadine. Modern antihistamines including acrivastine, loratadine, desloratadine, cetirizine, L-cetirizine, fexofenadine, and mizolastine are effective H_1 antihistamines with an extremely low (or absent) potential for cardiac side effects.

H_1-selective antihistamines can also be given as a topical nasal spray (azelastine) which is more effective than an oral antihistamine in reducing rhinitis but without impact on histamine-mediated effects elsewhere such as the skin. Antihistamines should be avoided when possible during pregnancy, particularly during the first trimester. If antihistamines are considered essential then recent guidelines from the United States Food and Drug Administration include (category B) the use of loratadine and cetirizine.

Topical corticosteroids are highly effective in allergic rhinitis, superior to oral antihistamine and leukotriene antagonists, and are first-line treatment in patients with moderate–severe disease. Preparations include beclomethasone dipropionate, budesonide, fluticasone propionate, triamcinolone acetonide, fluticasone furoate, and mometasone furoate. Aqueous formulations are better tolerated and have a better local distribution in the nose. Recent data suggests that intranasal steroids may also improve allergic eye symptoms by suppressing the nasolacrimal reflex. Treatment should begin before the hay fever season for maximal effect, and the importance of regular treatment, even when symptoms are absent, should be emphasized. Ease of use of different devices may influence adherence with treatment. Side effects are minor, although around 5% develop nose bleeds which is a class effect and may require their discontinuation. Systemic effects are virtually absent at conventional doses, but caution should be exercised in children, particularly those receiving additional corticosteroids by other routes (e.g. for associated asthma and/or eczema).

The topical anticholinergic agent ipratropium bromide is a potent inhibitor of glandular secretion and may be effective where watery nasal discharge is the dominant symptom, uncontrolled by the measures described here earlier.

Sodium cromoglycate is available as a topical nasal spray for use four times daily. It is less effective than topical corticosteroids. Topical cromoglycate eye drops are effective for allergic eye symptoms. Olopatadine (an antihistamine) eye drops have the advantage of a longer duration of action, allowing twice daily administration.

A combination nasal spray containing fluticasone propionate and azelastine has recently been shown to have an earlier onset of action and be more effective for allergic rhinoconjunctivitis than either drug administered separately. At present it should be reserved for patients who do not respond to intranasal corticosteroids alone. In patients whose symptoms are not otherwise controlled, there is a place for a short course of prednisolone (e.g. 20 mg daily for 5 days). This approach may unblock the nose, thereby improving access for topical corticosteroids, which may then be more effective. Topical decongestants (oxymetazoline) are effective in treating nasal blockage, although they should only be used for short periods (no more than 2 weeks) in view of the risk of tachyphylaxis and rebound persistent nasal blockage (so-called rhinitis medicamentosa).

Allergen immunotherapy

Immunotherapy (desensitization) is a treatment option in patients with severe summer hay fever unresponsive to topical steroids and antihistamines, and in those reluctant to take long-term medication. This involves the subcutaneous injection of increasing concentrations of allergen (standardized pollen extract) at weekly intervals for 6–12 weeks, followed by monthly injections of a maintenance dose for 3 years. It should only be given by those who are properly trained, with adrenaline (epinephrine) and facilities for cardiopulmonary resuscitation immediately available. In view of known occasional systemic side effects following injections, patients should be kept under medical observation for at least 60 min following injections.

Randomized controlled trials have confirmed the efficacy of immunotherapy, particularly for patients with summer hay fever. Recent studies have also shown efficacy in those with perennial rhinitis due to house dust mite allergy, although careful selection of patients in whom mite is the dominant cause of symptoms is required. Perennial rhinitis is frequently heterogeneous with multiple allergic sensitivities and/or other causes of ongoing symptoms. The risk/benefit ratio is less favourable in patients with chronic bronchial asthma, in whom the risks of systemic adverse reactions are greater.

Recent data suggests that pollen immunotherapy may confer long-term benefits including prolonged disease remission, prevention of onset of new sensitizations and—in one controlled trial—a threefold reduction in the risk of progression of rhinitis to asthma in children with pollen-induced rhinitis that persisted for 10 years after initiating treatment. The data suggest that allergen immunotherapy, unlike pharmacotherapy, has the potential to modify the course of the disease (see proposed mechanisms in **Fig. 18.6.2**).

The sublingual route has emerged as an effective and safe alternative form of immunotherapy suitable for home use, although the initial prescription and first dose should be administered by physicians trained in the diagnosis and treatment of allergic disorders. Recent data confirms efficacy of sublingual treatment in perennial mite allergy and that 3 years' grass pollen sublingual immunotherapy confers long-term benefits for at least 2 years after discontinuation of the treatment. At present there is equipoise regarding choice of either the injection or sublingual route for immunotherapy. Both treatments are effective, but the sublingual route appears safer and can

be self-administered. An adequately powered head-to-head trial of allergen vaccines of proven value is needed.

Future prospects for immunotherapy include the use of adjuvants (lipopolysaccharide derivatives, bacterial CpG-containing DNA oligonucleotides) combined with conventional allergen extracts for subcutaneous immunotherapy, and the use of recombinant natural allergens and their mutated hypoallergenic variants. In addition to proven sublingual immunotherapy, alternative routes currently being tested include intradermal administration and the intralymphatic route involving direct injection of allergen into the inguinal lymph nodes under ultrasound guidance. Low-molecular-weight allergen peptides have the potential to modify human T-cell responses with clinical benefit without the potential for IgE cross-linking and attendant risk of serious IgE-mediated side effects. T-cell peptides derived from the major cat allergen Fel d 1 have been shown to be effective in an environmental chamber model and a phase 3 trial is ongoing. All these approaches aim to improve safety and tolerability while preserving the efficacy and long-term benefits that are associated with the subcutaneous and sublingual routes.

Role of surgery

For the small group of patients with allergic rhinitis and predominant nasal obstruction and no appreciable response to medical therapy, surgery may be indicated. Clinically, significant inferior turbinate hypertrophy must be present for surgery to be effective. Inferior turbinate reduction is mostly preformed endoscopically and can be done under local or general anaesthetic. Submucous resection together without fracture of the turbinate bone is the most effective method.

In some patients with allergic rhinitis, symptoms of chronic rhinosinusitis may prevail. These may include postnasal drip/purulence, sinus pain/pressure and hyposmia in addition to endoscopic signs of infection/inflammation. In these patients CT scanning and the need for surgery is assessed if medical treatment fails.

FURTHER READING

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