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Optimal management of allergic rhinitis

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ABSTRACT

Allergic rhinitis (AR), the most common chronic disease in childhood is often ignored, misdiagnosed and/or mistreated. Undertreated AR impairs quality of life, exacerbates asthma and is a major factor in asthma development. It can involve the nose itself, as well as the organs connected with the nose manifesting a variety of symptoms. Evidence-based guidelines for AR therapy improve disease control. Recently, paediatric AR guidelines have been published by the European Academy of Allergy and Clinical Immunology and are available online, as are a patient care pathway for children with AR and asthma from the Royal College of Paediatrics and Child Health. Management involves diagnosis, followed by avoidance of relevant allergens, with additional pharmacotherapy needed for most sufferers. This ranges, according to severity, from saline sprays, through non-sedating antihistamines, oral or topical, with minimally bioavailable intranasal corticosteroids for moderate/severe disease, possibly plus additional antihistamine or antileukotriene. The concept of rhinitis control is emerging, but there is no universally accepted definition. Where pharmacotherapy fails, allergen-specific immunotherapy, which is uniquely able to alter long-term disease outcomes, should be considered. The subcutaneous form (subcutaneous immunotherapy) in children has been underused because of concerns regarding safety and acceptability of injections. Sublingual immunotherapy is both efficacious and safe for grass pollen allergy. Further studies on other allergens in children are needed. Patient, carer and practitioner education into AR and its treatment are a vital part of management.

INTRODUCTION

Rhinitis, which can be allergic, infectious or neither of these, is defined as at least two nasal symptoms, including rhinorrhoea, blockage, sneezing and itching. It is a common problem in childhood and adolescence which impacts negatively on physical, social and psychological well-being.

Allergic rhinitis (AR) is an under-recognised inflammatory condition of the nasal mucosa, caused by immunoglobulin E (IgE)-mediated early-phase and late-phase hypersensitivity responses, usually to inhalant allergens, similar to those in allergic asthma.[1–3] Typical allergens include house dust mite, grass and tree pollens, dander from animals such as cat, dog, horse and, occasionally, moulds.[4] Different phenotypes exist; those with obvious symptoms of sneezing and running, who are easily recognised, and others with predominant blockage, where the diagnosis may be missed. Children with AR can present with symptoms related to nasal connections, such as lungs, throat, ears, (table 1) or to quality-of-life impairment, often related to poor quality sleep and consequent fatigue, poor concentration and school performance.

AR is often part of a systemic inflammatory process associated with other inflammatory conditions, including allergic conjunctivitis (AC), rhinosinusitis and asthma. Asthma shows an increased prevalence in children with both allergic[5] and non-allergic rhinitis.[6] A higher prevalence of asthma is found among those suffering from persistent and more severe rhinitis.[7]Over three-quarters of children with asthma also have AR[8] which is associated with poor asthma control.[9 10] Minimal persistent allergic inflammation of the nasal mucosa[11] synergises with infective inflammation; thus, subjects with AR have more problems with viral colds,[12] and the combination in children of allergic sensitisation, relevant allergen exposure and viral cold gives a high risk for hospital admission for asthma in children.[13] Poor asthma control is found in children with moderate to severe rhinitis, which should be identified and treated.[1 9 10]

AR precedes asthma development in preadolescence, adolescence or adult life and carries a threefold risk of it persisting into middle age.[14] Bronchial hyper-responsiveness, raised exhaled nitric oxide and reduced lung function have been observed in children with AR.[15]

Pharmacotherapy for AR improves asthma control;[16 17] allergen-specific immunotherapy (SIT) for rhinitis may decrease the progression of rhinitis to asthma.[18]

Rhinitis affects well-being, both physical and psychological,[19 20] with a direct relationship to allergen exposure.[21] Family dynamics can be disturbed.[22] Uncontrolled AR reduces sleep quality[23] impairing concentration, school attendance and performance,[24] including at General Certificate of Secondary Education (GCSE) level.[25] Rhinitis health-related quality of life is reduced, again in direct correlation with allergen exposure.[26]

Sedating antihistamines further reduce learning ability and impinge on examination results.[25 27]

AETIOLOGY

Environmental factors (tobacco smoke, pollution, infections, diet) acting on a genetic background (family history) contribute to the development of AR which may follow earlier atopic dermatitis[28] but also occurs as the initial manifestation of allergy. Sensitisation may take place via the nose. Local IgE production can occur without evidence of systemic sensitisation.[29]

MANAGEMENT

Guideline-directed management has been shown to improve disease control.[30] The global Allergic Rhinitis and its Impact on Asthma guideline (ARIA),[1] which includes quality-of-life measures in evaluation

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Table 1 Recognising rhinitis in childhood

	Pre-school	School	Adolescent
Classic symptoms and signs of rhinitis	**Rhinorrhoea** – clear or discoloured discharge, sniffing **Pruritus** - nose rubbing, the "allergic salute", "allergic crease", "paroxysmal sneeze", may be associated with complaints of an itchy mouth or throat in older children **Congestion** - mouth breathing, snoring, sleep apnoea, allergic shiners		
Potential atypical presentations	**Eustachian tube dysfunction** - ear pain on pressure changes (eg flying), reduced hearing, chronic otitis media with effusion **Cough** – often mislabelled as asthma **Poorly controlled asthma** – may co-exist with asthma **Sleep problems** - tired, poor school performance, irritability **Prolonged and frequent respiratory tract infections**		
		Rhinosinusitis - catarrh, headache, facial pain, halitosis, cough, hyposmia **Pollen-food syndrome**, particularly with pollen driven allergic rhinitis	

Adapted from Roberts *et al*[33] (with permission). Other rare causes include hormonal rhinitis in teenagers, neurogenic rhinitis and aspirin-sensitive rhinitis.

and treatment, and provides an evidence-based approach to treatment of AR, has recently been updated using GRADE (Grading of Recommendations, Assessment, Development and Evaluations) methodology.[31] The UK has its own guidelines, which are currently being updated.[32] More recent, specifically paediatric guidelines, include those from the European Academy for Allergy and Clinical Immunology (EAACI)[33] and patient pathways from the Royal College of Paediatrics and Child Health.[34] The following is a synopsis of their content.

Diagnosis

AR is diagnosed by detailed history, including questions about possible asthma, and nasal examination, together with inspection of throat, ears and chest where possible, backed up by specific allergy tests, either skin prick or blood tests, for specific IgE to allergens suggested by the history.

Clinical history: symptom type, duration and frequency and exacerbating factors are the cornerstone for diagnosing and classifying paediatric rhinitis which is characterised by two or more nasal symptoms: itching, sneezing, obstruction and rhinorrhoea. The timing of these in relation to exposure to allergen (ie, specific season or animal) is highly relevant. Upon such exposure, symptoms of AR occur in minutes and last for hours. Late-phase symptoms can include nasal obstruction, hyposmia, postnasal mucous discharge and nasal hyper-reactivity.[35] AC occurs in approximately 50%–70% of patients with AR[6] and is the symptom which best differentiates AR from other forms of rhinitis.

In children, rhinitis may present via associated comorbidities (table 1) depending on the child's age. Nasal obstruction with chronic mouth breathing can sometimes be the only presenting symptom in small children: adenoidal hypertrophy and recurrent viral colds are frequent misdiagnoses. Adenoidal hypertrophy with or without sleep apnoea can, in fact, be associated with AR, and in some studies, a response to AR treatment has been noted with an improvement in sleep or hypoxia.[36] Adenoidectomy has not been reported as improving AR, although it may have a role in treating chronic paediatric rhinosinusitis.[37] Otitis media with effusion and Eustachian tube dysfunction can be detected in children with AR.[38] In recent years, oral allergy syndrome (OAS), also known as pollen fruit syndrome, has more often been reported by patients suffering with pollen-induced AR, although the paediatric prevalence of this problem is uncertain.[39] The history of oral pruritus and/or local angioedema in response to fresh fruits and vegetables, for example, apples, hazelnuts, carrots, celery and peanuts, in children with seasonal AR can be misdiagnosed as a primary food allergy (FA). In fact, the initial sensitisation is to pollen, with subsequent cross-reactivity to identical molecules in fruits and vegetables. In doubtful cases, molecular allergy diagnosis may help to distinguish OAS from FA.[39]

Pan airway involvement should be considered, both in the history and on examination.

The ARIA classification of AR as mild intermittent, moderate to severe intermittent, mild persistent or moderate to severe persistent may also be made and used as a guide to therapy (figure 1). This classification has been recently validated in children through an epidemiological survey involving 1275 children between 6 and 12 years of age.[40]

Rhinitis has many underlying causes. (table 2). Approximately two-thirds of children and one-third of adult patients with rhinitis will present with AR; the remainder have other forms and some defy classification (idiopathic rhinitis).[1] Recurrent viral colds are more frequent in small children; AR is more common in older ones. Unilateral symptoms, nasal obstruction without other symptoms, mucopurulent discharge, pain or recurrent epistaxis suggest other diagnoses including rarer conditions that can mimic AR.[35] Chronic unremitting rhinitis present from birth should lead to tests for primary ciliary diskinesia. One-sided persistent nasal blockage, especially with purulent discharge, suggests a foreign body or unilateral choanal atresia. Watery discharge from one side of the

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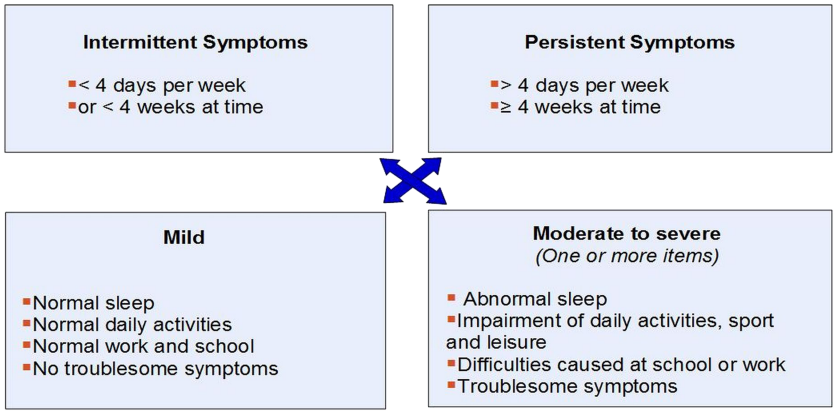

Figure 1 The Allergic Rhinitis and its Impact on Asthma guideline classification in untreated patients.[2] The historical classification of allergic rhinitis (AR) as seasonal or perennial in relation to triggering environmental allergens is useful in some geographical regions and is important for pollen immunotherapy and has, therefore, been additionally maintained in the British Society of Allergy and Clinical Immunology UK classification of AR.[1]

nose, especially on bending forward, can represent a cerebrospinal fluid leak. Cystic fibrosis should be sought if nasal polyps are found. Oral contraceptives can cause rhinitis in adolescents.

EXAMINATION

Allergic children may give the 'allergic salute', rubbing their nose upwards, leading to a crease across the nasal bridge, and may also have an extra skin fold or line under their lower

Table 2 Differential diagnosis of rhinitis in children (level D)

Diagnosis	Pre-school	School	Adolescent
Choanal atresia or stenosis	Obstruction without other features of allergic rhinitis		
Immuno-deficiency	Persisting mucopurlent discharge		
Encephalocoele	Unilateral nasal "polyp"		
Adenoidal hypertrophy	Mouth breathing, discoloured nasal secretions, snoring in the absence of other features of allergic rhinitis		
Foreign body	Unilateral discoloured nasal secretions, foul smell		
Rhinosinusitis		Discoloured nasal secretions, headache, facial pain, poor smell, halitosis, cough	
Cystic fibrosis	Bilateral nasal polyps, poor smell, chest symptoms, symptoms of malabsorption, failure to thrive		
Primary ciliary dyskinesia	Persisting mucopurlent discharge without respite between "colds", bilateral stasis of mucus and secretions at the nasal floor, symptoms from birth		
CSF leakage	Colourless nasal discharge often with a history of trauma		
Coagulopathy	Recurrent epistaxis with minimal trauma		
Septal deviation		Obstruction in the absence of other features of allergic rhinitis	

Adapted from Roberts *et al* [33] (with permission).
CSF, cerebrospinal fluid.

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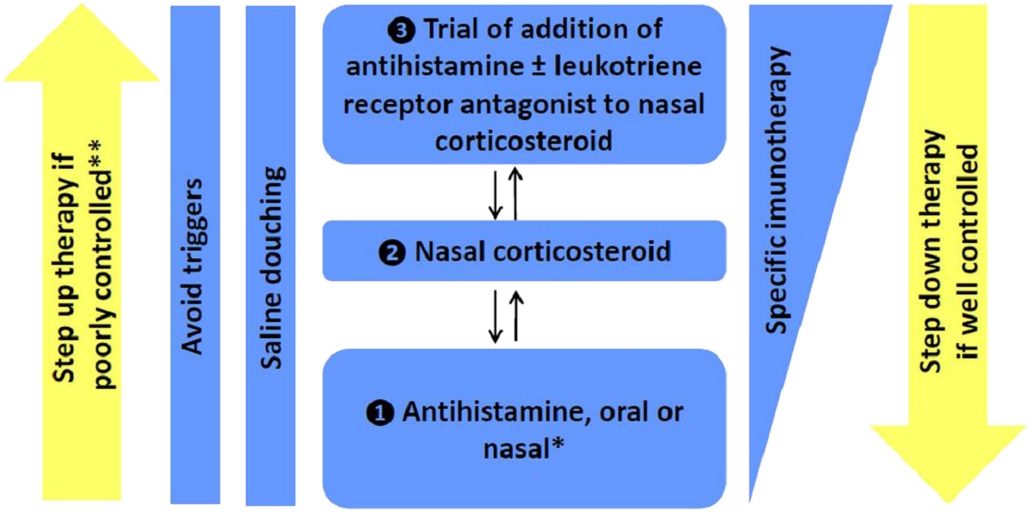

Figure 2 Entry to therapy can occur at 1, 2 or 3 year, depending on severity of presenting symptoms. Poor control should lead to a step up, good control to a step down, so that the minimum therapy necessary is used. For seasonal disease, regular therapy should be commenced 2 weeks before the anticipated start of symptoms. *Oral antihistamines may be better tolerated, while intranasal antihistamines have a more rapid onset of action. **Reconsider diagnosis if not controlled within 1–2 weeks. If <2 years of age and unresponsive to antihistamine within a week, reconsider diagnosis before stepping up therapy. If poorly controlled, consider a short rescue course of a decongestant or low-dose oral prednisolone to gain symptom control; topical ipratropium may be useful for rhinorrhoea (adapted from Roberts *et al* [33] (with permission)).

eyelids (Denny–Morgan lines). Allergic shiners (dark eye shadows beneath the lower eye lid), caused by fluid accumulation in the infraorbital groove, are typical of childhood AR being darker in severe chronic AR.[41] Frequent throat clearing or hoarseness can be another feature. Internal nasal examination, by otoscope or endoscope, is essential, to rule out alternatives such as nasal polyps.[1 33 34]

INVESTIGATIONS

Confirmation of the diagnosis of AR requires evidence of specific IgE reactivity to airborne allergens relevant to the history via either skin-prick testing or the demonstration of serum-specific IgE. This information is also relevant to environmental control measures and allergen-SIT. Immediate hypersensitivity skin testing provides results within 15 min of performing skin tests, whereas blood tests for specific IgE take days and may be less cost-effective than skin-prick testing, but are useful in patients with dermatographism, severe atopic dermatitis or those unable or unwilling to temporarily stop antihistamine use. All IgE test results must be interpreted in the light of the history since both false negative and false positive (sensitisation without clinical disease) tests occur.[29 42 43] AR is triggered mainly by inhalant allergens, of which house dust mites, grass and tree pollens are the most common in most parts of the world.[5] It should be noted that an isolated positive IgE test with no relevant symptoms represents sensitisation and not clinical disease and does not require treatment; therefore, 'fishing expeditions', in which multiple allergy tests are undertaken, are not recommended.

If IgE tests are unavailable, then a possible alternative is a trial of antiallergy therapy using an intranasal corticosteroid or antihistamine or both.

Other tests measuring nasal patency and lung function may be helpful. The latter should always be done in persistent rhinitis or where there are any chest symptoms.

Treatment

This aims at safe and effective symptom relief plus prevention of complications and disease progression. There is evidence that outcomes are improved when evidence-based guidelines are applied.[31] The ARIA guidelines are currently the most widely used in Europe for AR treatment. A recent revision published in 2010 answers specific paediatric questions.[32] The EAACI guideline similarly suggests a stepwise therapeutic approach (figure 2).

Allergen avoidance, where possible, is recommended across the spectrum of disease severity. Those suffering from hay fever are asymptomatic outside the pollen season and symptoms in nose and eyes are reduced by nasal air filters,[44] and pet avoidance shows clear benefits; for house dust mite (HDM) reduction, individual measures gave equivocal results or lack of benefit.[45] FA rarely causes isolated rhinitis, but can be relevant where there are additional gastrointestinal problems, asthma and/or atopic eczema in toddlers.

Saline douching: This reduces symptoms of AR and improves the effect of intranasal steroids (INS)[46] and is effective in rhinosinusitis, where douching is guideline-recommended. Isotonic solutions are well tolerated, inexpensive, easy to use, with no evidence showing that regular, daily use adversely affects health. Other complementary therapies, such as homeopathy, acupuncture, butterbur and herbal medicines are not recommended.[32]

New-generation, non-sedating, antihistamines are recommended alone for mild to moderate AR and in combination with INS for moderate to severe disease.[47] Sedating antihistamines, all of which cause psychomotor retardation, should no longer be used.[48] Intranasal antihistamine alone is faster in onset (15 min, compared with 1 h) and is more effective on nasal symptoms than oral antihistamines[49] and is underused.

INS are superior, for all symptoms, (excluding eye symptoms for which they are equal) to antihistamines (oral or topical), to antileukotrienes and to the combination of antihistamine and antileukotriene in meta-analyses.[50–52] In particular, they are more effective in relieving nasal obstruction.[50] INS are recommended for moderate to severe disease; concerns relating to systemic effects are unfounded when the latest molecules are used, as their systemic bioavailability is extremely low (figure 3). Mometasone furoate and fluticasone proprionate have been extensively studied in children, and no adverse effects on cortisol levels, the hypothalamic-pituitary-adrenal axis or growth

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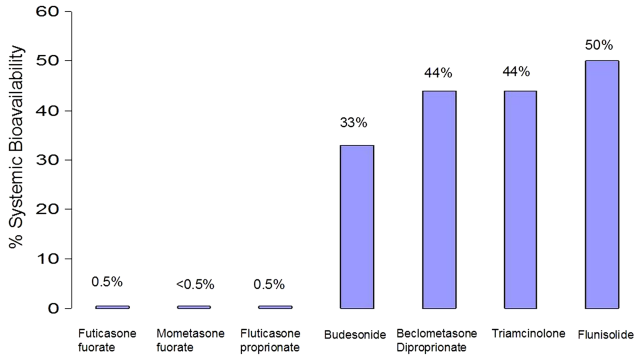

Nasonex Summary of Product Characteristics. 2011
Rhinocort: Summary of Product Characteristics. 2011
Beconase Summary of Product Characteristic 2011
Daley-Yates P et al Br J Clin PharmPharmacol
2001Kariyawasam H and Scadding GK Journal of Asthma and Allergy 2011
Scadding GK Paediatric Drugs 2008

Figure 3 Systemic bioavailability of intranasal steroids.

over 1 year have been detected,[53 54] unlike beclamethasone.[55] Fluticasone furoate, similarly, has low bioavailability, but the use of a double-dose 110 mcg per day has been associated with reduction in growth.[56] It is sensible to use the lowest dose of minimally bioavailable INS needed to maintain control and to administer this in the morning. 'Holidays' from treatment are ineffective in reduction of systemic effects and are liable to result in loss of control. Regular monitoring of growth is a sensitive marker for systemic effects and is sensible, particularly in children receiving corticosteroids to skin, lung and nose. The contribution to systemic effects is greater from skin than lung, with very little from the nose compared with skin or lung, so if growth is slowed, attempts to reduce those areas of treatment should be made first. Considering the adverse impact of uncontrolled rhinitis upon asthma, it may be possible to reduce or even stop inhaled corticosteroids once INS are started, since INS may reduce ocular symptoms and also bronchial hyperreactivity, probably by reduction of inflammation-induced neural reflexes,[57] at which recently available molecules such as fluticasone furoate appear more consistently effective.[58] There is some evidence that INS can benefit asthma,[17 59–61] but randomised, controlled prospective trials are needed of the addition of long-term INS to regular inhaled corticosteroids, both for efficacy and safety. It is logical to treat AR and asthma as one with a corticosteroid inhaled via the nose. Attempts have been made,[62 63] but the practice has not yet been accepted.

It is vital to explain the safety and correct use of INS to children and their carers. The delay in onset of action should be explained, plus the need for regular treatment, how to administer the spray (figure 4) and linking use to a regular daily activity, such as teeth cleaning. Provision of contact details for advice should also aid concordance, since well-meaning uninformed relatives, friends and even primary care practitioners may state that temporary use is all that is allowed, or may switch the prescription to an older, cheaper, more bioavailable molecule.

Nasal biopsies do not show mucosal atrophy after 1 year of regular INS use in adults.[64–66] INS improve mucociliary clearance, and have shown benefits when used in acute rhinosinusitis, so continuation during viral colds is recommended.

A combined nasal spray containing fluticasone propionate and azelastine, an antihistamine, is under trial for use in children.

Systemic corticosteroid is available as a brief rescue therapy for very severe symptoms, the lowest dose for the shortest time should be accompanied by an INS. Depot corticosteroid

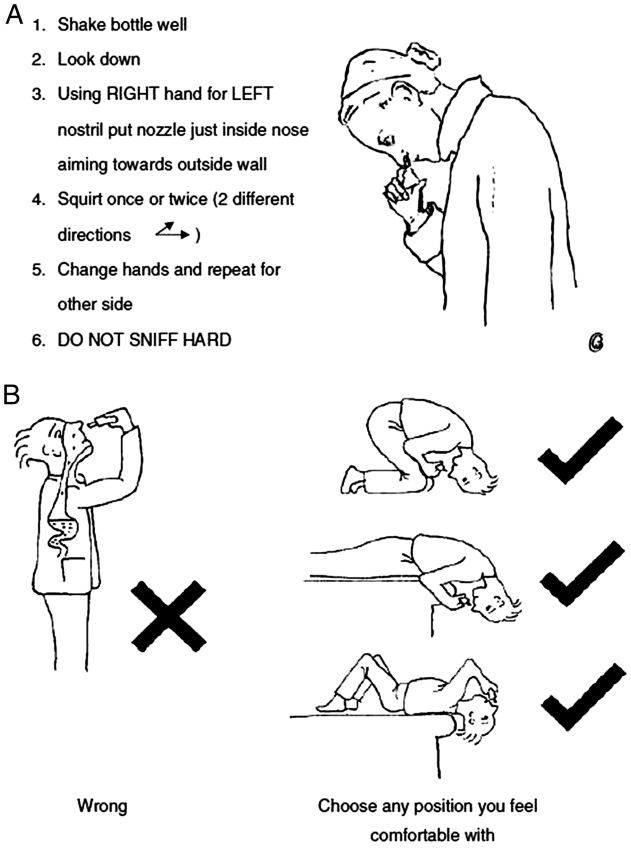

Figure 4 (A) shows how to use a nasal spray so as to avoid the septum and spray as much of the lateral wall mucosa as possible, allowing subsequent mucociliary clearance to distribute the liquid all over the mucosa. (B) shows how nasal drops (superior for rhinosinusitis) should be used with the head completely upside down so that drops reach the ostiomeatal complex in the upper nose where sinuses drain and ventilate (adapted from Scadding *et al* [1] (with permission)).

injections are not recommended, as risk outweighs benefit.[33 67]

Leukotriene receptor antagonists have similar effects as oral antihistamines, with minimal additional benefit when the two are used in combination.[33 68] Use in children with seasonal AR, in preschool children with persistent AR and in children with AR and concomitant asthma, where concerns exist about the use of glucocorticoids, is suggested by ARIA 2010.

ALLERGEN-SIT

At present, this is recommended for severe AR uncontrolled by pharmacotherapy.[33] There is good evidence in pollen-induced AR that SIT reduces symptoms in the nose and eyes.[69–71] In some trials, SIT improves allergic asthma.[69–71]

SIT can be subcutaneous or sublingual. Currently, only 1%–5% of European children suffering with AR are treated with SIT: with 75% receiving subcutaneous immunotherapy (SCIT) and 25% sublingual immunotherapy (SLIT).[71]

Benefits of therapy must always be weighed against risks. A recent review of UK SIT practice[72] confirmed a low incidence of severe adverse reactions and no fatalities, even though guidelines about excluding chronic asthma subjects were not observed, and patients with chronic asthma were treated with SIT. Adrenaline injections are still sometimes

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needed for anaphylaxis in SCIT which, because it is not completely risk-free, must only be administered by those competent in its use.

SLIT in children shows efficacy in hay fever; HDM desensitisation gives variable results.[73 74] Local reactions are common with itching and swelling in mouth and throat, worst on first application and usually disappearing in 2 weeks, systemic reactions rarely occur and no fatalities have been reported. A meta-analysis of 49 SLIT studies, including 15 paediatric papers with over 1400 children, suggests that it is more effective in the paediatric group.[75]

SIT is the only treatment with a disease-modifying effect during the treatment period and in the years following. It appears to be capable of preventing the progression of rhinitis to asthma and new allergic sensitisations. The Prevention of Asthma Study demonstrated a reduction in cases of new asthma in children receiving 3 years of SCIT for hay fever at 3, 5 and 10 years, compared with those treated by pharmacotherapy alone,[19] but was not blinded. A double-blind, randomised trial is in progress to test the effectiveness of grass pollen SLIT in asthma prevention. Another is in progress comparing the efficacy of SCIT and SLIT. It seems likely that SIT administered correctly to appropriately selected patients is socioeconomically beneficial.[75]

Concordance with long-term therapy, like SIT, is challenging: good contact and communication are again necessary.

CONCLUSION

AR is worth treating effectively, even when it is part of a myriad of allergic conditions; as the nose is the gateway to the respiratory tract, good rhinitis control can facilitate control of symptoms elsewhere. AR, if poorly controlled, results in troublesome symptoms and impacts on daily activities, quality of life and on other areas of the respiratory tract, such as ears, sinuses, throat and lungs. Possible causes for difficult-to-treat cases include doctor factors such as misdiagnosis and undertreatment or patient factors such as lack of concordance with therapy. This can be reduced by information leaflets on specific allergen avoidance, the correct technique in the application of nasal preparations (avoiding the septum and leaving in place rather than sniffing back) and explanation of potential side effects. Clearly written treatment plans are useful, particularly if several preparations are prescribed.

AR can sometimes copresent in association with other forms of rhinitis (or rhinosinusitis) leading to increased severity (mixed rhinitis). Associated comorbidities should be considered in the differential diagnosis in order to determine the most appropriate therapeutic approach. Allergen-SIT should be considered for patients with genuinely difficult-to-control allergic disease, despite guideline-directed pharmacotherapy properly taken. Grade A evidence via meta-analysis confirms its efficacy and it is unique in its ability to alter the long-term disease course.

Local primary care directives, such as use of the cheapest, significantly bioavailable INS and inhaled corticosteroids molecules, and minimal provision of SIT are misguided and liable to result in extra-disease manifestations, reduced quality of life, and will increase costs in the long term.[76]

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