Allergy

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Allergic rhinitis

Introduction

Allergic rhinitis is a prevalent yet underappreciated inflammatory disorder of nasal mucosa, which is characterised by pruritus, sneezing, rhinorrhoea, and nasal congestion. It is mediated by early-phase and late-phase hypersensitivity responses—similar to thosein allergic asthma—to indoor and outdoor environmentalallergens.

Although commonly regarded as merely a seasonal nuisance, allergic rhinitis can entail minimum persistent inflammation of mucosa, which synergises with infective inflammation: thus, individuals with allergic rhinitis have additional difficulties with viral colds. In children, the combination of rhinoviral infection, allergic sensitisation, and allergen exposure gives an odds ratio of for admission to hospital for asthma.

Findings of basic science and epidemiological studies show that allergic rhinitis is part of a systemic inflammatory process and is associated with other inflammatory disorders of mucous membranes, including asthma, rhinosinusitis, and allergic conjunctivitis. An especially robust association is recorded with asthma, since most individuals with allergic and non-allergic asthma have rhinitis. Poor asthma control is linked to moderate-to severe rhinitis, which should be identified and treated.

A high prevalence of asthma is recorded in people with persistent and severe rhinitis. Allergic rhinitis adversely affects social life, school performance, and work productivity, particularly in patients with severe disease. Rhinitis symptoms have a detrimental effect on academic performance. Akin to other functional domains, achievement at school is impaired further by use of suboptimum pharmacotherapy, notably antihistamines that cause sedation. Loss of productivity, missed school and work days, and direct costs associated with treatment of allergic rhinitis create substantial costs to society. Severe financial losses per year in Sweden due to rhinitis have been reported.

The ARIA (Allergic Rhinitis and its Impact on Asthma) guideline focuses on quality of life as a principal consideration in assessment and treatment. It provides a global, evidence-based, pragmatic, stepwise approach to treatment of allergic rhinitis and has been updated and evaluated in recent years with GRADE (grading of recommendations assessment, development, and evaluation) methodology. Avoidance of allergens is still a guiding principle, although this idea is typically difficult to implement. Intranasal corticosteroids are the one most effective class of drug because of anti-inflammatory effects on several different cell types, with some molecules showing no systemic bioavailability with longterm use, even in children. Immunotherapy is available via sublingual and subcutaneous routes at present, mainly for individuals with allergic rhinitis uncontrolled by pharmacotherapy and allergen avoidance. Immunotherapy is also the only treatment currently available that probably alters disease course, reducing progression not only of sensitisation but also of rhinitis to asthma.

Epidemiology

Allergic rhinitis affects 400 million people worldwide, with high prevalence recorded in industrialised nations, especially English-speaking ones. This increase in prevalence has been noted in all allergic diseases for reasons that have not been fully explained (see Cause). Researchers on the International Study of Asthma and Allergies in Childhood (ISAAC) project investigated the prevalence and possible causes of atopic diseases. ISAAC was divided into three phases: phase 1 allowed for comparisons of prevalence within and between countries; phase 2 provided a framework for aetiological research into genetic, lifestyle, environmental, and medical care variables; and phase 3 reassessed prevalence and severity measurements at least 5 years after initial responses were obtained.

The first phase of ISAAC took place between 1992 and 1998. Prevalence of rhinitis with itchy watery eyes within the past year was 0·8–14·9% (median 6·9%) in children aged 6–7 years and 1·4–39·7% (median 13·6%) in those aged 13–14 years. The lowest prevalence was in parts of eastern Europe and south and central Asia. The third phase of ISAAC (at least 5 years later) showed prevalence of rhinitis with itchy watery eyes in the past year was 1·8–24·2% in children aged 6–7 years (median 8·5%) and 1·0–45·0% (median 14·6%) in those aged 13–14 years. In the 6–7 years age-group, 67% of centres registered a substantial increase in prevalence, whereas 14% showed a decrease. In the 13–14 years age-group, 45% of centres had a substantial rise in prevalence, whereas 25% showed a fall. Wide variations in actual percentage changes for prevalence were seen across centres, ranging from –3·88% to 2·12% per year. The number of countries in which rhinitis is increasing exceeds those in which it is stable or decreasing, by contrast with asthma, for which prevalence seems to be stabilising or diminishing.

About 80% of individuals diagnosed with allergic rhinitis develop symptoms before age 20 years. At least half the children with allergic rhinitis had severe persistent symptoms. Sensitisation to aero-allergens (adjusted odds ratio 18·9 [95% CI 9·3–38·4]) and having two parents with allergies (odds ratio 3·1 [1·1–9·3]) were significantly associated with allergic rhinitis.

Although boys are more likely than girls to have allergic

rhinitis, this tendency reverses in puberty so that, by adulthood, men and women are affected equally. Most individuals with allergic or non-allergic asthma have rhinitis. Asthma and rhinitis frequently coexist in the same people throughout the world with asthma being most prevalent in those with persistent and severe rhinitis. An association possibly exists between severity of asthma and rhinitis or rhinosinusitis.

Cause

Atopy is the abnormal tendency to develop specific IgE in response to innocuous and ubiquitous environmental allergens. Atopic diseases include allergic rhinoconjunctivitis, asthma, atopic dermatitis, and food allergies, and they tend to run in families. Other risk factors for allergic rhinitis include ethnic origin other than white European, high socioeconomic status, environmental pollution, birth during a pollen season, no older siblings, late entry into nursery or preschool education (eg, at age 4 years and older), heavy maternal smoking during the first year of life, exposure to indoor allergens such as animal dander and dust mites, high concentrations in serum of IgE (>100 IU/mL before age 6 years), positive allergen skinprick tests, and early introduction of foods or formula. In adults, heavy alcohol consumption could be a risk factor as well. Findings of several studies have shown that early environmental exposure to various infectious agents— such as hepatitis A, Mycobacterium spp, Toxoplasma gondii, the products of these agents (eg, endotoxins and lipopolysaccharides), or a combination of these—protects against development of atopy. This finding is consistent with principles of the hygiene hypothesis.

Workers	Agents
High-molecular-weight agents (IgE-mediated skin-prick and specific IgE tests possible)	
Laboratory workers	Laboratory animals
Swine confinement workers	Animal-derived allergens
Laboratory workers and farm workers	Insects and mites
Grain elevator	Grain dust
Tobacco, tea, coffee, cacao, carpet, hot pepper, saffron, and dried fruit workers	Other plant allergens
Hospital and textile workers	Latex
Bakers	Flour, a amylase
Pharmaceutical and detergent industry	Biological enzymes
Fish industry and factory workers	Fish and seafood proteins
Low-molecular-weight agents (some evidence for IgE)	
Platinum refinery	Platinum salts
Epoxy resin production	Anhydrides
Reactive dyes, synthetic fibre, cotton, persulfate hairdressing, pulp and paper, shoe manufacturing	Chemicals
Low-molecular-weight agents (no or little evidence for IgE)	
Wood workers	Wood dust
Painters and urethane mould workers	Di-isocyanates
Health-care and pharmaceutical workers	Drugs

Tests for IgE are only relevant as shown when an IgE mechanism is implicated .

Table 1: Triggering factors in occupational rhinitis

Comorbidities

Allergic rhinitis is closely linked to other inflammatory diseases affecting respiratory mucous membranes, such as asthma, rhinosinusitis, and allergic conjunctivitis. Epidemiological evidence has repeatedly and consistently shown the co-existence of rhinitis and asthma. Both allergic and non-allergic rhinitis are risk factors for development of asthma, with occupational factors (table 1) such as farming and woodworking giving high odds ratios also. This association is important because early diagnosis and prevention by avoidance of these risks could be possible.

Evidence also exists to support a link between sinus disease and allergic rhinitis. 25–30% of individuals with acute sinusitis have allergic rhinitis, as do 40–67% of those with unilateral chronic sinusitis and up to 80% with chronic bilateral sinusitis.

A link between rhinitis and otitis media with effusion has been proposed, with Eustachian tube dysfunction a suggested relevant factor. However, no data from published controlled trials are available as yet to support this idea.

Allergic conjunctivitis is characterised by ocular itching, swelling, and discharge. Eye symptoms are present in 70% of people with seasonal allergic rhinitis and around 50% of those with perennial rhinitis.

Quality of life

Until recent times, the focus on allergic rhinitis and its treatment revolved around symptoms and their improvement rather than on quality of life. Children can have difficulties at school because of learning impairment, secondary to distraction, fatigue, poor sleep, or irritability. Children in the USA miss about 2 million school days a year because of allergic rhinitis. They might also be unable to take part in family or social events, resulting in emotional disturbances that manifest as anger, sadness, frustration, and withdrawal.

Classification

Allergic rhinitis has been classified traditionally as seasonal or perennial, depending on sensitisation to cyclic pollens or year-round allergens such as dust mites, animal dander, cockroaches, and moulds. This scheme fails globally since seasons do not exist in many areas of the globe, and even where they do, many affected individuals have both seasonal and perennial allergen sensitisation.

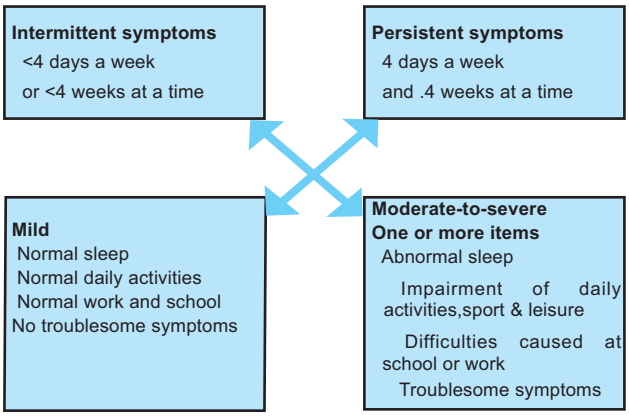

Figure 1: ARIA classification of allergic rhinitis

Every box can be subclassified further into seasonal or perennial on the basis of timing of symptoms or when causative and allergen therapeutic factors are considered. For example, a UK patient with grass pollen allergy might have moderate-to-severe persistent seasonal rhinitis in June and July and be suitable for specific allergen immunotherapy.

The ARIA guidelines for classification and treatment of allergic rhinitis have led to the definition of allergic nasal disease as intermittent or persistent and mild or moderate-to-severe (figure 1). This categorisation can be useful to establish pharmacotherapy. However, allergen specific treatment needs to be incorporated with the seasonal and perennial classifi cation to ascertain the correct allergen to be used in desensitisation.

This localised IgE production is known as entopy, and it can arise in some individuals with non-allergic rhinitis with eosinophilia, in which nasal eosinophils are found without systemic evidence of allergen-specific IgE. Entopy could be missed by traditional allergen testing, which relies on the presence of allergen-specific IgE on cutaneous mast cells (for skin testing) or on circulating allergen-specific IgE (for serum testing, such as the radioallergosorbent [RAST] test). Unless allergen provocation tests are done, individuals with entopy might be classified falsely with non-allergic rhinitis or rhinopathy.

Diagnosis and differential diagnosis

Rhinitis is characterised clinically by one or more of the following symptoms: nasal itching, sneezing, nasal obstruction or congestion, rhinorrhoea (anterior or posterior), and sometimes, reduction of sense of smell (hyposmia). On exposure to allergen, symptoms of allergic rhinitis arise within minutes and can last for 1–2 h before improvement. Late-phase nasal symptoms can include nasal obstruction, hyposmia, postnasal mucous discharge, and nasal hyper-reactivity. Allergic conjunctivitis is characterised by intense eye itching, hyperaemia, watering, and occasionally, periorbital oedema. It occurs in about 50–70% of people with allergic rhinitis. Allergic conjunctivitis is the symptom that differentiates allergic rhinitis best from other forms of rhinitis. Conjunctivitis is related to both direct allergen contact with conjunctival mucosa and activation of nasal-ocular reflex.

People with pollen-induced allergic rhinitis (particularly, birch pollen) could have an associated oral allergy syndrome. Typical immediate symptoms in such individuals include oral and pharyngeal hypersensitivity (itchiness, tingling, erythema, and angioedema of the tongue, lip, and soft palate) after oral contact with various fresh fruits and vegetables. This finding is consistent with the oral allergy syndrome.

Rhinitis can be classified as allergic, non-allergic, and occupational and, thus, has many underlying causes. About two-thirds of children and a third of adults with rhinitis will present with allergic rhinitis; the remainder have other forms, and some individuals cannot be classified (idiopathic rhinitis). Although the definition of rhinitis is applied to diseases of the nasal passages, because of the anatomical relation with the paranasal sinuses, nasopharynx, middle ear, and lower airway, panairway involvement by the underlying disease process can happen and should be actively sought. As a result, rarely does rhinitis present as a single-organ disease entity, and an appropriate diagnosis can only be made if the upper airway is assessed in relation to associated structures. The link with the lower airway must always be considered. Importantly, a range of multisystem non-allergic diseases can mimic rhinitis (eg, Churg-Strauss syndrome, Wegener's granulomatosis, and sarcoidosis), although these disorders are much less common than allergic rhinitis. A detailed comprehensive history—including questions about comorbidities—and thorough clinical examination are the two most important methods to aid accurate diagnosis, which is essential for delivery of targeted treatments. A patient's history can suggest allergenic triggers, reveal other allergic diseases, or provide a family history of allergy.

To confirm a diagnosis of allergic rhinitis, specific IgE reactivity to airborne allergens (relevant to the patient's history) needs to be recorded, via either skin-prick testing or by noting specific IgE in serum. This testing also provides information to direct environmental control measures or allergen-specific immunotherapy. Immediate hypersensitivity skin testing provides results within 15 min of doing the test, whereas results of RAST blood tests for specific IgE take several days to arrive, and the test can be less cost effective than skin-prick testing. However, RAST tests are useful in patients with dermographism, severe atopic dermatitis, or those unable or unwilling to temporarily stop antihistamine use. All IgE test results must be interpreted with patient's history in mind, since both false-positive(sensitisation without clinical disease) and false-negative test results can arise. Allergic rhinitis is triggered mainly by inhalant allergens, of which house dust mite and grass and tree pollens are the most usual, in most parts of the world.

Non-allergic rhinitis encompasses a range of nasal pathological findings, and targeted investigation might be needed. Occupational rhinitis (table 1) includes a

heterogeneous group of pathological findings (both via allergic and non-allergic mechanisms) that share a causal relation between work exposure and development of symptoms.

The proposed diagnostic algorithm (figure 3) has been created by consideration of the most important points needed for assessment of rhinitis as well as the wide range of pathological findings manifesting with or mimicking the disorder. Differential diagnosis of rhinitis in children needs separate consideration.

Treatment

A successful therapeutic approach to allergic rhinitis should contain: patients' education, prevention of allergen or irritant contact, pharmacotherapy, and consideration of immunotherapy. Figure 4 presents an algorithm for treatment.

Patients' education

Patients should be educated about the nature of allergic disease, the likelihood of disease progression, and the need for treatment in addition to addressing any concerns about safety of the treatment modalities used. Patients should be informed about factors that aggravate nasal symptoms because avoidance of these could alleviate them.

Allergen and irritant avoidance

Complete allergen avoidance stops symptoms of allergic rhinitis completely—for example, individuals who are allergic to pollen are asymptomatic at times when pollen is not prevalent. However, in trials of allergen reduction (eg, for house dust mite), complete avoidance has not been achieved and equivocal results or sparse benefits have been reported. In a placebo-controlled study, nasal filters (which prevent access of pollen to nasal mucosa) reduced

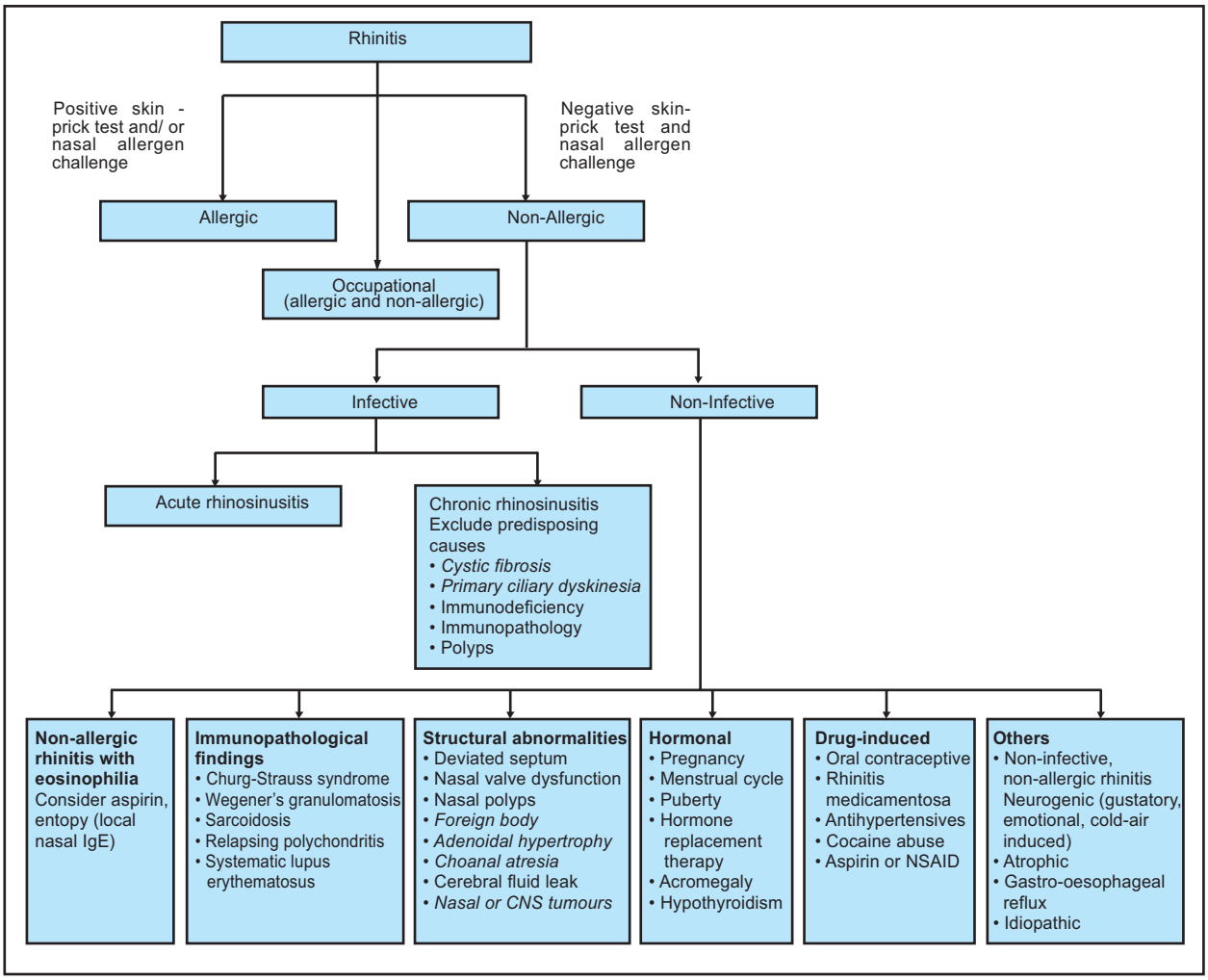

Figure 3: Diagnostic algorithm for rhinitis. Nasal allergen challenge is a research procedure and is not undertaken routinely. Causes likely to be seen in children are highlighted in italics. NSAID=non-steroidal anti-inflammatory drug.

rhinitis symptoms in people who were allergic to pollen. Occupational rhinitis can sometimes be cured by early removal of the affected individual from the allergen or by implementation of adequate control measures. This approach is important to prevent progression to occupational asthma.

Many patients with allergic rhinitis have nasal hyperreactivity to non-specific stimuli—eg, changes in temperature, air conditioning, pollution, and cigarette smoke. Thus, exposure to these stimuli should be avoided if possible. Saline douching, although most typically used in rhinosinusitis, might also prove useful, allowing a reduction in the amount of pharmacotherapy needed to control symptoms in both children and pregnant women.

Pharmacotherapy

Despite the availability of guidelines for treatment, undertreatment of rhinitis is common. Guideline-directed management provides better control of symptoms and improved quality of life than does non-directed treatment. The ARIA classification can be used to ascertain the best pharmacotherapy, which can be given topically or orally.

The panel shows treatment modalities available and their major advantages and disadvantages. The two most effective treatments are intranasal corticosteroids and immunotherapy, with corticosteroids less likely to cause harm (table 2).

Intranasal corticosteroids are the most effective therapeutic agents for allergic rhinitis and they are superior or equal to the combination of an antihistamine and an antileukotriene. Intranasal corticosteroids should be used for moderate-to-severe rhinitis, even in children, for whom good long-term safety data are available.

Two pharmacological treatments are not advised for people with allergic rhinitis. First, antihistamines that cause sedation worsen academic and work performance and are associated with automobile and industrial accidents. Second, intramuscular corticosteroid injections are associated with potentially severe adverse events such as systemic side-effects and subcutaneous and muscular necrosis.

Immunotherapy

By contrast with symptom suppression by pharmacotherapy, immunotherapy aims to alter the immune system and could represent a cure for allergic rhinitis. Subcutaneous immunotherapy is effective in people with allergic rhinitis, with long-lasting reduction of symptoms and drug requirements, and it seems to prevent new sensitisations and asthma. Prevention of asthma was noted in a cohort of children aged 6–14 years (n=205) with at least moderate rhinitis and eye symptoms—from grass or birch allergies—but no chronic asthma.

Subcutaneous immunotherapy entails repeated injections with allergen extracts. It is reserved for people with severe allergic rhinitis whose symptoms are not controlled sufficiently with pharmacotherapy or who get side-effects from drugs that restrict treatment choices.

Although subcutaneous allergen immunotherapy is effective, a small but definite risk of inducing a systemic allergic reaction is possible, which arises in less than 0·1% of those treated. Patients should only be given subcutaneous allergen immunotherapy in clinics

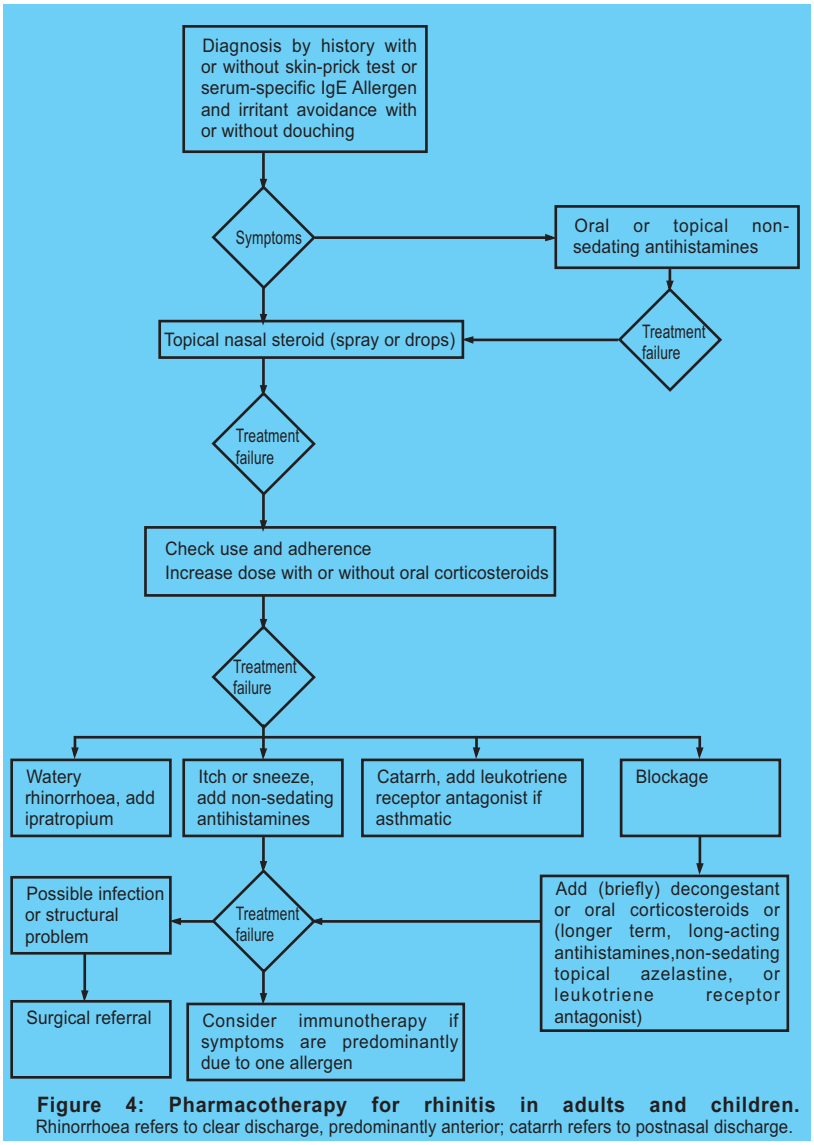

Figure 4: Pharmacotherapy for rhinitis in adults and children.
Rhinorrhoea refers to clear discharge, predominantly anterior; catarrh refers to postnasal discharge.

supervised by doctors who are trained and skilled in adjustment of doses of immunotherapy.

Sublingual immunotherapy—for which only the initial dose needs medical supervision—is also effective in adults and children. It seems to be safer than subcutaneous immunotherapy because side-effects are usually restricted to the upper airways and gastrointestinal tract; rare anaphylactic episodes, but no deaths, have been reported. Evidence suggests that clinical and immunological benefits of sublingual immunotherapy persist after 3 years of continuous use, similar to benefits noted with subcutaneous immunotherapy.

Furthermore, local oral changes unique to sublingual immunotherapy are seen. Although further studies on longevity and concordance, especially in children, are needed, we are cautiously optimistic about sublingual immunotherapy as an effective treatment and possible preventer of asthma.

Surgery

Surgery is needed very rarely, except to improve the route for topical nasal treatment in patients with either turbinate hypertrophy or anatomical deformities, such as severe septal deviations or nasal-valve dysfunction that impairs nasal breathing. Endoscopic sinus surgery could be needed in people with chronic rhinosinusitis who are unresponsive to medical treatment.

The future

Prevalence of allergic rhinitis continues to increase and will undoubtedly have substantial effects on the lives of many sufferers. Since 20% of people with rhinitis are not helped by guideline-directed pharmacotherapy, other treatments—such as allergen immunotherapy— obviously need to be more widely available, and new and more effective treatments should be sought.

Panel: Advantages and disadvantages of pharmacotherapy for allergic rhinitis

Topical nasal treatments

Corticosteroids
- Sprays—fluticasone, mometasone, ciclesonide, triamcinolone, flunisolide, beclametasone
- Drops—fluticasone, betamethasone
- Advantages—most potent anti-inflammatory treatment; strong suppression of all nasal symptoms; effect on conjunctival symptoms; superior to other pharmacological treatments; clinically relevant improvement of quality of life; low bioavailability with recent molecules such as fluticasone
- Disadvantages—reduction of symptoms could take several days; incorrect use leads to treatment failure or adverse events such as epistaxis (in 10–15% of patients)

Antihistamines
- Azelastine, olopatadine
- Advantages—effective and safe treatment for nasal itch, sneezing, and rhinorrhoea; rapid onset of action (within 15 min)
- Disadvantages—neglect of systemic nature of allergic rhinitis; sparse effects on comorbid conditions (eg, conjunctival symptoms)

Chromones
- Sodium cromoglicate, nedocromil sodium
- Advantages—safe treatment with effect on nasal symptoms related to allergic rhinitis
- Disadvantages—several applications per day; weak effect on symptoms of allergic rhinitis

Anticholinergics
- Ipratropium bromide
- Advantages—good effect on rhinorrhoea only; nasal treatment with few adverse events
- Disadvantages—three applications per day; occasional reports of adverse events such as dry nose, epistaxis, urinary retention, and glaucoma

Decongestants
- Ephedrine, pseudoephedrine, xylometazoline
- Advantages—potent vasoconstrictive agents acting on nasal congestion only; rapid onset of action (within 10 min)
- Disadvantages—overuse by patients is common; development of rhinitis medicamentosa after prolonged use; occasional adverse events (eg, nasal irritation and increased rhinorrhoea)

Oral treatments

Antihistamines
- Second-generation antihistamines—levocetirizine and cetirizine, desloratadine and loratadine, fexofenadine, acrivastine, rupatadine, carebastine and ebastine
- First-generation antihistamines not recommended because of sedation and psychomotor retardation
- Advantages—effective for nasal symptoms of itch, sneezing, and rhinorrhoea; reduction of conjunctival, oral, and skin symptoms; rapid onset of action (within 1 h); few interactions with drugs or alcohol
- Disadvantages—regular treatment is more effective than on-demand therapy; modest effect on nasal congestion; sedation still happens in some patients

Corticosteroids
- Hydrocortisone, prednisolone
- Advantages—most potent rescue treatment, with beneficial effects for all symptoms, including nasal obstruction; systemic anti-inflammatory treatment
- Disadvantages—adverse events related to oral corticosteroid treatment; rarely indicated; only for short-term use

Antileukotrienes
- Leukotriene receptor antagonists (montelukast and zafirlukast) and leukotriene synthesis inhibitors (zileuton)
- Only montelukast is approved for allergic rhinitis in association with asthma in the UK
- Advantages—effective for nasal obstruction, rhinorrhoea, and conjunctival symptoms; effective for bronchial symptoms in patients with allergic rhinitis; generally well tolerated
- Disadvantages—not consistently effective; occasional reports of adverse events, such as headache, gastro intestinal symptoms, rash, and Churg-Strauss syndrome

Decongestants
- Pseudoephedrine
- Advantages—reduces nasal obstruction only available in combination with an antihistamine in some countries, but no better than antihistamine alone after a few days
- Disadvantages—frequent reports of side-effects, such as hypertension, insomnia, agitation, and tachycardia

Ref: Allergic rhinitis. Alexander N Greiner, Peter W Hellings, Guiseppina Rotiroti, Glenis K Scadding. Lancet 2011; 378: 2112–22

Dear Doctor,

Square pharma proudly announce the inauguration of Allergy newsletter.

Allergy is a common but often neglected issue in medical progress. This newsletter will try to change the scenario. The latest and relevant article published here will help you to keep yourself updated to these rapidly changing topics.

Please let us know your demand, advice and suggestion to improve the publications.

Best regards.

For further information : **Product Management Department**, Square Centre, 48 Mohakhali C/A, Dhaka-1212, ***web*** : www.squarepharma.com.bd
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