


# BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis (Revised Edition 2017; First edition 2007)

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## Abstract

This is an updated guideline for the diagnosis and management of allergic and non-allergic rhinitis, first published in 2007. It was produced by the Standards of Care Committee of the British Society of Allergy and Clinical Immunology, using accredited methods. Allergic rhinitis is common and affects 10–15% of children and 26% of adults in the UK, it affects quality of life, school and work attendance, and is a risk factor for development of asthma. Allergic rhinitis is diagnosed by history and examination, supported by specific allergy tests. Topical nasal corticosteroids are the treatment of choice for moderate to severe disease. Combination therapy with intranasal corticosteroid plus intranasal antihistamine is more effective than either alone and provides second line treatment for those with rhinitis poorly controlled on monotherapy. Immunotherapy is highly effective when the specific allergen is the responsible driver for the symptoms. Treatment of rhinitis is associated with benefits for asthma. Non-allergic rhinitis also is a risk factor for the development of asthma and may be eosinophilic and steroid-responsive or neurogenic and non-inflammatory. Non-allergic rhinitis may be a presenting complaint for systemic disorders such as granulomatous or eosinophilic polyangiitis, and sarcoidosis. Infective rhinitis can be caused by viruses, and less commonly by bacteria, fungi and protozoa.

## KEYWORDS

allergen, allergic, allergy, antihistamine, anti-leukotriene, aspirin, asthma, BSACI, cat allergen, child, corticosteroid, cromoglycate, decongestant, guideline, house dust mite, idiopathic rhinitis, IgE, immunotherapy, ipratropium bromide, lactation, non-allergic, non-infectious rhinitis, nitric oxide, non-allergic, non-infectious rhinitis, occupational, pregnancy, quality of life, rhinitis, rhinitis control, skin prick test, Standards of Care Committee, subcutaneous immunotherapy, sublingual immunotherapy, surgery

## 1 | INTRODUCTION

Allergic rhinoconjunctivitis (AR) remains the most common immunological disease in man and is still subject to under-recognition and poor management. This matters because AR significantly reduces quality of life (QOL),<sup>1</sup> interferes with both attendance and performance at school and work<sup>2,3</sup> and results in substantial societal costs.<sup>4</sup> In addition, as the nose is the gateway to the respiratory tract, rhinitis is associated with symptoms in the eyes,<sup>5</sup> sinuses,<sup>6</sup> middle ear,<sup>7</sup> the nasopharynx and lower airways.<sup>8</sup> Both AR and non-allergic rhinitis (NAR) are risk factors for the development of asthma.<sup>9</sup> Rhinitis impairs asthma control<sup>10,11</sup> and increases its costs.<sup>11</sup> All patients presenting with nasal symptoms require accurate diagnosis and appropriate treatment. These guidelines are intended to facilitate this.

Evidence for the recommendations was obtained using electronic literature searches using the primary keyword—rhinitis. Further searches were carried out by combining this search term with key words listed above through MEDLINE and EMBASE from 2007 to 2014.

Additional references were hand searched and provided by committee members, experts and reviewers from 2014 to 2017. Recent advances since the 2007 guidelines include evidence for local allergic rhinitis, demonstration of the greater effectiveness than either alone of combined topical preparations of antihistamine and corticosteroids, the concept of rhinitis control and of severe chronic upper airways disease (SCUAD) and better evidence for the efficacy of sublingual immunotherapy. Each article was reviewed according to criteria for suitability for inclusion. Recommendations were evidence graded, see Appendix A1.<sup>12,13</sup> During guideline development, a web-based system was used to allow consultation with all BSACI members. The draft guidelines were amended by the Standards of Care Committee (SOCC) after careful consideration of all comments and suggestions. Where evidence was lacking, a consensus was reached among the experts on the committee. Conflicts of SOCC members' interests were recorded.

The draft was reviewed by a lay person.

## 2 | DEFINITIONS/CLASSIFICATION

Rhinitis describes inflammation of the nasal mucosa but is clinically defined by symptoms of nasal discharge, itching, sneezing and nasal blockage or congestion. When the conjunctivae are also involved, the term rhinoconjunctivitis is more accurate. Involvement of the sinus linings in more widespread disease is known as rhinosinusitis. Rhinitis has multiple phenotypes, usually divided into allergic, non-allergic and infective as well as mixed forms.

### 2.1 | Classification of Allergic Rhinitis (AR)

The WHO ARIA workshop "Allergic Rhinitis and its impact on Asthma" classification<sup>14</sup> of AR based on frequency and severity of

symptoms has been validated.<sup>15</sup> Additionally clinical classification into seasonal and perennial rhinitis is useful in UK practice for diagnosis and allergen-specific therapy.

### 2.2 | Infective rhinitis

Any cause of congestion of the nasal mucosa can lead to occlusion of the sinus ostia, predisposing to acute rhinosinusitis and/or Eustachian tube dysfunction.

### 2.3 | Non-allergic rhinitis (NAR)

The numerous diagnoses in this category need to be borne in mind for patients with negative skin prick tests (SPTs). Table 1 summarizes the causes and disease patterns of NAR.

## 3 | EPIDEMIOLOGY

In the UK, rhinitis prevalence is 10.1% and 15.3% in 6-7 and 13-14 year olds respectively,<sup>32</sup> and 26% in UK adults.<sup>33</sup> Peak prevalence occurs in the 3rd and 4th decades,<sup>34,35</sup> with some evidence for remission during adult life.<sup>36</sup> The prevalence in the UK and Western Europe has increased dramatically over the past 4-5 decades.<sup>37,38</sup>

Some studies suggest a plateau may have been reached,<sup>32,38-40</sup> whilst others report continued increases since the 1990s.<sup>41-43</sup> There is a male preponderance before adolescence<sup>41,44-46</sup> reversing post-adolescence.<sup>35,47,48</sup> World-wide, there appears to be a correlation between economic and industrial development and the prevalence of AR.<sup>32,49</sup> Post-communist Eastern Europe has seen accelerating occurrence.<sup>50</sup> Local AR, confirmable only by nasal provocation, has been found to have a prevalence of over 25% in some centres.<sup>51</sup> A prevalence ratio of allergic to non-allergic rhinitis of 3:1 has been suggested.<sup>52</sup>

Rhinitis is strongly associated with asthma: 74%-81% of asthmatics report symptoms of rhinitis.<sup>53</sup> Rhinitis, both allergic and non-allergic, is a strong risk factor for new-onset asthma.<sup>54,55</sup>

## 4 | AETIOLOGY

Genetic predisposition is probably the most important factor in rhinitis development, but identification of specific susceptibility genes has proved difficult. Large scale genome-wide association studies (GWAS) have allowed identification of several candidate loci and genes for asthma and atopic dermatitis.<sup>56-59</sup> To date, only one such GWAS has been carried out for AR.<sup>60</sup>

Of note, classical genetic change (i.e change in DNA nucleotide sequence) is unable to account for the rapid increase in prevalence of AR seen in recent years, suggesting environmental factors (and possible gene-environment interactions) are important. Epidemiological evidence suggests smaller family size, urban environments and reduced exposure to infectious diseases is involved and appear to

**TABLE 1** Triggers for non-allergic rhinitis

Type	Suggested triggers/cause	Signs/symptoms
Eosinophilic or NARES (non-allergic rhinitis with eosinophilia syndrome)	50% develop aspirin sensitive disease with asthma and nasal polyposis later in life <sup>16</sup>	Skin tests-negative but nasal smears show eosinophilia. Perennial symptoms with paroxysmal episodes. About 50% have bronchial hyperreactivity <sup>16</sup>
Autonomic, formerly known as(vasomotor)	Triggered by physical/chemical agents	More common in middle age with clear rhinorrhoea especially in the morning. Less favourable course than allergic. Possibly caused by parasympathetic hyperactivity <sup>17</sup>
Drugs	$\alpha$ -adrenergic blockers, ACE inhibitors, Beta-blockers, chlorpromazine Cocaine Nasal decongestants (with prolonged use) Aspirin/NSAIDs	Nasal blockage Rhinorrhoea, crusting, pain and nasal septum perforation reduced olfaction <sup>18</sup> Rhinitis medicamentosa with chronic nasal blockage <sup>19</sup> Acute rhinitis symptoms $\pm$ asthma
Hormonal	Pregnancy, <sup>20</sup> puberty, HRT, contraceptive pill. <sup>21,22</sup> Possibly hypothyroidism, acromegaly <sup>23,24</sup>	All can cause nasal blockage and/or rhinorrhoea
Food	Alcohol, spicy foods, pepper, sulphites	Rhinorrhoea, facial flushing Gustatory rhinorrhoea
Atrophic	Klebsiella Ozaena <sup>25</sup> or secondary to trauma, surgery, radiation	Foul-smelling odour, crusting, hyposmia, nasal blockage <sup>26</sup>
Primary mucus defect	Cystic fibrosis	Children with polyps must be screened for cystic fibrosis <sup>27</sup>
Primary ciliary dyskinesias	Kartagener and Young syndromes	Rhinosinusitis, bronchiectasis and reduced fertility.
Systemic/Inflammatory	Sjogren, SLE, rheumatoid arthritis, Churg-Strauss <sup>28</sup>	Nasal blockage Polyps, sinusitis, asthma, eosinophilia
Immunodeficiency	Antibody deficiency	Chronic infective sinusitis
Malignancy	Lymphoma, melanoma, squamous cell carcinoma	Bloody, purulent discharge, pain and nasal blockage – symptoms may be unilateral
Granulomatous diseases	Sarcoidosis Granulomatosis with polyangiitis	External nasal swelling or collapse, sinusitis, swelling, crusting, bleeding, septal perforation
Structural abnormalities	Nasal septal deviation	Unilateral nasal obstruction unlikely to present unless additional cause, e.g. rhinitis
Idiopathic	Unknown cause—Diagnosis of exclusion	May respond to topical capsaicin <sup>29-31</sup>
Local AR	Allergens as for AR (see Table 1)	Skin test-negative

Multiple factors need to be considered in skin test-negative patients. Mixed forms of rhinitis, allergic plus non- allergic, also occur.

have a particular effect during early life.<sup>61-64</sup> Epigenetic modifications, such as DNA methylation, may be involved in the mechanism of gene-environment interactions in allergic diseases.<sup>65</sup>

## 5 | ALLERGIC RHINITIS

### 5.1 | Pathophysiology

The basic mechanisms of AR are illustrated in Figure 1.

Co-morbid associations of rhinitis (Table 2).

AR-associated comorbid disorders can be subdivided into:

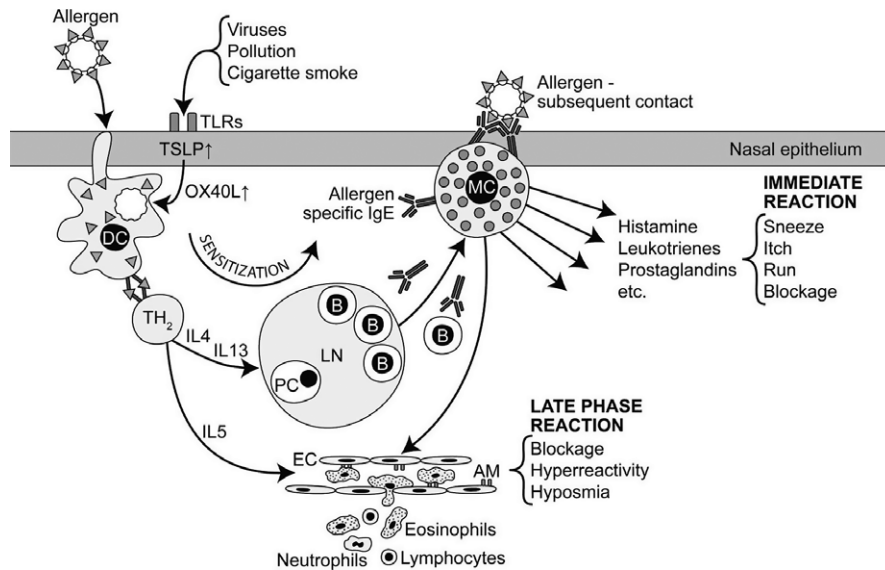
- other allergic diseases, particularly asthma
- problems related anatomically to the nose: conjunctivitis, rhinosinusitis, hyposmia, middle ear problems, throat and laryngeal effects

- Sleep problems and secondary effects of symptoms on concentration, mood and behaviour

The most important co-morbidity is asthma: not only is rhinitis a risk factor for subsequent asthma but 80% of asthma sufferers according to ARIA have concomitant rhinitis, poor control of which is a risk factor for asthma exacerbations.<sup>10,11,104-106</sup>

## 6 | NON-ALLERGIC RHINITIS (NAR)

This group consists of patients with symptoms of rhinitis but without any identifiable allergic triggers. It is a diagnosis of exclusion in patients negative for systemic IgE, when the many other causes of rhinitis have



**FIGURE 1** Immunological mechanisms of Allergic Rhinitis. Sensitized patients with allergic rhinitis have IgE antibodies for specific allergen(s) bound to receptors on the surface of mast cells. On re-exposure to the specific allergen(s), cross-linking of adjacent IgE molecules occurs, and mast cell degranulation results. Pre-formed mediators such as histamine stimulate sensory nerve endings within seconds, causing itch and sneezing, and promote dilatation of local vasculature and glandular secretion, causing obstruction and rhinorrhoea, respectively. Newly synthesized mediators, including leukotrienes, as well as chemokines and cytokines contribute to a delayed eosinophil and Th2 T cell predominant inflammation, the late-phase response, characterized by nasal obstruction and hyperreactivity.<sup>66</sup> Additional mechanisms are likely to be relevant. These include neuro-immune interactions, such as release of neuropeptides (substance P, calcitonin gene-related peptide) and neurokinins from sensory nerve endings in response to inflammatory mediators.<sup>67</sup> The role of the epithelium, particularly its interaction with newly defined type 2 innate lymphoid cells (ILC2), has been scrutinized in murine asthma and allergy models<sup>68,69</sup> as well as in human asthma.<sup>70,71</sup> Further research is needed to confirm the relevance epithelial-derived cytokines such as TSLP, IL-33 and IL-25 as well as ILC2 cells in allergic rhinitis<sup>72</sup>

been ruled out (Table 1). The inaccurate term, vasomotor rhinitis should no longer be used. Infective rhinitis is not considered in this guideline.

## 6.1 | Pathophysiology

At least two subgroups exist: one with nasal inflammation on histology,<sup>107</sup> the other without inflammation or local IgE production.<sup>108</sup> The former includes local allergic rhinitis<sup>109</sup> and non-allergic rhinitis with eosinophilia (NARES). A proportion of patients within this latter group are aspirin/NSAID sensitive.<sup>110</sup> There is evidence that some patients with apparently non-allergic rhinitis share similar histologic mucosal features as those with allergic rhinitis characterized by increased numbers of mast cells and eosinophils and produce local IgE,<sup>107,111,112</sup>

Patients with non-inflammatory type rhinitis are thought to suffer from dysfunction of the autonomic nerve supply to the nasal mucosa.<sup>67,113</sup>

## 6.2 | Occupational rhinitis

Occupational rhinitis, which can be allergic or non-allergic, describes abnormalities of the nasal mucosa mediated by airborne substances in the work environment. It is distinct from work-exacerbated rhinitis, which refers to individuals with pre-existing rhinitis who experience an exacerbation of symptoms due to

workplace exposures. Over 300 agents can cause occupational rhinitis, and these are the same as those which can induce occupational asthma.<sup>114</sup>

HMW agents are protein allergens derived from plants or animals, for example, flour, latex, laboratory animals and evidence of sensitization are usually seen on skin testing or serum-specific IgE.<sup>115</sup> LMW agents cause mucosal inflammation either via airway immune sensitization, (e.g di-isocyanates and glutaraldehyde) or via irritant exposures (e.g chlorine and ammonia). Occupational rhinitis is three times more frequent than occupational asthma; the two conditions frequently occur together.<sup>116,117</sup> The early identification of a causative occupational agent and the avoidance of exposure are important for the prevention of progression to occupational asthma<sup>118-121</sup> (Grade B).

Diagnosis is based on a detailed history, including symptom diary review, improvement of nasal symptoms during weekends and holidays, skin prick testing and measurement of specific IgE when appropriate.

Latex is a cause of both occupational rhinitis and asthma. Prevention of latex allergy by removing powdered gloves or substituting non-latex ones is essential. All healthcare environments should have a latex policy<sup>119,122</sup> (Level of evidence=2+ and 4; Grade of recommendation=D, C for adults and children with perennial rhinitis or adults and children with latex allergy).

**TABLE 2** Co-morbid associations with rhinitis

Authors	Study	No patients	Age, y	Aim of the study	Results
<b>Conjunctivitis</b>					
Virchow et al. (2011) <sup>73</sup>	Observational	1009	Adults	study to assess extra burden associated with ocular symptoms	Ocular symptoms reduces quality of life and work productivity
Bozkurt et al. (2010) <sup>74</sup>	Prospective ENT examination in children with VKC	26 males 1 female	12±4.4	AR prevalence in children with VKC	37% of children with VKC suffer from AR. Median IgE in AR +ve was 262.5 Ku/L vs 40.2 in non-AR. Patients with VKC should see an ophthalmologist and an allergist
Ibanez et al. (2010) <sup>75</sup>	Multicentre study	1275 recruited from 271 centres	6-12	AR (60.7% seasonal and 39.3% perennial) conjunctivitis co-morbidities	Persistent/Severe AR has more co-morbidities. The most frequent is conjunctivitis (53%)
Bertelesen et al. (2010) <sup>76</sup>	Parental interviews of 1019 cohort	254 with rhinitis (=25%)	Children	Prevalence of rhinitis co-morbidities	87.4% had at least one rhinitis co-morbidity. Conjunctivitis was present in 75.6% (11.8% of them also had asthma & eczema)
Kim et al. (2013) <sup>77</sup>	ISAAC Questionnaire (12 mo evaluation)	615	3-6	Prevalence of rhinitis in children with conjunctivitis and conjunctivitis in children with rhinitis	Prevalence of rhinitis in children with conjunctivitis was 64.8%. Prevalence of conjunctivitis in children with rhinitis was 23.6%
Williams et al. (2013) <sup>90</sup>	Questionnaire and direct question	187	Adults	To identify the incidence of allergic conjunctivitis in patients with allergic rhinitis	55% of patients with AR were identified as having AC by direct questioning and the use of the TOSS questionnaire. A further 41% were identifiable by asking additional questions and performing therapeutic challenge with olopatadine
<b>Otitis media with effusion</b>					
Umapathy et al. (2007) <sup>78</sup>	Questionnaire	332	Primary school children	To evaluate the association between symptoms suggestive of otitis media with effusion (OME), rhinitis and asthma in an unselected population of primary school children	32.8% OME 36.6% Rhinitis 24% asthma
Ibanez et al. (2013) <sup>79</sup>	Multi centre prospective	1275 271 centres	6-12	Evaluation of ear co-morbidities in AR	23.8% of AR had OME; 17.3% of AR had adenoidal hypertrophy
Singh et al. (2011) <sup>80</sup>	Prospective	30 patients 20 controls	Adults	Audiological and ontological status in AR	All patients had sensorineural hearing loss >high frequency & otoacoustic emission abnormalities

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TABLE 2 (Continued)

Authors	Study	No patients	Age, y	Aim of the study	Results
Bozkurt et al. (2010) <sup>74</sup>	Prospective	26 males 1 female	12.1±4.4	Prevalence of Eustachian tube dysfunction (ETD) in VKC and AR	Patients with AR and VKC have 3x more abnormal tympanograms and suffer from ETD more than controls
<b>Depression/ADHD/ Altered sleeping patterns/anxiety in families</b>					
Chen et al. (2013) <sup>81</sup>	Nationwide Prospective	1673	12-15	Association AR and depression after 10 y FU	Severe depression 2.5% vs 1.2% Any other depression 4.9% vs 2.8%
Tsai et al. (2011) <sup>82</sup>	Nationwide on Taiwan National Health Research Database	226 550	<18	Prevalence & risk of ADHD in AR children	Increased ADHD rate. P<.001 (eczema & asthma do not carry the same risk)
Kalpakliglu et al. (2009) <sup>83</sup>	Observational study on sleeping symptoms	48	Adults	Prevalence of OSA in AR vs NAR	OSA 36% in AR vs 83% in NAR (OSA OR in NAR 6.4). AR & NAR subjects were snorers
Emin et al. (2009) <sup>84</sup>	Prospective	82 vs 70 mothers of AR	7-15	Anxiety parameters scores in mothers of AR children vs controls	Anxiety scores significantly higher in mothers with AR children P<.02
Lavigne et al. (2013) <sup>85</sup>	Prospective for 12/wk	34 AR 21 NAR	Adults	Effects of mometasone on sleep parameters & upper airway inflammation on biopsies	Significant improvement on sleeping parameters & reduction of eosinophils in AR only
Messias et al. (2010) <sup>86</sup>	National co-morbidity survey	5692	Adults	Association of seasonal allergic with suicidal ideation	Significant association (OR 1.27) but not with suicide attempts
Vuurman et al. (2014) <sup>87</sup>	Double blind randomized cross-over following nasal provocation with pollen extract and during the season	19 (9 females/10 men)	Adults	Effect of untreated AR on driving performance compared with treated AR	Magnitude of impairment (evaluated on standard deviation of lateral position of performance) comparable to that seen driving with 0.03% alcohol. Rx with anti H1 or steroids reduces the effects on driving performance
<b>Rhinosinusitis/anosmia</b>					
Ibanez et al. (2013) <sup>79</sup>	Multi centre prospective	1275 271 centres	Children	Co-morbidities in children with AR	26.1% of AR had rhinosinusitis
Guss et al. (2009) <sup>88</sup>	Prospective	51 (80% allergic)	Adults	Investigate the olfactory function in AR (with Smell Identification Test and also CT scan)	50% of AR with normal CT scored in the 30th percentile on olfactory test. 50% of allergic patients had hyposmia
<b>Asthma</b>					
Shaaban et al. (2008) <sup>55</sup>	Longitudinal population based study	6461	Adults	Development of new asthma	RR of asthma development: 1.63 atopy, 2.71 NAR, 3.53 AR

(Continues)

TABLE 2 (Continued)

Authors	Study	No patients	Age, y	Aim of the study	Results
Leynaret et al. (2004) <sup>53</sup>	Cross sectional study	3000 (1500 male and 1500 female)	Young adults	Identification of sensitization, BHR, asthma	74%-81% had asthma, BHR (OR 3.02) and asthma (OR 6.63) more frequent in rhinitis. Asthma risk 2% without rhinitis, 6.7% with pollen rhinitis, 11.9% with animal rhinitis, 18.8% both. Strong association between asthma and rhinitis not fully explained by atopy
Settipane et al. (2000) <sup>89</sup>	Questionnaire	1601	Adults	Asthma and rhinitis/AR improvement associated with a resolution of asthma symptoms	Asthma and rhinitis present in 85.7% of asthmatics, asthma in 21.3% of rhinitis. In 44.8% of those with both rhinitis appeared first, in 20.7% at the same time
Magnan et al. (2008) <sup>91</sup>	Cross sectional French study, Questionnaire	14 703	Adults	Questionnaire in asthma patients	81% of asthma patients treated for rhinitis. Severity of rhinitis and of asthma corresponded. AR associated with more severe asthma, more difficult to control asthma and substantial quality of life impairment
Ciprandi et al. (2011) <sup>92</sup>	Prospective	89 AR 940 controls	Adults	Follow up of patients with AR every 2 y for 8 y to investigate spirometric abnormalities /BHR	34/89 AR patients develop BHR after 8 y Sensitization for mite, birch, parietaria as well as rhinitis duration are risk factors
Yilmaz et al. (2014) <sup>93</sup>	Prospective	57	Children with asthma ex'ion	Evaluate the risk factors for recovery of lung function tests after moderate/severe asthma exacerbation	AR is a significant factor affecting the recovery time of pulmonary function tests and impacts asthma management
Ibanez et al. (2013) <sup>79</sup>	Prospective multicentre	1275	Children From 271 centres	Evaluation of comorbidities for AR in a Spanish population	49.5% co-morbidity with asthma: allergy is a systemic disease
Navarro et al. (2008) <sup>94</sup>	Epidemiologic prospective Multi centre	942 with asthma	Mean age 35.5 63% female	Investigate the link between the upper and lower airways	89.5% had AR Correlation between severity of rhinitis and asthma ( $P<.001$ )
de Andrade et al. (2008) <sup>95</sup>	Cross sectional study using ISAAC questionnaire	3083 students (47.3% males)	13-14 y old, 47.3% male	Evaluation of Asthma and AR co-morbidity	Comorbidity of asthma and rhinitis symptoms was 8.4% Among asthmatic adolescents, AR symptoms were reported in 46.5%

(Continues)

TABLE 2 (Continued)

Authors	Study	No patients	Age, y	Aim of the study	Results
Ko et al. (2010) <sup>96</sup>	Cross sectional on questionnaire	600 (with asthma)	267 male 333 female	Evaluation of prevalence of AR in asthma	77% of asthmatic had rhinitis in the past 12 mo (of whom 96% were previously diagnosed with AR) Patients with asthma and rhinitis: nasal steroid usage (49%) had <ED visits 13% vs 25%) and <hospitalization for asthma (5% vs 13%)
Eriksson et al. (2011) <sup>97</sup>	Postal Questionnaire on respiratory health	18 087 (62% responded)	Adults	Evaluation between rhinitis phenotypes and symptoms presentation and risk factor patterns in asthma	Prevalence of asthma in AR was 19.8% Prevalence of AR in asthma was 63.9% Asthma with chronic rhinitis had more asthma symptoms and bronchitis ( $P<.01$ ) FH of allergy has a higher OR for asthma and AR than for asthma and CRS
Bertelasan R	Parental interviews	254	Children with rhinitis	Evaluation of co morbidities of rhinitis	87.4% had at least one allergy related co-morbidity Children with rhinitis and allergic sensitization (72.8%) had >BHR, severe BHR (7.5% vs 5.8%) and conjunctivitis
Valero et al. (2009) <sup>98</sup>	Cross sectional international population study based on questionnaire	3225 (one +ve skin test)	10-50 53% Male	Evaluation on the link between AR, asthma and skin test sensitization	Asthma was present in 49% of AR Asthma severity was associated with longer time since the onset and allergic rhinitis severity. Patients with asthma have higher number of allergen sensitization and sensitization intensity than those without asthma ( $P<.01$ )
Kim et al. (2013) <sup>77</sup>	Cross sectional Study using ISAAC questionnaire	615	Children (306)	Evaluation of allergic co-morbidities in pre-school children	Prevalence of AR in children with asthma was 64.3% Prevalence of asthma in children with R was 21.6%
<b>Oral allergy syndrome/food pollen syndrome/food allergy</b>					
Westman et al. (2012) <sup>99</sup>	Prospective	2024	Children IgE tested (inhalants) at 4 and 8 y	Natural course of AR and co-morbidities in children	Increase AR from 5% to 14% from 4 to 8 y; decrease of NAR from 8% to 6%. 4 y sensitized but not allergic had AR at 8 y in 56% of cases 25% of 8 y with AR has also OAS

(Continues)



TABLE 2 (Continued)

Authors	Study	No patients	Age, y	Aim of the study	Results
Caliskaner et al. (2011) <sup>100</sup>	Prospective	111 78 men 33 women	Adults	Clinical parameters comparison between AR with OAS and without	OAS >in women ( $P=.01$ ) (OR M/F3.80). OAS relates to nasal itching ( $P<.05$ ). OAS >IgE (ns) Regression analysis: association with asthma, age and severity of nasal symptom score
Sahin-yilmaz et al. (2010) <sup>101</sup>	Retrospective	283		Peanut, shrimp and milk IgE and rhinitis	23.4% peanut IgE +ve and 22.2% IgE+ shrimp in inhalant +patients Peanut and shrimp were the >common sensitivities in rhinitis patients
<b>Laryngeal symptoms</b>					
Verguts MM et al. (2011) <sup>102</sup>	Observational prospective	6 control 6 AR adult singers	4 females 2 men	Effects of nasal provocation with pollen extracts and during the HF on Laryngeal parameters	Rapid induction of laryngeal irritation/globus (no objective laryngeal changes on provocation and during the season)
<b>Rhinitis/atopic disease and migraine</b>					
Munoz-Jarena et al. (2011) <sup>103</sup>	Retrospective study FU for 6 mo	216	5-15	Prevalence of atopy in children with migraine	Prevalence of rhinoconjunctivitis, asthma and atopic dermatitis are statistically significant in children with migraine (OR 7.3; $P<.01$ for rhinoconjunctivitis; OR 4.69; $P<.01$ for asthma; OR 7.1; $P<.01$ for atopic dermatitis)

Some co-morbidities appear as consequences of AR, for example, concentration and sleep problems, others co-exist with it as a consequence of underlying allergy, for example atopic dermatitis. The mechanism of the association between asthma and rhinitis is uncertain, but the tendency for asthma to succeed rhinitis, the demonstration that nasal allergen challenge in AR gives lower respiratory tract inflammation and the prevention of progression of AR to asthma by allergen immunotherapy suggest that the asthma is consequential in individuals in whom rhinitis is the initial manifestation of atopic disease.

## 7 | DIAGNOSIS OF RHINITIS

### 7.1 | History

A detailed history is required, including seasonality (pollen, moulds), indoors/outdoors location (dust mite, the presence of house pets), work location (occupational), improvement of holidays and, relationship to potential triggers which can impact on the patient's quality of life. Symptoms of sneezing, nasal itching, itching of the palate are more likely to lead to allergic rhinitis.

### 7.2 | Rhinorrhoea

Rhinorrhoea is either anterior, posterior or both.

- Clear—infection unlikely if continuously clear, although secretions are clear early in viral rhinitis
- Unilateral—is uncommon and cerebrospinal fluid (CSF) leak should be excluded<sup>123</sup>
- Coloured
  1. yellow—allergy or infection; green—usually infection; blood tinged
  2. unilateral—tumour, foreign body, nose picking or misapplication of nasal spray
  3. bilateral—misapplication of nasal spray, granulomatous disorder, bleeding diathesis, infection, nose picking.

### 7.3 | Nasal obstruction

- Can be partial or complete; severity often correlates with systemic manifestations
- Bilateral—most likely rhinitis or nasal polyps but maybe septal (sigmoid) deviation
- Unilateral—usually septal deviation but also consider foreign body, antrochoanal polyp and tumours
- Alternating—due to rhinitis exposing the nasal cycle<sup>124</sup>

### 7.4 | Nasal crusting

Severe crusting especially high inside the nose is an unusual symptom in rhinitis and requires further investigation. Consider: chronic rhinosinusitis,<sup>125</sup> nose picking, granulomatous polyangiitis, sarcoidosis or other vasculitides, (particularly if crusting is associated with bleeding), cocaine abuse, ozaena (wasting away of the bony ridges and mucous membranes inside the nose), non-invasive ventilation. Topical steroids rarely cause crusting.

### 7.5 | Eye symptoms

Include intense itching, redness and swelling of the white of the eye, watering, lid swelling and (in severe cases) periorbital oedema, which can be aggravated by eye rubbing.

### 7.6 | Lower respiratory tract symptoms

- Cough, wheeze, shortness of breath—can occur with rhinitis alone since bronchial hyper-reactivity can be induced by upper airway inflammation.<sup>126-128</sup>

Disorders of the upper and lower respiratory tract often coexist:

- 80% of asthmatics have rhinitis—see section on rhinitis and asthma

### 7.7 | Other symptoms

- Snoring, sleep problems, repeated sniffing, nasal intonation of the voice
- Pollen-food syndrome is triggered by ingestion of cross-reacting antigens in some fruits, vegetables and nuts<sup>129</sup>
- A proportion of patients suffering from allergic (mainly seasonal) rhinitis have an associated nasal hyper-reactivity which is generally not recognized/treated

### 7.8 | Family history

A diagnosis of allergic rhinitis is more likely when rhinitis is seasonal, or with a family history of AR. However, it can arise de novo.

### 7.9 | Social history

Consider pets or other contact with animals, occupation or schooling.

### 7.10 | Drugs

A number of drugs can cause or aggravate rhinitis symptoms, and therefore, a drug history should include details of the use of alpha- and beta-blockers and other anti-hypertensives, aspirin and other non-steroidal anti-inflammatory drugs, oral contraceptives as well as topical sympathomimetics (see Table 1). It is also important to enquire about the efficacy of previous treatments for rhinitis and details of how they were used and for how long.

## 8 | EXAMINATION

### 8.1 | Visual assessment

- Allergic salute and/or horizontal nasal crease across dorsum of nose and/or eye involvement supports a diagnosis of allergic rhinitis
- Chronic mouth breathing
- Allergic shiners
- An assessment of nasal airflow—(e.g metal spatula misting in young children)

- Depressed nasal bridge—post surgery, granulomatous polyangiitis or cocaine misuse
- Widened bridge; polyps (see also BSACI guideline on rhinosinusitis and nasal polyposis<sup>130</sup>;
- Purple nasal tip due to sarcoidosis

## 8.2 | Anterior rhinoscopy

- Hypertrophic, pale and boggy inferior or middle turbinates suggest inflammation, but nasal appearance may be normal in AR
- The presence or absence of clear, coloured or purulent secretions
- A deviated septum does not usually cause rhinitis
- The presence or absence of nasal polyps, but it may not be possible to see small ones or if they are confined to the sinuses. Larger polyps can be seen in the nasal vestibule sometimes extending as low as the nares and can be distinguished from the inferior turbinate by their lack of sensitivity, yellow/grey colour and the ability to get between them and the side wall of the nose.
- Yellow submucosal nodules with a cobblestone appearance suggest sarcoidosis.<sup>131</sup>
- Crusting and granulations raise the possibility of vasculitis
- Septal perforation may occur after septal surgery or due to chronic vasoconstriction (cocaine, alpha agonists), granulomatous polyangiitis, anti-phospholipid antibody syndrome and nose picking
- Throat examination-cobblestoned lymphoid hyperplasia, post-nasal drip

## 8.3 | Nasal endoscopy

Used in specialist centres to examine both the anterior and posterior parts of the nasal cavity this is more specific than rhinoscopy and alters the diagnosis in up to a fifth of patients with nasal disease.<sup>132</sup>

## 9 | INVESTIGATIONS

Allergen-specific IgE can be detected with skin prick tests (SPTs) or by serum immunoassay.

### 9.1 | Skin prick tests (SPT)

- Should be carried out routinely to determine if the rhinitis is allergic or non-allergic, and have a high negative predictive value. They should be interpreted in the light of the clinical history
- At least 15% of people with a positive skin prick test do not develop symptoms on exposure to the relevant allergen<sup>133</sup>
- Prick to Prick tests with fresh food can be used to diagnose oral allergy syndrome

### 9.2 | Serum total and specific IgE

Serum-specific IgE may be requested when skin tests are not possible or when the SPT together with the clinical history give equivocal results. Total IgE alone can be misleading but may aid interpretation of specific IgE. Currently available SPTs and allergen-specific IgE show similar sensitivity for house dust mite (HDM), but SPTs are more sensitive to other inhaled allergens such as cat epithelium, mould and grass pollen.<sup>134</sup>

### 9.3 | Laboratory investigations

Usually unnecessary, their use is guided by the history, examination and results of skin prick tests. Examples include:

- Full blood count (FBC) and differential white cell count, C-reactive protein (CRP), immunoglobulin profile, microbiological examination of sputum and sinus swabs when chronic infection is suspected
- Thyroid function tests in unexplained nasal obstruction
- Nasal secretions-asialotransferrin for CSF identification
- Urine toxicology when cocaine abuse is suspected

### 9.4 | Olfactory tests

The University of Pennsylvania Smell Identification Test (UPSIT) is well validated, and can be helpful when there is suspicion of malingering,<sup>135</sup> it is accepted for legal cases.

### 9.5 | Cytology

The techniques for obtaining cells for cytology in secretions, lavage, scraping, cotton buds or brushings have not been standardized, nor have the criteria for evaluating cell counts.<sup>136</sup>

Nevertheless the presence of eosinophils implies inflammation and may be helpful in predicting response to corticosteroids.<sup>137,138</sup>

### 9.6 | Exhaled nitric oxide (eNO)

Exhaled nitric oxide (FeNO=fractional exhaled nitric oxide) measurement can be useful clinically in the diagnosis and monitoring of asthma. Normal levels are less than 20 ppb, but become elevated in eosinophilic lower respiratory tract inflammation.<sup>139</sup>

### 9.7 | Nasal NO

Levels are complex as there are two sources of NO: sinuses and nasal epithelium. However, very low levels (<100 ppb) indicate the likelihood of primary ciliary dyskinesia, but can also be observed in cystic fibrosis and in sinus obstruction caused by large polyps. NO measurements are restricted to specialist centres.

## 9.8 | Radiology

Radiology is not routinely recommended for simple rhinitis. However, when rhinosinusitis or nasal polyposis is suspected, especially non-responsive to medical therapy, CT scan is helpful.

## 9.9 | Nasal challenge

It is not routinely available outside specialist centres; there is no standardized methodology and asthmatic reactions can occur. It may be useful to confirm aspirin sensitivity or in occupational allergic rhinitis, where there is discrepancy between history and when there are potentially important occupational implications.

## 9.10 | Objective measures of nasal airway

Objective measurements of the nasal airway are not made in routine clinical practice but can be useful when allergen or aspirin challenges are undertaken and may be helpful when septal surgery or turbinate reduction are being contemplated.

## 9.11 | Tests for asthma

Measurements of lung function should be considered in all patients with persistent rhinitis.

## 9.12 | ENT referral

Patients with unilateral symptoms, heavily blood stained discharge or pain, require ENT referral. Those with nasal blockage unrelieved by pharmacotherapy or structural abnormalities, such as septal deviation, sufficient to render nasal therapy difficult should be seen by a surgeon.

# 10 | TREATMENT

## 10.1 | Allergen avoidance

Allergen avoidance clearly works in seasonal allergic rhino-conjunctivitis: hayfever sufferers are symptom-free outside the pollen

season. For patients with house dust mite-sensitive AR the situation is complicated by the difficulties of reducing exposure to mites in the home. A systematic review of trials of mite allergen avoidance in rhinitis concluded that trials are generally small and of poor methodological quality and meta-analysis could not be performed.<sup>140</sup> Large studies of a combination of strategies to reduce exposure to dust mites have not been conducted but should probably include measures to reduce mites in cars, at school and work (see Figure 2).

Evidence from randomized studies is summarized in Table 3. For occupational AR complete avoidance of exposure to the causal agent is recommended.<sup>115</sup> Irritants such as smoke, traffic pollution can worsen rhinitis symptoms and should be avoided, where possible.

In a DBRPC study, the application of a cellulose powder (Nasaleze™) three times daily resulted in significant reductions in severity scores for sneezing, runny nose, stuffy nose and symptoms from eyes and lower airways with no clinically significant adverse effects (Grade B).<sup>141</sup>

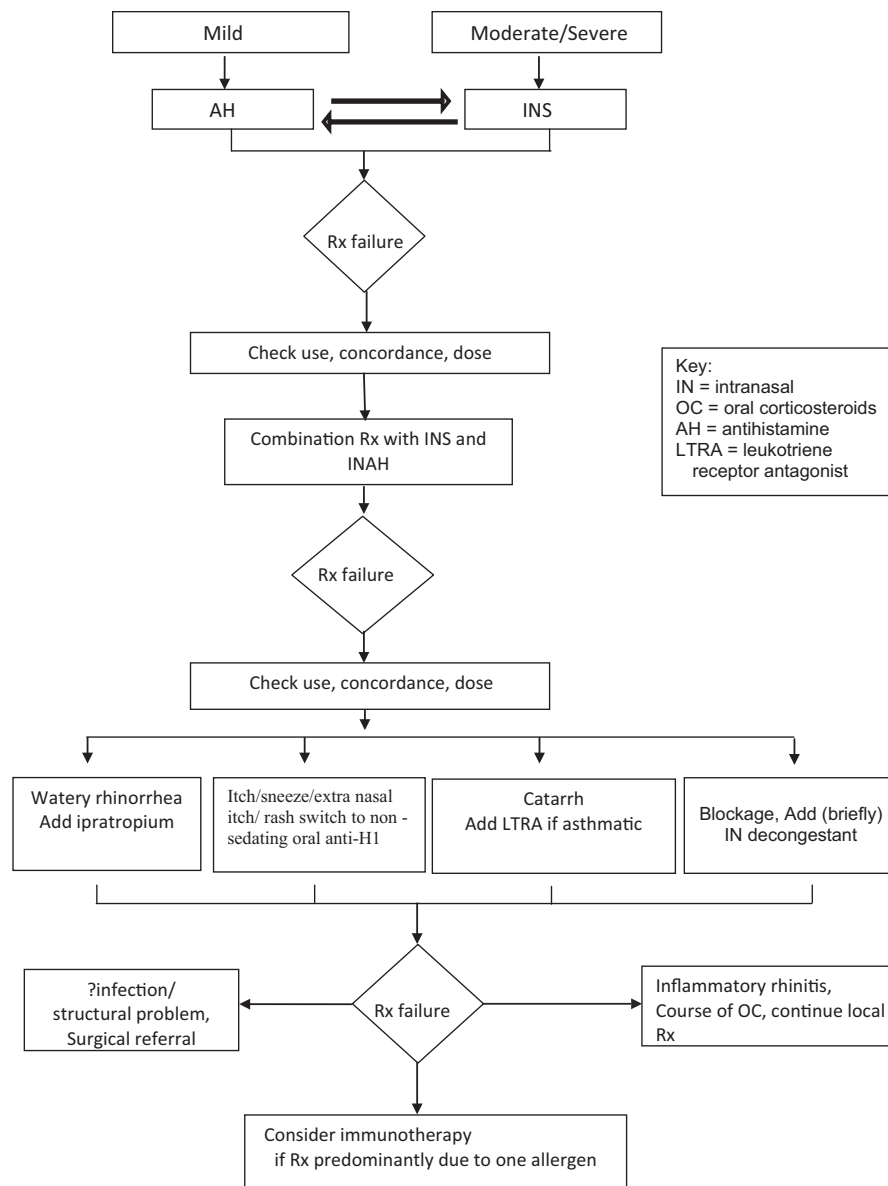
Interventions that may help to reduce symptoms during the pollen season include patients wearing sunglasses (Grade C),<sup>142</sup> nasal filters,<sup>121</sup> balms and ointments applied to the nose.<sup>143</sup> Other practical/common sense measures that may reduce exposure to pollen are summarized in Table 3 but have not been tested in studies.

## 10.2 | Pet allergens

For patients with AR sensitized to and symptomatic on contact with pets such as cats, dogs and horses, avoidance of the animal should be advised. For those who wish to keep pets to which they are sensitized, there is limited information from randomized studies on which to base recommendations<sup>144</sup> HEPA filters alone do not seem useful for cat allergic patients with cats.<sup>145</sup> Cat allergen exposure can be reduced using temperature-controlled laminar airflow treatment,<sup>145</sup> and although this treatment has shown to improve asthma-related quality of life, this has not been tested for rhinitis.<sup>147</sup>

**TABLE 3** Allergen avoidance measures and their effectiveness

House Dust Mite—recommendations from trials	Grade of recommendation
Encase mattress, pillow and duvet in allergen-impermeable fabric	A (against use as a single intervention)
Use of acaricides on carpets and soft furnishing	B
Pollen—Other practical avoidance measures not tested in trials	
Minimizing outdoor activity when pollen is highest (early morning, early evening, during mowing)	D
Avoiding going out during/after thunderstorms	D
Planning holidays to avoid the pollen season.	D
Keeping windows closed (house and car).	D
Shower/wash hair following high exposures	D
Avoid drying washing outdoors when count is high	D



**FIGURE 2** Rhinitis treatment algorithm. Additional therapies can be accomplished using two different medications, or a combination treatment in one device. There is, as yet, no comparative evidence on which to base this choice; however, concordance appears more likely when the regime is simple

### 10.3 | Saline irrigation

Isotonic saline irrigation in both adults and children with allergic rhinitis was well tolerated,<sup>148</sup> inexpensive, easy to use with no evidence of adverse effect to health with regular use.<sup>149,150</sup> It has a small beneficial effect in symptom reduction and may reduce the amount of pharmacotherapy needed (Grade B).

### 10.4 | Carbon dioxide washing

The use of a ten second burst of carbon dioxide from a pressurized container into the nasal airway, with the mouth open, reduces all the

symptoms of rhinitis within minutes. It is now available over the counter for rescue treatment as Serenz.<sup>151,152</sup>

## 11 | PHARMACOTHERAPY

Allergen and irritant avoidance are difficult, and many rhinitis sufferers continue to have persistent symptoms, the nature of which should help determine the selection of medication. Available treatments and their effects upon individual symptoms are detailed in Table 4. All have Grade A level of recommendation. Following diagnosis and classification according to disease severity, therapy using a

stepwise pharmacotherapeutic approach should be undertaken. A combination of treatments is often needed for more severe disease, and it is here that the option of immunotherapy should also be considered (Figure 3).

### 11.1 | Antihistamines

Antihistamines are available as oral, intranasal and ocular preparations.

All demonstrate clinical efficacy. It is important to use a drug with the least adverse effect and that is considered safe for the current situation (i.e such as pregnancy, breastfeeding).

Second-generation antihistamines are long acting and are largely non-sedating and have no clinically significant anti-cholinergic activity at therapeutic doses, although there is variation in individual susceptibility to such effects.<sup>154</sup>

### 11.2 | Oral H1-antihistamines

Reduce mean daily rhinitis symptom scores (in absolute terms) by an estimated 7% versus placebo<sup>155</sup> and can significantly improve quality of life.<sup>156,157</sup>

They act predominantly on neurally mediated symptoms of itch, sneeze and rhinorrhoea and have only a modest effect on nasal congestion.<sup>158-164</sup> Additionally, they reduce histamine driven symptoms such as itch<sup>165</sup> at sites other than just the nose such as conjunctiva, palate and skin.<sup>166-168</sup> They should be used regularly rather than "as needed" use in persistent rhinitis.<sup>169,170</sup> Acrivastine has the fastest onset of action, but needs to be used 8 hourly; fexofenadine is the least sedating oral antihistamine with a wide therapeutic index.

### 11.3 | Adverse effects

First-generation antihistamines are less useful due to sedation and cognitive impairment, which can worsen driving and examination results already impaired by rhinitis.<sup>171,172</sup> Their use is not recommended. Antihistamines with an anticholinergic effect are associated with development of dementia.<sup>173</sup>

#### 11.3.1 | Second-generation antihistamines

Terfenadine and astemizole were implicated in deaths from ventricular fibrillation via QT interval prolongation.<sup>174</sup> Ebastine and mizolastine also need to be used with caution in those with cardiac risk factors,<sup>175</sup> but even cetirizine, desloratadine, diphenhydramine, fexofenadine, loratadine were possibly associated with cardiac arrhythmias in a single large European pharmacovigilance study.<sup>176</sup>

Interaction with other medications is rare other than for mizolastine with certain anti-arrhythmics, antibiotics and beta-blockers leading to an increased risk of arrhythmia. Rupatadine should not be coprescribed with known CYP3A4 inhibitors.<sup>177</sup>

### 11.4 | Place in therapy

- First-line therapy for mild-to-moderate intermittent and mild persistent rhinitis
- Addition to intranasal steroids for moderate/severe persistent rhinitis uncontrolled on topical intranasal corticosteroids alone, particularly when eye symptoms are present.<sup>178-180</sup> Evidence for this combination is less good than for the addition of intranasal antihistamine to topical intranasal corticosteroids in a guinea-pig model.<sup>181</sup>

**TABLE 4** Pharmacotherapy effects on individual rhinitis symptoms (adapted from 152)

	Sneezing	Rhinorrhea	Nasal obstruction	Nasal itch	Eye symptoms
<b>H1-antihistamines</b>					
Oral	++	++	+	+++	++
Intranasal	++	++	+	++	0
Eye drops	0	0	0	0	+++
<b>Corticosteroids</b>					
Intranasal	+++	+++	++	++	++
<b>Chromones</b>					
Intranasal	+	+	+	+	0
Eye drops	0	0	0	0	++
<b>Decongestants</b>					
Intranasal	0	0	++++	0	0
Oral	0	0	+	0	0
Anti-cholinergics	0	++	0	0	0
Anti-leukotrienes	0	+	++	0	++
Intranasal steroids and Intranasal antihistamine 1	+++	+++	+++	+++	+++

## 11.5 | Topical H1-antihistamines

### 11.5.1 | Nasal

These are superior to oral antihistamines in attenuating rhinitis symptoms,<sup>182</sup> and in decreasing nasal obstruction,<sup>183,184</sup> although they do not improve symptoms due to histamine at other sites, such as skin. There is a rapid onset of action (15 minutes), faster than oral antihistamines,<sup>185</sup> thus, the drug can be used on demand as rescue therapy for symptom breakthrough. Continuous treatment is, however, more clinically effective than on demand use.<sup>186</sup> They can be effective in patients who have previously failed oral antihistamines.<sup>187</sup> Treatment with both an intranasal and oral antihistamine confers no additional advantage in alleviating nasal symptoms.<sup>187</sup> They are less effective than an intranasal steroid in relieving the symptoms of allergic rhinitis.<sup>188</sup>

Adverse effects include local nasal irritation and taste disturbance with Azelastine (dysgeusia). Azelastine nasal spray is the only available intranasal antihistamine in the UK.

### 11.5.2 | Place in therapy

This is the first line of therapy for mild-to-moderate intermittent and mild persistent rhinitis.

Intranasal steroids used for moderate/severe persistent rhinitis which are not controlled on topical intranasal corticosteroids alone.

## 12 | CORTICOSTEROID THERAPY

### 12.1 | Intranasal corticosteroids (INS)

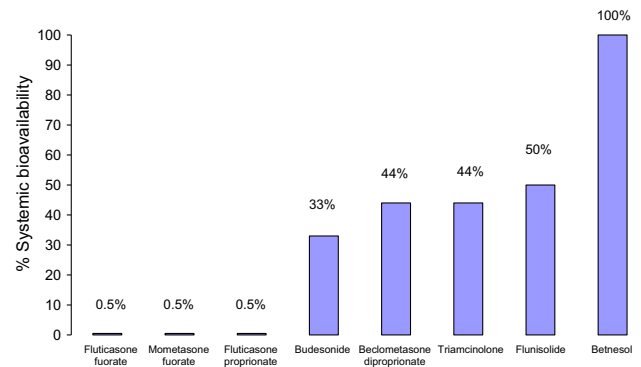
Topical corticosteroids are the mainstay of anti-inflammatory intervention in AR. Factors which need consideration are systemic drug bioavailability, safety and cost.<sup>189</sup> Ease of device use may influence concordance. INS reduces all symptoms of rhinitis by about 17% more than placebo, with a variable effect on associated allergic conjunctivitis.<sup>190,191</sup> Meta-analysis shows that INS is superior to oral antihistamines or leukotriene receptor antagonist alone on all aspects of allergic rhinitis<sup>155,192</sup> (Grade Ia).

Unlike other treatments, INS reduce nasal congestion.<sup>192</sup> Onset of action is 6-8 hours after the first dose, clinical improvement may not be apparent for a few days and maximal effect may not be apparent until after two weeks.<sup>192</sup> Starting treatment two weeks prior to a known allergen season improves efficacy.<sup>193</sup> Similar clinical efficacy for all INS, but bioavailability varies considerably (see Figure 3).

Systemic absorption negligible with mometasone furoate, fluticasone furoate and fluticasone propionate and these preparations are favoured for children. Systemic absorption is modest for the remainder, and high for betamethasone which should be used short-term only.<sup>194,195</sup>

### 12.2 | Adverse events

Local nasal irritation, sore throat and epistaxis affect around 10% of users. Benzalkonium chloride is used as a preservative in several topical



**FIGURE 3** Bioavailability of intranasal corticosteroids. The more recent molecules have little systemic uptake and are suitable for use in children and for long-term therapy (Grade A evidence)

corticosteroids, and may irritate the nose, but does not adversely affect mucociliary clearance.<sup>196</sup> In patients with nasal irritation symptoms such as burning, for example, a trial with a benzalkonium free preparation, for example rhinocort, flixonase nasules are suggested. Reduction of local adverse effects such as nasal crusting, bleeding and pain can be achieved in many cases by correct use of the intranasal device, see Figure 4a; (Grade of recommendation=D). Nasal drops are useful for severe obstruction and should be used in the “head upside down” position to reach the ostiomeatal complex (OMC), see Figure 4b.

Hypothalamic-pituitary axis suppression may occur when multiple sites are treated with topical corticosteroids in the same person (e.g skin, nose and chest).<sup>197</sup> If corticosteroids are used in multiple sites, then a low bioavailability preparation should be favoured.

Raised intra-ocular pressure has been described with INS<sup>198</sup> thus limiting its use in patients with predisposition to high ocular pressure/glaucoma is important.

### 12.3 | Place in therapy

First-line therapy for moderate-to-severe persistent symptoms.<sup>14</sup> First line of therapy if presenting with severe nasal obstruction,<sup>192</sup> possibly combined with a short-term nasal decongestant. In severe nasal obstruction steroid drops or oral steroids should be used initially for up to one week. For oral or topical antihistamines in uncontrolled rhinitis—see below.

## 13 | COMBINATION THERAPY

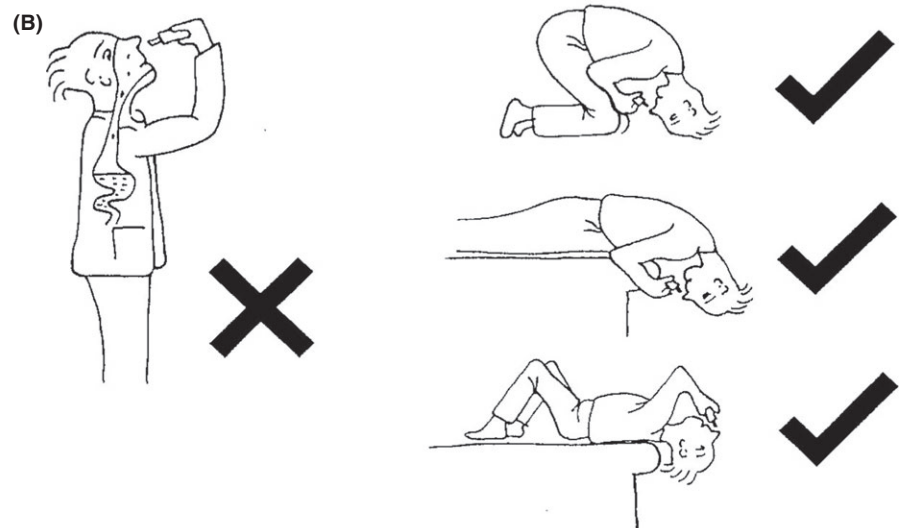
### 13.1 | INS and oral preparations

INS demonstrate similar or greater efficacy to an oral antihistamine plus a leukotriene receptor antagonist<sup>199,200</sup> (see Appendix A2).

### 13.2 | INS and topical H1-antihistamine combination

Currently available as a combination spray containing azelastine and fluticasone propionate (FP), dymista leads to greater symptom

- (A)
1. Shake bottle well
  2. Look down
  3. Using right hand for left nostril put nozzle just inside nose aiming towards outside wall
  4. Squirt once or twice (2 different directions ↗ → )
  5. Change hands and repeat for other side
  6. Breathe in gently through the nose
  7. Do not sniff



**FIGURE 4** (A and B) How to use a nasal spray and nasal drops Evidence grade D

improvement than using either agent alone in SAR (Grade A).<sup>201</sup> All symptoms of allergic rhinitis were significantly improved with onset of action by 30 minutes.<sup>202</sup> The combination approach leads to clinical improvement of symptoms days earlier than seen with azelastine or FP monotherapy.<sup>201</sup> Ocular symptoms of allergy were better treated with the combination spray rather than FP or azelastine alone.<sup>202</sup> Efficacy over FP is demonstrated in perennial allergic rhinitis.<sup>203</sup>

### 13.3 | Adverse effects

The main side-effect is the bitter taste of azelastine, which is experienced by a small proportion of users.

### 13.4 | Place in therapy

Combination of topical AH with INS should be used in patients when symptoms remain uncontrolled on AH or INS monotherapy or on a combination of oral AH plus INS.

### 13.5 | Systemic glucocorticoids

There are no trials of oral steroid use and efficacy in AR, although there is grade A evidence in chronic rhinosinusitis with nasal polyposis where inflammation is more severe. Use is rarely indicated in the management of allergic rhinitis except for:

## 14 | SEVERE NASAL OBSTRUCTION

In order to obtain control, short-term rescue medication is used during severe exacerbation despite compliance on conventional pharmacotherapy. It is important to ensure intranasal steroid therapy is co-administered alongside oral steroids with or without a short-term decongestant spray to allow intranasal drug penetration (see below). There is no definite consensus on the dose and duration of systemic steroid therapy. A suggested regime for adults is 0.5 mg per kg for



5-10 days. Oral preparations of steroids as a short course are recommended over depot injectable preparations, which cannot be removed if adverse effects occur. Frequent oral steroid rescue should prompt immunotherapy as a treatment option.

#### 14.1 | Injectable corticosteroids

Injected preparations are not recommended as compared to other available treatments the risk-benefit profile for intramuscular corticosteroids is poor.<sup>204,205</sup>

#### 14.2 | Intranasal decongestants

Topical formulations allow relief of nasal congestion via vasoconstriction within minutes, faster and with greater impact than intranasal steroids.<sup>206,207</sup> A decongestant spray may allow delivery of intranasal drugs beyond the inferior turbinates. For example, oxymetazoline and fluticasone furoate when used together further improved nasal congestion more than either alone.<sup>207</sup> There is no licensed INS plus decongestant combination preparation in the UK at present.

#### 14.3 | Adverse events

Only short-term use (generally fewer than 10 days) is recommended as a paradoxical increase in nasal congestion secondary to rebound vasodilatation (rhinitis medicamentosa) can occur.<sup>208</sup> The risk of this occurrence increases with duration of 3-5 days maximum.<sup>209,210</sup> Intranasal decongestants are less likely to lead to rhinitis medicamentosa when used short-term and alongside an intranasal steroid.<sup>210</sup> They can also cause nasal irritation and may increase rhinitis.

#### 14.4 | Place in therapy

- Eustachian tube dysfunction when flying (evidence level D)
- To increase nasal patency before douching (Grade D) or intranasal administration of nasal steroids<sup>211</sup>

#### 14.5 | Oral decongestants (pseudoephedrine)

- Weakly effective in reducing nasal obstruction<sup>212</sup> and have many side-effects, so are not recommended.<sup>213</sup>

#### 14.6 | Anti-leukotrienes

These have a therapeutic profile similar to antihistamines, with efficacy comparable to loratadine in seasonal allergic rhinitis,<sup>214</sup> and are less effective than topical nasal corticosteroids.<sup>214-217</sup> The response is less consistent than that observed with antihistamines.<sup>218-220</sup> LTRAs reduce the mean daily rhinitis symptom scores by 5% more than placebo.<sup>155</sup>

Combination of anti-leukotriene plus antihistamine has no advantage over either drug used alone<sup>221-224</sup> and is not any more effective

than topical corticosteroid alone.<sup>198,224</sup> Anti-leukotrienes may have a place in asthma patients with seasonal allergic rhinitis.<sup>226</sup>

#### 14.7 | Adverse events

They are usually well tolerated; occasional headache, gastrointestinal symptoms or rashes. Neuropsychiatric manifestations have been reported in children, especially adolescents. There is a possible causal link between LTRA use and eosinophilic polyangiitis.<sup>227,228</sup>

#### 14.8 | Place in therapy

Montelukast is licensed in the UK for those with seasonal allergic rhinitis who also have concomitant asthma (UK licence for age > 6 months; Zafirlukast UK licence > 12 years).

### 15 | TOPICAL ANTI-CHOLINERGIC

#### 15.1 | Ipratropium bromide

Used three times daily it decreases rhinorrhoea (particularly if neurogenic rather than inflammatory origin) but has no effect on other nasal symptoms.<sup>19,229-231</sup> Regular use may be effective as an "add-on" for allergic rhinitis when watery rhinorrhoea persists despite topical steroids and antihistamines.<sup>229,232</sup>

#### 15.2 | Adverse events

Dry nose and epistaxis,<sup>145</sup> systemic anti-cholinergic effects are unusual.<sup>233,234</sup> Caution is advised in the elderly in whom periodic revisions of its requirement may have to be instigated.

#### 15.3 | Place in therapy

Patients with watery rhinorrhoea despite compliance with INS or INS plus antihistamine

### 16 | CHROMONES (SODIUM CROMOGLYCATATE (=CROMOLYN) AND NEDOCROMIL SODIUM)

Sodium cromoglycate and nedocromil sodium inhibit the degranulation of sensitized mast cells, inhibiting the release of mediators.<sup>235</sup> Sodium cromoglycate is weakly effective in rhinitis with some effect on nasal obstruction.<sup>236,237</sup> The spray needs to be used several times (3-4× up to 6×) per day.

#### 16.1 | Adverse events

Generally very well tolerated (including in pregnancy) but these include local irritation, taste disturbance and headache.

## 16.2 | Place in therapy

- Children and adults with mild symptoms only and sporadic problems in season or on limited allergen exposure.<sup>238</sup> Useful for individuals unable to take other medications, for example pregnant females.
- Cromoglycate and nedocromil eye drops are useful in conjunctivitis as topical therapy.<sup>236,239</sup>

## 17 | OCULAR THERAPY

Sunglasses reduce eye symptoms,<sup>142</sup> but as these can occur reflexively secondary to nasal inflammation complete protection is impossible. The ocular manifestations of seasonal rhinoconjunctivitis can often be suppressed by oral antihistamines, usually H1 receptor antagonists, and by intranasal agents, including corticosteroids, antihistamines and combination products. However, they are often better treated using topical eye drops. Mast cell stabilisers such as sodium cromoglycate, nedocromil sodium and lodoxamide are generally effective and safe.<sup>239</sup> Antihistamines such as azelastine, emedastine and epinastine may be preferred by some patients.<sup>240</sup> A drug with both mast cell stabilising and antihistaminic properties, olopatadine, is often effective and well tolerated, and has the advantage of twice daily application, which particularly suits contact lens wearers. Some patients find that tear supplement drops ("artificial tears") provide a good measure of symptomatic relief. Topical steroids are effective in suppressing inflammation but can have potentially sight-threatening adverse effects including ocular hypertension/glaucoma, cataract and the enhancement of infection.

If indicated, for example vernal conjunctivitis,\* use should be supervised by an ophthalmologist. Immunotherapy, where indicated, is effective for ocular symptoms.

## 18 | IMMUNOTHERAPY

Allergen immunotherapy can improve symptoms, reduce medication requirements and improve quality of life.<sup>241-243</sup>

### 18.1 | Subcutaneous injection immunotherapy (SCIT)

SCIT is effective for both seasonal rhinitis due to pollens (Cochrane meta-analysis<sup>244</sup> evidence level 1++) and perennial rhinitis due to house dust mite,<sup>245</sup> evidence level 1+). There are few randomized

\*Vernal keratoconjunctivitis is a rare allergic disorder of children, especially atopic boys. Its complex immunopathology involves raised IgE levels, mast cells, eosinophils and other inflammatory cells in the conjunctival epithelium. Seasonal exacerbations are common (hence the name), but if severe the disease can be active year round. The condition is sight-threatening because the corneal epithelium is under attack from the products of immune reactions in the conjunctiva. Topical steroid therapy is usually needed, and this too has sight-threatening aspects.

controlled trials of immunotherapy for cat allergy,<sup>246,247</sup> (level 1) SCIT requires weekly up-dosing regimens followed by 4-6 weekly maintenance injections for 3-5 yr. Pre-seasonal SCIT is effective for pollen allergy. In view of the risk of systemic side-effects SCIT should only be given in specialist clinics by trained personnel with immediate access to adrenaline and resuscitation facilities.<sup>248</sup>

### 18.2 | Sublingual Immunotherapy (SLIT)

SLIT has emerged as an effective and safe alternative for the treatment of allergic rhinitis with/without seasonal asthma<sup>242</sup> due to grass pollen<sup>249-255</sup> ragweed,<sup>256,257</sup> evidence level 1++) and house dust mite (evidence level 1).<sup>249,258</sup>

Sublingual immunotherapy is well tolerated, with side-effects largely confined to local itching and swelling in the mouth and throat. After supervision of the first dose by the prescribing physician with a one-hour period of observation, SLIT is self-administered daily at home.

SLIT has an excellent safety record, although there are case reports of systemic reactions and of eosinophilic oesophagitis, but no deaths have been reported. Oral antihistamine given prior to SLIT initiation and for the first two weeks of the course of therapy can reduce local oral irritation (level D).

### 18.3 | Long-term benefits

Immunotherapy is the only treatment that can modify the course of allergic rhinitis, with long-term remission following discontinuation.<sup>259-261</sup> Subcutaneous immunotherapy in children with seasonal rhinitis reduces progression to asthma, an effect that persisted for 10 years.<sup>262</sup> Immunotherapy may prevent development of new sensitizations.<sup>263,264</sup>

### 18.4 | Place in rhinitis therapy

Allergen immunotherapy within the United Kingdom is recommended in patients with a history of symptoms on allergen exposure and objective confirmation of IgE sensitivity (skin prick test positive and/or elevated allergen-specific IgE) in the following circumstances<sup>265</sup>:

1. Seasonal pollen induced rhinoconjunctivitis in patients whose symptoms persist despite maximal drug therapy (combinations of intranasal corticosteroid and antihistamine taken regularly) (Evidence level 1++, category A). The choice of SCIT or SLIT is based largely on patient preference as there are no adequately powered head-to-head comparative trials
2. Perennial allergic rhinoconjunctivitis in patients with an allergy to house dust mite who respond inadequately to anti-allergic drugs and where the allergen is not easily avoided (e.g veterinary surgeons and public sector workers)

## 19 | COMPLEMENTARY THERAPIES

The levels of evidence for all complementary therapies, including acupuncture, herbal medicine, phototherapy and homoeopathy are not considered sufficient for recommendation for clinical use at present.

## 20 | TREATMENT OF NAR

Evidence quality from trials is reduced by inadequate patient selection, which is often based solely on negative skin prick tests, without elucidation of NAR phenotypes. A search to identify knowledge gaps and research needs in a database is being undertaken by a working party of the American Academy of Asthma, Allergy and Clinical Immunology and their full report are awaited. Present conclusions, based on a search of literature from 1960 to 2010 and using 40% of 2000 articles, (personal communication), suggests the following:

### 20.1 | Intranasal ipratropium

This is effective for watery rhinorrhoea (level 1b; Bronsky et al.<sup>234</sup>,<sup>266-278</sup>

### 20.2 | Topical capsaicin

Desensitization reduced symptoms for several months in non-allergic, non-infectious rhinitis, NINAR.<sup>279-281</sup>

### 20.3 | Topical corticosteroids

Topical corticosteroids have an effect in skin prick test-negative rhinitis patients (level 1b), probably on those with underlying inflammation, since studies give variable results,<sup>282-286</sup> and relief was limited in subjects with low levels of nasal eosinophils in a recent study.<sup>287</sup>

### 20.4 | Topical nasal antihistamines

Azelastine and olopatadine<sup>288-291</sup> (level 1b) and a combination of azelastine with fluticasone (level 3) reduced symptoms in skin prick test-negative patients over one year.<sup>203</sup>

Decongestants and oral antihistamines are ineffective.

### 20.5 | Montelukast

It has not been formally trialled in NAR but low quality studies<sup>224</sup> suggest a possible effect in SP-negative patients.

TRPV1 was considered a prime target for neurogenic rhinitis therapy, but a recent study proved negative when cold dry air challenges were used,<sup>292</sup> but antagonism did reduce the response to capsaicin.<sup>293</sup>

### 20.6 | Aspirin desensitization

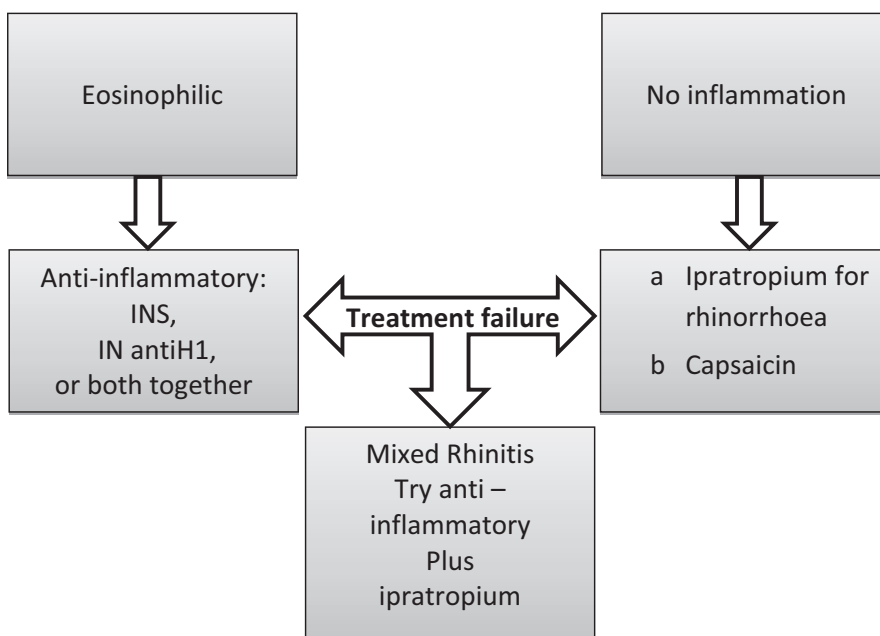
This may be effective in those with aspirin-sensitive NAR, but should be preceded by nasal or oral aspirin challenge to establish the diagnosis.<sup>294-297</sup> A suggestion for NAR therapy is given in Figure 5.

## 21 | SURGERY

Surgery is offered in only a minority of cases. The indications for surgical intervention are as follows:

1. Anatomical variations of the septum with functional relevance.<sup>298</sup>
2. Drug-resistant inferior turbinate hypertrophy [Poor objective evidence to support this indication other than in the short-term].

There are no well-conducted (prospective and randomized) studies supporting the use of coblation, laser or surgery to the inferior turbinates in patients with rhinitis which demonstrate benefit, supported by objective measurements, other than in the short-term. Studies of this nature show that surgery to the inferior turbinate does not confer any lasting benefit.<sup>299</sup> If in future trials of surgery are to be done it would seem that, in the first instance, they should be limited to patients who have failed to respond to medical treatment given the evidence that is currently available for the benefit



**FIGURE 5** Treatment of non-allergic rhinitis. Therapy in NAR depends upon the phenotype. The division into those with and without nasal inflammation can be made on the basis of nasal smears. Those with inflammation may respond to anti-inflammatory therapy, although less well than in AR and higher INS doses and combinations of therapy may be needed. If these fail a nasal aspirin challenge could be undertaken, followed by desensitization if positive.<sup>295,296</sup> Non-inflammatory NAR may respond to anti-cholinergic therapy or to capsaicin. Some patients require both anti-inflammatory and anti-neurogenic treatments. (Grade D evidence)

that concordant medical treatment provides in the majority of patients.

## 22 | ASSESSMENT OF RHINITIS CONTROL

Since 2001, the ARIA patient classification system for allergic rhinitis has been used in both clinical and research settings. It focuses on patient symptoms, their time patterns (either “intermittent” or “persistent”) and their severity (“mild” vs “moderate/severe”) and is a simple and quick to administer tool (Figures 6, 7, 8).

In response to a World Health Organisation endorsed trend, disease control rather than severity is considered a preferable metric to measure and monitor. Three rigorously developed and validated assessments are available (Control of Allergic Rhinitis and Asthma Test (CARAT),<sup>300</sup> Rhinitis Control Assessment Test (RCAT)<sup>301,302</sup> and Allergic Rhinitis Control Test (ARCT).<sup>303</sup> More recently the simple and quick MACVIA visual analogue scale has been developed.<sup>304</sup> To date, there has been no head-to-head comparison of these tools so it is not possible to rank their utility and validity.

## 23 | SEVERE CHRONIC UPPER AIRWAY DISEASE (SCUAD)

SCUAD is a recently adopted term that defines those patients whose symptoms are inadequately controlled despite (i.e guideline directed, safe and acceptable) pharmacological treatment based on guidelines.<sup>305</sup> Severe uncontrolled allergic rhinitis, of whatever aetiology, can be classified as SCUAD which affects 18.5% of allergic rhinitis patients. It is important to differentiate between this situation, and those patients who are symptomatic because they are incorrectly treated or have poor adherence. The pathophysiology, genotype-phenotype relationships and natural history of SCUAD are currently poorly understood.

## 24 | IMPROVING PATIENT ADHERENCE IN RHINITIS

Poor adherence is a challenge in the management of allergic and non-allergic rhinitis, just as it is in other chronic diseases where generic estimates of non-adherence range from 30 to 60% and from 50 to 80% for preventive measures.<sup>306</sup>

There are few very few “real life” studies of adherence in rhinitis to antihistamines and nasal corticosteroids, and there are no data available for adherence with intranasal anti-cholinergics and cromolyn.<sup>307</sup> Adherence to specific immunotherapy (SIT) has been documented in greater detail with estimates for compliance with subcutaneous (SCIT) regimes ranging from 33 to 89%, and the reasons for discontinuation being time taken. Sublingual therapy adherence rates range from 44 to 97% initially, but discontinuation rates are high with fewer than 20% of patients progressing to the third year of therapy. The frequency of follow-up visits, perception of poor efficacy and cost contribute to these high rates of attrition.<sup>307</sup>

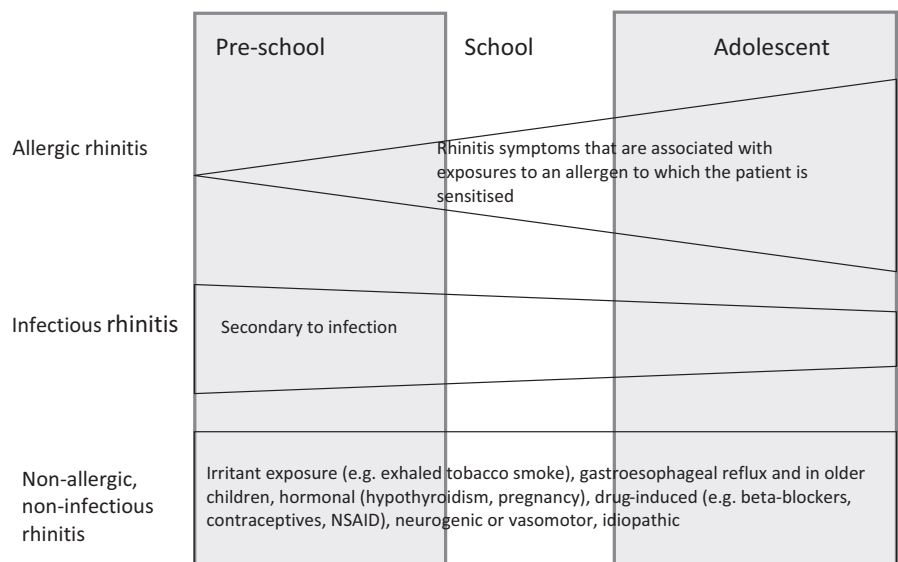
Unlike some chronic disorders, there has been little effort expended to date in understanding and improving adherence in rhinitis; however, there is evidence to support the importance of:

### 24.1 | Frequent monitoring visits for SLIT

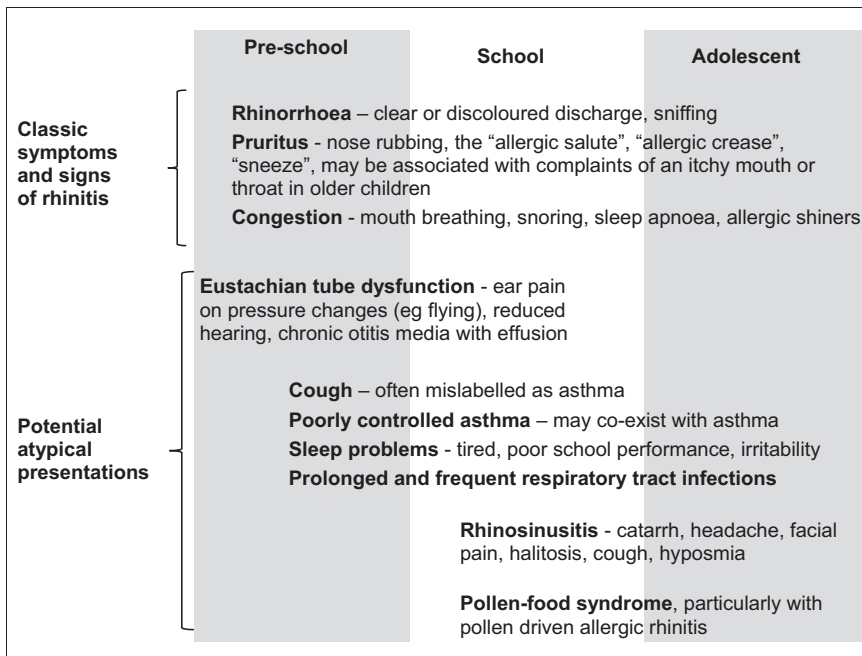
Paediatric patients who were reviewed at three monthly intervals were significantly more adherent than those reviewed twice or once a year.<sup>308</sup>

### 24.2 | Enhanced patient education

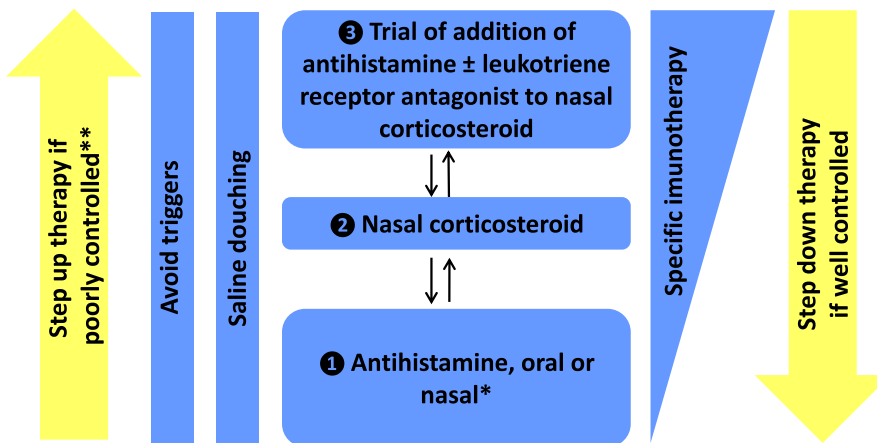
A 3-hour educational programme together with written information achieved greater compliance than standard oral instruction.<sup>309</sup>



**FIGURE 6** Rhinitis in children, with permission from EAACI



**FIGURE 7** Recognition of rhinitis in children at different ages, with permission from EAACI



**FIGURE 8** Approach to therapy for paediatric allergic rhinitis

## 25 | RHINITIS IN PREGNANCY AND DURING BREASTFEEDING

Rhinitis affects at least 20% of pregnancies<sup>310,311</sup> and can start during any gestational week.<sup>310,312</sup> Although the pathogenesis is multifactorial, nasal vascular engorgement and placental growth hormone are likely to be involved.<sup>312,313</sup> Rhinitis patients have higher levels of oestrogen and IGF1 during the third trimester. Rhinitis in pregnancy may not be adequately treated during routine antenatal care, and patients benefit from a multidisciplinary approach.<sup>310</sup> Rhinitis in pregnancy impacts negatively on quality of life, especially during the third trimester and women with pre-existing allergic rhinitis are more severely affected.<sup>314</sup> Informing the patient that pregnancy-induced rhinitis is a self-limiting condition is often reassuring. Women developing rhinitis during pregnancy are more likely to deliver female babies,<sup>315</sup> and children of mothers developing rhinitis

in early pregnancy are more likely to develop rhinitis themselves.<sup>316</sup>

During pregnancy, most medications cross the placenta, and should only be prescribed when the apparent benefit is greater than the risk to the foetus.<sup>317</sup> Nasal lavage is safe and effective in pregnant women, reducing the need for antihistamines.<sup>318</sup> Chromones have not shown teratogenic effects in animals and are the safest drug recommended in the first 3 months of pregnancy, although they require multiple daily administrations. The safety of nasal steroids in pregnancy has not been established through clinical trials. Only minimal amounts of steroid pass into the bloodstream after using a nasal spray and it is good practice to treat with “tried and tested” drugs.<sup>317</sup> Beclomethasone, FP and budesonide have good safety records and are widely used in pregnant asthmatic women of these fluticasone has least systemic bioavailability when used nasally.<sup>319-321</sup>

There is considerable clinical experience with chlorphenamine, loratadine and cetirizine in pregnancy, which may be used in addition, but decongestants should be avoided.<sup>322,323</sup> Patients already on immunotherapy may continue if they have already reached the maintenance phase, but each case must be considered individually. The initiation of immunotherapy and up-dosing is contraindicated.<sup>311</sup> Similar recommendations can be made about the treatment of AR during lactation. Nasal lavage is safe to use, whilst breastfeeding. Nasal administration of sodium cromoglycate is not known to have any harmful effects when used by breastfeeding mothers. Antihistamines and nasal steroids should only be used when the clinical imperative outweighs the potential harm to the child. Antihistamines are excreted in breastmilk and, although not known to be harmful, the manufacturers of most antihistamines advise avoidance, whilst breastfeeding. Chlorphenamine may cause drowsiness and poor feeding in the baby. Both loratadine<sup>324</sup> and cetirizine appear safer with low levels found in breastmilk.<sup>325</sup> The lowest dose should be used for the shortest duration.

## 26 | RHINITIS IN CHILDREN

Acute viral rhinitis is common and usually easy to distinguish. It peaks during the winter. The frequency of episodes varies with age, birth order and degree of day-care exposure. Between 1 and 10 episodes per year is usual, with a peak between 6 months and 6 years of age. Thereafter, 1-2 episodes per year, occurring mainly during the winter<sup>326</sup> retained foreign body, nasal septum deviation, unilateral choanal atresia, cerebrospinal fluid leak and nasal polyposis can all present with rhinitis. Chronic infective rhinitis (rhinosinusitis) (>3 months), particularly if severe, can be a manifestation of underlying pathologies such as primary ciliary dyskinesia, cystic fibrosis or antibody deficiency. Allergic rhinitis affects 3% of 4 year olds, increasing to 27% of 18 year olds (Figure 6).<sup>327</sup>

Allergic rhinitis in early childhood is a risk factor for developing asthma in later childhood and adulthood.<sup>328,329</sup> It has a significant impact on children's quality of life and can have detrimental effects on sleep, behaviour, school performance and family dynamics.<sup>171</sup> It often presents alongside other atopic disorders, asthma and eczema and food allergy. Its presentation may be influenced by co-morbidities, such as conjunctivitis, impaired hearing, rhinosinusitis, sleep problems and pollen-food syndrome<sup>330</sup> (Figure 7).

Entopy (local allergic rhinitis), diagnosed by nasal allergen challenge, is found in children (level D).<sup>331,332</sup>

- The approach to diagnosis in children is similar to that in adults: history, skin prick test and anterior rhinoscopy
- Entopy (local allergic rhinitis), diagnosed by nasal allergen challenge is found in this age group (level D)<sup>331,333</sup>
- Therapy of rhinitis in children is based on the same principles as in adults; however, it should take into account specific paediatric needs, such as acceptability, practicality for both children and parents and concern for potential side-effects (Figure 8)

- Nasal saline irrigation is effective in the treatment of AR in children<sup>149,334</sup>
- Brief concomitant use (3 days) of topical decongestants can be helpful in children with significant nasal blockage to aid introduction of topical nasal steroid therapy
- Recommendation for continuous use of intranasal steroids can often create anxiety in parents; intranasal steroids with low bio-availability have a better safety profile at recommended doses and should be used in preference (Figure 4)<sup>335,336</sup>
- It is advisable to monitor growth in children, especially if they are receiving steroids by multiple routes<sup>335</sup> (see also Table 3)
- A short course (3 to 7 days) of oral corticosteroids may be required in severe cases. Intramuscular steroids have no role in the treatment of AR
- Immunotherapy is recommended in subjects who have not adequately responded to maximal pharmacotherapy; the potential added benefit in disease prevention should be considered when treating children<sup>337,338</sup>
- Education on therapy plays an important role on treatment outcome. Both children and carers should be provided with the relevant information and appropriate training<sup>339</sup>
- Otitis media with effusion and/or adenoidal hypertrophy may be associated with AR; the mechanistic link is unknown. Some studies suggest benefit to these common paediatric conditions from rhinitis treatment<sup>340</sup>

## 27 | QUALITY OF LIFE QUESTIONNAIRES FOR RHINITIS

The burden of rhinitis for an individual patient can be estimated using Patient-Reported Outcome Measures (PROMs). Generic PROMs such as the EQ-5D allow a comparison between different diseases and are particularly useful when calculating the incremental cost of new treatments. However, a disease-specific validated quality of life (QoL) questionnaire is more sensitive when assessing severity of disease and response to treatment. In routine clinical practice, the use of such tools allows greater focus on symptoms important to the patient.

Commonly used and validated quality of life disease-specific scoring systems include the RQLQ for allergic rhinitis and rhino-conjunctivitis, the SNOT-22 or RSOM-31 in chronic rhinosinusitis and a modified SNOT-16 in acute rhinosinusitis.

## 28 | FUTURE RESEARCH

### 28.1 | AR

- Prevention of AR development: for example environmental changes, use of synbiotics
- Adoption of single unified scheme for assessing rhinitis control

- Prevention of progression from AR to asthma: confirmation of effect of immunotherapy, investigation of AR well-controlled by pharmacotherapy
- Reduction of proportion of SCUAD sufferers by combination therapies

## 28.2 | NAR

Prevalence—accurate figures needed

## 28.3 | Endotypes

Trials of therapy in well-selected endotypes

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This guideline is the revised edition for the management of allergic and non-allergic rhinitis. Adherence to this guideline does not constitute an automatic defence for negligence, and conversely non-adherence is not indicative of negligence. It is anticipated that this guideline will be reviewed 5 yearly.

## REFERENCES

1. Laforest L, Bousquet J, Pietri G, et al. Quality of life during pollen season in patients with seasonal allergic rhinitis with or without asthma. *Int Arch Allergy Immunol*. 2005;136:281-286.
2. Blaiss MS. Allergic rhinitis and impairment issues in schoolchildren: a consensus report. *Curr Med Res Opin*. 2004;20:1937-1952.
3. Cockburn IM, Bailit HL, Berndt ER, Finkelstein SN. Loss of work productivity due to illness and medical treatment. *J Occup Environ Med*. 1999;41:948-953.
4. Blaiss MS. Cognitive, social, and economic costs of allergic rhinitis. *Allergy Asthma Proc*. 2000;21:7-13.
5. Hom MM, Bielory L. The anatomical and functional relationship between allergic conjunctivitis and allergic rhinitis. *Allergy Rhinol (Providence)*. 2013;4:e110-e119.
6. Slavin RG. Complications of allergic rhinitis: implications for sinusitis and asthma. *J Allergy Clin Immunol*. 1998;101 Pt 2:S357-S360.
7. Doyle WJ. The link between allergic rhinitis and otitis media. *Curr Opin Allergy Clin Immunol*. 2002;2:21-25.
8. Passalacqua G, Ciprandi G, Pasquali M, Guerra L, Canonica GW. An update on the asthma-rhinitis link. *Curr Opin Allergy Clin Immunol*. 2004;4:177-183.
9. Barry B. Rhino-sinus manifestations of systemic diseases. *Rev Prat*. 2000;50:1548-1550.
10. Clatworthy J, Price D, Ryan D, Haughney J, Horne R. The value of self-report assessment of adherence, rhinitis and smoking in relation to asthma control. *Prim Care Respir J*. 2009;18:300-305.
11. Thomas M, Kocevar VS, Zhang Q, Yin DD, Price D. Asthma-related health care resource use among asthmatic children with and without concomitant allergic rhinitis. *Pediatrics*. 2005;115:129-134.
12. British Thoracic Society. British guideline on the management of asthma. *Thorax*. 2003;58(Suppl 1):i1-i94.
13. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. *BMJ*. 1999;318:593-596.
14. Bousquet J, Van CP, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol*. 2001;108(5 Suppl):S147-S334.
15. Demoly P, Allaert FA, Lecasble M, Bousquet J. Validation of the classification of ARIA (allergic rhinitis and its impact on asthma). *Allergy*. 2003a;58:672-675.
16. Leone C, Teodoro C, Pelucchi A, et al. Bronchial responsiveness and airway inflammation in patients with nonallergic rhinitis with eosinophilia syndrome. *J Allergy Clin Immunol*. 1997;100 Pt 1:775-780.
17. Garay R. Mechanisms of vasomotor rhinitis. *Allergy*. 2004;59(Suppl 76):4-9.
18. Yewell J, Haydon R, Archer S, Manaligod JM. Complications of intranasal prescription narcotic abuse. *Ann Otol Rhinol Laryngol*. 2002;111:174-177.
19. Tan R, Corren J. Optimum treatment of rhinitis in the elderly. *Drugs Aging*. 1995;7:168-175.
20. Canonica GW, Passalacqua G. Noninjection routes for immunotherapy. *J Allergy Clin Immunol*. 2003;111:437-448.
21. Drake-Lee A, Ruckley R, Parker A. Occupational rhinitis: a poorly diagnosed condition. *J Laryngol Otol*. 2002;116:580-585.
22. Shusterman D. Toxicology of nasal irritants. *Curr Allergy Asthma Rep*. 2003;3:258-265.
23. Cullinan P, Cook A, Gordon S, et al. Allergen exposure, atopy and smoking as determinants of allergy to rats in a cohort of laboratory employees. *Eur Respir J*. 1999;13:1139-1143.
24. Petrick MM, Slavin RG. Occupational rhinitis. *Immunol Allergy Clin North Am*. 2003;23:193-203, vi.
25. Gautrin D, Infante-Rivard C, Ghezze H, Malo JL. Incidence and host determinants of probable occupational asthma in apprentices exposed to laboratory animals. *Am J Respir Crit Care Med*. 2001b;163:899-904.
26. Gautrin D, Ghezze H, Infante-Rivard C, Malo JL. Natural history of sensitization, symptoms and occupational diseases in apprentices exposed to laboratory animals. *Eur Respir J*. 2001a;17:904-908.
27. Cartier A, Malo JL, Forest F, et al. Occupational asthma in snow crab-processing workers. *J Allergy Clin Immunol*. 1984;74:261-269.
28. Houba R, Heederik D, Doekes G. Wheat sensitization and work-related symptoms in the baking industry are preventable. An epidemiologic study. *Am J Respir Crit Care Med*. 1998;1:1499-1503.
29. Gwaltney JM. Clinical significance and pathogenesis of viral respiratory infections. *Am J Med*. 2002;112(Suppl 6A):13S-18S.
30. Johnston SL, Pattemore PK, Sanderson G, et al. Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. *BMJ*. 1995;310:1225-1229.
31. Wernfors M, Nielsen J, Schutz A, Skerfving S. Phthalic anhydride-induced occupational asthma. *Int Arch Allergy Appl Immunol*. 1986;79:77-82.
32. Asher MI, Montefort S, Bjorksten B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet*. 2006;368:733-743.
33. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J*. 2004;24:758-764.
34. Blomme K, Tomassen P, Lapeere H, et al. Prevalence of allergic sensitization versus allergic rhinitis symptoms in an unselected population. *Int Arch Allergy Immunol*. 2013;160:200-207.

35. Eriksson J, Ekerljung L, Ronmark E, et al. Update of prevalence of self-reported allergic rhinitis and chronic nasal symptoms among adults in Sweden. *Clin Respir J*. 2012;6:159-168.
36. Warm K, Backman H, Lindberg A, Lundback B, Ronmark E. Low incidence and high remission of allergic sensitization among adults. *J Allergy Clin Immunol*. 2012;129:136-142.
37. Braback L, Hjern A, Rasmussen F. Trends in asthma, allergic rhinitis and eczema among Swedish conscripts from farming and non-farming environments. A nationwide study over three decades. *Clin Exp Allergy*. 2004;34:38-43.
38. Gupta R, Sheikh A, Strachan DP, Anderson HR. Time trends in allergic disorders in the UK. *Thorax*. 2007;62:91-96.
39. Bjorksten B, Clayton T, Ellwood P, Stewart A, Strachan D. Worldwide time trends for symptoms of rhinitis and conjunctivitis: phase III of the International Study of Asthma and Allergies in Childhood. *Pediatr Allergy Immunol*. 2008;19:110-124.
40. Braun-Fahrlander C, Gassner M, Grize L, et al. No further increase in asthma, hay fever and atopic sensitisation in adolescents living in Switzerland. *Eur Respir J*. 2004;23:407-413.
41. Duggan EM, Sturley J, Fitzgerald AP, Perry IJ, Hourihane JO. The 2002-2007 trends of prevalence of asthma, allergic rhinitis and eczema in Irish schoolchildren. *Pediatr Allergy Immunol*. 2012;23:464-471.
42. Ghouri N, Hippisley-Cox J, Newton J, Sheikh A. Trends in the epidemiology and prescribing of medication for allergic rhinitis in England. *J R Soc Med*. 2008;101:466-472.
43. McNeill G, Tagiyeva N, Aucott L, Russell G, Helms PJ. Changes in the prevalence of asthma, eczema and hay fever in pre-pubertal children: a 40-year perspective. *Paediatr Perinat Epidemiol*. 2009;23:506-512.
44. Alm B, Goksor E, Thengilsdottir H, et al. Early protective and risk factors for allergic rhinitis at age 4(1/2) yr. *Pediatr Allergy Immunol*. 2011;22:398-404.
45. Alm JS, Swartz J, Lilja G, Scheynius A, Pershagen G. Atopy in children of families with an anthroposophic lifestyle. *Lancet*. 1999;353:1485-1488.
46. de Bot, Moed H, Schellevis FG, de Groot H, van Wijk RG, van der Wouden JC. Allergic rhinitis in children: incidence and treatment in Dutch general practice in 1987 and 2001. *Pediatr Allergy Immunol*. 2009;20:571-577.
47. Kellberger J, Dressel H, Vogelberg C, et al. Prediction of the incidence and persistence of allergic rhinitis in adolescence: a prospective cohort study. *J Allergy Clin Immunol*. 2012;129:397-402.
48. Mai XM, Chen Y, Camargo CA Jr, Langhammer A. Serum 25-hydroxyvitamin D levels and self-reported allergic rhinitis in Norwegian adults - The HUNT Study. *Allergy*. 2014;69:488-493.
49. Katelaris CH, Lee BW, Potter PC, et al. Prevalence and diversity of allergic rhinitis in regions of the world beyond Europe and North America. *Clin Exp Allergy*. 2012;42:186-207.
50. von Mutius E, Weiland SK, Fritzsche C, Duhme H, Keil U. Increasing prevalence of hay fever and atopy among children in Leipzig, East Germany. *Lancet*. 1998;351:862-866.
51. Rondon C, Campo P, Galindo L, et al. Prevalence and clinical relevance of local allergic rhinitis. *Allergy*. 2012;67:1282-1288.
52. Settiple RA. Epidemiology of vasomotor rhinitis. *World Allergy Organ J*. 2009a;2:115-118.
53. Leynaert B, Neukirch C, Kony S, et al. Association between asthma and rhinitis according to atopic sensitization in a population-based study. *J Allergy Clin Immunol*. 2004;113:86-93.
54. Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol*. 2002;109:419-425.
55. Shaaban R, Zureik M, Soussan D, et al. Rhinitis and onset of asthma: a longitudinal population-based study. *Lancet*. 2008;372:1049-1057.
56. Moffatt MF, Gut IG, Demenais F, et al. A large-scale, consortium-based genomewide association study of asthma. *N Engl J Med*. 2010;363:1211-1221.
57. Moffatt MF, Kabesch M, Liang L, et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. *Nature*. 2007;448:470-473.
58. Paternoster L, Standl M, Chen CM, Ramasamy A, Bonnelykke K, Duijts L, et al. Meta-analysis of genome-wide association studies identifies three new risk loci for atopic dermatitis. *Nat Genet*. 2012;44:187-192.
59. Portelli MA, Hodge E, Sayers I. Genetic risk factors for the development of allergic disease identified by genome wide association. *Clin Exp Allergy*. 2015;45:21-31.
60. Ramasamy A, Curjuric I, Coin LJ, et al. A genome-wide meta-analysis of genetic variants associated with allergic rhinitis and grass sensitization and their interaction with birth order. *J Allergy Clin Immunol*. 2011;128:996-1005.
61. Matricardi PM, Rosmini F, Panetta V, Ferrigno L, Bonini S. Hay fever and asthma in relation to markers of infection in the United States. *J Allergy Clin Immunol*. 2002;110:381-387.
62. Riedler J, Braun-Fahrlander C, Eder W, et al. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. *Lancet*. 2001;358:1129-1133.
63. Strachan D. Damp housing and ill health. *BMJ*. 1989a;299:325.
64. Strachan DP. Hay fever, hygiene, and household size. *BMJ*. 1989b;299:1259-1260.
65. Kabesch M. Epigenetics in asthma and allergy. *Curr Opin Allergy Clin Immunol*. 2014;14:62-68.
66. Hansen I, Klimek L, Mosges R, Hormann K. Mediators of inflammation in the early and the late phase of allergic rhinitis. *Curr Opin Allergy Clin Immunol*. 2004;4:159-163.
67. Van Gerven L, Boeckxstaens G, Hellings P. Up-date on neuro-immune mechanisms involved in allergic and non-allergic rhinitis. *Rhinology*. 2012;50:227-235.
68. Licona-Limon P, Kim LK, Palm NW, Flavell RA. TH2, allergy and group 2 innate lymphoid cells. *Nat Immunol*. 2013;14:536-542.
69. Lloyd CM. IL-33 family members and asthma - bridging innate and adaptive immune responses. *Curr Opin Immunol*. 2010;22:800-806.
70. Saglani S, Lui S, Ullmann N, et al. IL-33 promotes airway remodeling in pediatric patients with severe steroid-resistant asthma. *J Allergy Clin Immunol*. 2013;132:676-685.
71. Ying S, O'Connor B, Ratoff J, et al. Expression and cellular provenance of thymic stromal lymphopoietin and chemokines in patients with severe asthma and chronic obstructive pulmonary disease. *J Immunol*. 2008;181:2790-2798.
72. Scadding G. Cytokine profiles in allergic rhinitis. *Curr Allergy Asthma Rep*. 2014;14:435.
73. Virchow JC, Kay S, Demoly P, Mullol J, Canonica W, Higgins V. Impact of ocular symptoms on quality of life (QoL), work productivity and resource utilisation in allergic rhinitis patients—an observational, cross sectional study in four countries in Europe. *J Med Econ*. 2011;14:305-314.
74. Bozkurt MK, Bozkurt B, Artac H, Arslan N, Reisli I. Vernal keratoconjunctivitis—a rare but serious comorbidity of allergic rhinitis and eustachian tube dysfunction. *Int J Pediatr Otorhinolaryngol*. 2010;74:60-63.
75. Ibanez MD, Navarro A, Sanchez MC, et al. Rhinitis and its association with asthma in patients under 14 years of age treated in allergy departments in Spain. *J Investig Allergol Clin Immunol*. 2010;20:402-406.
76. Bertelsen RJ, Carlsen KC, Carlsen KH. Rhinitis in children: co-morbidities and phenotypes. *Pediatr Allergy Immunol*. 2010;21:612-622.
77. Kim HY, Kwon EB, Baek JH, et al. Prevalence and comorbidity of allergic diseases in preschool children. *Korean J Pediatr*. 2013a;56:338-342.



78. Umapathy D, Alles R, Scadding GK. A community based questionnaire study on the association between symptoms suggestive of otitis media with effusion, rhinitis and asthma in primary school children. *Int J Pediatr Otorhinolaryngol.* 2007;71:705-712.
79. Ibanez MD, Valero AL, Montoro J, et al. Analysis of comorbidities and therapeutic approach for allergic rhinitis in a pediatric population in Spain. *Pediatr Allergy Immunol.* 2013;24:678-684.
80. Singh S, Nagarkar AN, Bansal S, Vir D, Gupta AK. Audiological manifestations of allergic rhinitis. *J Laryngol Otol.* 2011;125:906-910.
81. Chen MH, Su TP, Chen YS, et al. Allergic rhinitis in adolescence increases the risk of depression in later life: a nationwide population-based prospective cohort study. *J Affect Disord.* 2013;145:49-53.
82. Tsai MC, Lin HK, Lin CH, Fu LS. Prevalence of attention deficit/hyperactivity disorder in pediatric allergic rhinitis: a nationwide population-based study. *Allergy Asthma Proc.* 2011;32:41-46.
83. Kalpaklioglu AF, Kavut AB, Ekici M. Allergic and nonallergic rhinitis: the threat for obstructive sleep apnea. *Ann Allergy Asthma Immunol.* 2009;103:20-25.
84. Emin O, Mustafa S, Nedim S. Psychological stress and family functioning in mothers of children with allergic rhinitis. *Int J Pediatr Otorhinolaryngol.* 2009;73:1795-1798.
85. Lavigne F, Petrof BJ, Johnson JR, et al. Effect of topical corticosteroids on allergic airway inflammation and disease severity in obstructive sleep apnoea. *Clin Exp Allergy.* 2013;43:1124-1133.
86. Messias E, Clarke DE, Goodwin RD. Seasonal allergies and suicidality: results from the National Comorbidity Survey Replication. *Acta Psychiatr Scand.* 2010;122:139-142.
87. Vuurman EF, Vuurman LL, Lutgens I, Kremer B. Allergic rhinitis is a risk factor for traffic safety. *Allergy.* 2014;69:906-912.
88. Guss J, Doghramji L, Reger C, Chiu AG. Olfactory dysfunction in allergic rhinitis. *ORL J Otorhinolaryngol Relat Spec.* 2009;71:268-272.
89. Settipane GA, Greisner WA III, Settipane RJ. Natural history of asthma: a 23-year followup of college students. *Ann Allergy Asthma Immunol.* 2000;84:499-503.
90. Williams DC, Edney G, Maiden B, Smith PK. Recognition of allergic conjunctivitis in patients with allergic rhinitis. *World Allergy Organ J.* 2013;6:4.
91. Magnan A, Meunier JP, Saugnac C, Gasteau J, Neukirch F. Frequency and impact of allergic rhinitis in asthma patients in everyday general medical practice: a French observational cross-sectional study. *Allergy.* 2008;63:292-298.
92. Ciprandi G, Cirillo I, Signori A. Impact of allergic rhinitis on bronchi: an 8-year follow-up study. *Am J Rhinol Allergy.* 2011;25:e72-e76.
93. Yilmaz O, Bakirtas A, Ertoy Karagol HI, Topal E, Demirsoy MS. Allergic rhinitis may impact the recovery of pulmonary function tests after moderate/severe asthma exacerbation in children. *Allergy.* 2014;69:652-657.
94. Navarro A, Valero A, Julia B, Quirce S. Coexistence of asthma and allergic rhinitis in adult patients attending allergy clinics: ONEAIR study. *J Investig Allergol Clin Immunol.* 2008;18:233-238.
95. de Andrade CR, da Cunha Ibiapina C, Goncalves AC, et al. Asthma and allergic rhinitis co-morbidity: a cross-sectional questionnaire study on adolescents aged 13-14 years. *Prim Care Respir J.* 2008;17:222-225.
96. Ko FW, Ip MS, Chu CM, So LK, Lam DC, Hui DS. Prevalence of allergic rhinitis and its associated morbidity in adults with asthma: a multicentre study. *Hong Kong Med J.* 2010;16:354-361.
97. Eriksson J, Bjerg A, Lotvall J, et al. Rhinitis phenotypes correlate with different symptom presentation and risk factor patterns of asthma. *Respir Med.* 2011;105:1611-1621.
98. Valero A, Pereira C, Loureiro C, et al. Interrelationship between skin sensitization, rhinitis, and asthma in patients with allergic rhinitis: a study of Spain and Portugal. *J Investig Allergol Clin Immunol.* 2009;19:167-172.
99. Westman M, Stjarne P, Asarnej A, et al. Natural course and comorbidities of allergic and nonallergic rhinitis in children. *J Allergy Clin Immunol.* 2012;129:403-408.
100. Caliskaner Z, Naiboglu B, Kutlu A, et al. Risk factors for oral allergy syndrome in patients with seasonal allergic rhinitis. *Med Oral Patol Oral Cir Bucal.* 2011;16:e312-e316.
101. Sahin-Yilmaz A, Nocon CC, Corey JP. Immunoglobulin E-mediated food allergies among adults with allergic rhinitis. *Otolaryngol Head Neck Surg.* 2010;143:379-385.
102. Verguts MM, Eggermont A, Decoster W, de Jong FI, Hellings PW. Laryngeal effects of nasal allergen provocation in singers with allergic rhinitis. *Eur Arch Otorhinolaryngol.* 2011; 268:419-427.
103. Munoz-Jareno N, Fernandez-Mayoralas DM, Martinez-Cervell C, Campos-Castello J. Relationship between migraine and atopy in childhood: a retrospective case-control study. *Rev Neurol.* 2011;53:713-720.
104. de Groot EP, Nijkamp A, Duiverman EJ, Brand PL. Allergic rhinitis is associated with poor asthma control in children with asthma. *Thorax.* 2012;67:582-587.
105. Lasmar LM, Camargos PA, Goulart EM, Sakurai E. Risk factors for multiple hospital admissions among children and adolescents with asthma. *J Bras Pneumol.* 2006;32:391-399.
106. Price D, Zhang Q, Kocevar VS, Yin DD, Thomas M. Effect of a concomitant diagnosis of allergic rhinitis on asthma-related health care use by adults. *Clin Exp Allergy.* 2005;35:282-287.
107. Powe DG, Huskisson RS, Carney AS, Jenkins D, Jones NS. Evidence for an inflammatory pathophysiology in idiopathic rhinitis. *Clin Exp Allergy.* 2001;31:864-872.
108. Kleinjan A, Vinke JG, Severijnen LW, Fokkens WJ. Local production and detection of (specific) IgE in nasal B-cells and plasma cells of allergic rhinitis patients. *Eur Respir J.* 2000;15:491-497.
109. Rondon C, Fernandez J, Canto G, Blanca M. Local allergic rhinitis: concept, clinical manifestations, and diagnostic approach. *J Investig Allergol Clin Immunol.* 2010;20:364-371.
110. Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIANE Investigators. European Network on Aspirin-Induced Asthma. *Eur Respir J.* 2000;16:432-436.
111. Powe DG, Bonnain AJ, Jones NS. 'Entopy': local allergy paradigm. *Clin Exp Allergy.* 2010;40:987-997.
112. Powe DG, Jagger C, Kleinjan A, Carney AS, Jenkins D, Jones NS. 'Entopy': localized mucosal allergic disease in the absence of systemic responses for atopy. *Clin Exp Allergy.* 2003;33:1374-1379.
113. Settipane RA, Kaliner MA. Chapter 14: nonallergic rhinitis. *Am J Rhinol Allergy.* 2013;27(Suppl 1):S48-S51.
114. Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI. Definition and classification of asthma in the workplace. In: Bernstein IL, Chan-Yeung M, Malo JL, ernstein DI, eds. *Asthma in the Workplace.* 3rd edn. ed. New York: Taylor & Francis; 2006:9-35.
115. Raulf M, Buters J, Chapman M, et al. Monitoring of occupational and environmental aeroallergens – EAACI Position Paper. Concerted action of the EAACI IG occupational allergy and aerobiology & air pollution. *Allergy.* 2014;69:1280-1299.
116. Karjalainen A, Martikainen R, Klaukka T, Saarinen K, Uitti J. Risk of asthma among Finnish patients with occupational rhinitis. *Chest.* 2003;123:283-288.
117. Siracusa A, Desrosiers M, Marabini A. Epidemiology of occupational rhinitis: prevalence, aetiology and determinants. *Clin Exp Allergy.* 2000;30:1519-1534.
118. Colloff MJ, Ayres J, Carswell F, et al. The control of allergens of dust mites and domestic pets: a position paper. *Clin Exp Allergy.* 1992;22(Suppl 2):1-28.

119. Filon FL, Radman G. Latex allergy: a follow up study of 1040 healthcare workers. *Occup Environ Med.* 2006;63:121-125.
120. Kronqvist M, Johansson E, Pershagen G, Johansson SG, van Hage-Hamsten M. Risk factors associated with asthma and rhinoconjunctivitis among Swedish farmers. *Allergy.* 1999;54:1142-1149.
121. O'Meara TJ, Sercombe JK, Morgan G, Reddel HK, Xuan W, Tovey ER. The reduction of rhinitis symptoms by nasal filters during natural exposure to ragweed and grass pollen. *Allergy.* 2005;60:529-532.
122. Hemery ML, Dhivert-Donnadieu H, Verdier R, Dujols P, Godard P, Demoly P. A clinical and serological follow-up study of health care workers allergic to natural rubber latex who had followed a latex avoidance programme. *Allergy.* 2004;59:1013-1014.
123. Marshall AH, Jones NS, Robertson IJ. CSF rhinorrhoea: the place of endoscopic sinus surgery. *Br J Neurosurg.* 2001;15:8-12.
124. Flanagan P, Eccles R. Spontaneous changes of unilateral nasal airflow in man. A re-examination of the 'nasal cycle'. *Acta Otolaryngol.* 1997;117:590-595.
125. Jennings CR, Jones NS, Dugar J, Powell RJ, Lowe J. Wegener's granulomatosis—a review of diagnosis and treatment in 53 subjects. *Rhinology.* 1998;36:188-191.
126. Laitinen LA. Histamine and methacholine challenge in the testing of bronchial reactivity. *Scand J Respir Dis Suppl.* 1974;86:1-48.
127. Laitinen LA, Kokkola K. Bronchial reactivity to histamine in pulmonary tuberculosis. *Scand J Respir Dis Suppl.* 1974;89:201-205.
128. Townley RG, Dennis M, Itkin IH. Comparative action on acetyl-beta-methylcholine, histamine, and pollen antigens in subjects with hay fever and patients with bronchial asthma. *J Allergy.* 1965;36:121-137.
129. Ortolani C, Ispano M, Pastorello E, Bigi A, Ansaloni R. The oral allergy syndrome. *Ann Allergy.* 1988;61 Pt 2:47-52.
130. Scadding GK, Durham SR, Mirakian R, et al. BSACI guidelines for the management of rhinosinusitis and nasal polyposis. *Clin Exp Allergy.* 2008;38:260-275.
131. Fergie N, Jones NS, Havlat MF. The nasal manifestations of sarcoidosis: a review and report of eight cases. *J Laryngol Otol.* 1999;113:893-898.
132. Hughes RG, Jones NS. The role of nasal endoscopy in outpatient management. *Clin Otolaryngol Allied Sci.* 1998;23:224-226.
133. Droste JH, Kerhof M, de Monchy JG, Schouten JP, Rijcken B. Association of skin test reactivity, specific IgE, total IgE, and eosinophils with nasal symptoms in a community-based population study. The Dutch ECRHS Group. *J Allergy Clin Immunol.* 1996;97:922-932.
134. Gleeson M, Cripps AW, Hensley MJ, Wlodarczyk JH, Henry RL, Clancy RL. A clinical evaluation in children of the Pharmacia ImmunoCAP system for inhalant allergens. *Clin Exp Allergy.* 1996;26:697-702.
135. Doty RL, Shaman P, Kimmelman CP, Dann MS. University of Pennsylvania Smell Identification Test: a rapid quantitative olfactory function test for the clinic. *Laryngoscope.* 1984;94:176-178.
136. Romero JN, Scadding G. Eosinophilia in nasal secretions compared to skin prick test and nasal challenge test in the diagnosis of nasal allergy. *Rhinology.* 1992;30:169-175.
137. Nielsen HK, Eriksen EF, Storm T, Mosekilde L. The effects of short-term, high-dose treatment with prednisone on the nuclear uptake of 1,25-dihydroxyvitamin D3 in monocytes from normal human subjects. *Metabolism.* 1988;37:109-114.
138. Nielsen LP, Bjerke T, Christensen MB, et al. Eosinophil markers in seasonal allergic rhinitis. Intranasal fluticasone propionate inhibits local and systemic increases during the pollen season. *Allergy.* 1998;53:778-785.
139. Prieto L, Berto JM, Gutierrez V, Tornero C. Effect of inhaled budesonide on seasonal changes in sensitivity and maximal response to methacholine in pollen-sensitive asthmatic subjects. *Eur Respir J.* 1994;7:1845-1851.
140. Nurmatov U, van Schayck CP, Hurwitz B, Sheikh A. House dust mite avoidance measures for perennial allergic rhinitis: an updated Cochrane systematic review. *Allergy.* 2012;67:158-165.
141. Aberg N, Ospanova ST, Nikitin NP, Emberlin J, Dahl A. A nasally applied cellulose powder in seasonal allergic rhinitis in adults with grass pollen allergy: a double-blind, randomized, placebo-controlled, parallel-group study. *Int Arch Allergy Immunol.* 2014;163:313-318.
142. Ozturk AB, Celebioglu E, Karakaya G, Kalyoncu AF. Protective efficacy of sunglasses on the conjunctival symptoms of seasonal rhinitis. *Int Forum Allergy Rhinol.* 2013;3:1001-1006.
143. Kennedy R, Robertson L, Lewis M. Haymax – confidential report. Worcester: The National Pollen and Aerobiology Research Unit (NPARU); 2012:1 p.
144. Bjornsdottir US, Jakobinudottir S, Runarsdottir V, Juliusson S. The effect of reducing levels of cat allergen (Fel d 1) on clinical symptoms in patients with cat allergy. *Ann Allergy Asthma Immunol.* 2003;91:189-194.
145. Wood CC, Fireman P, Grossman J, Wecker M, MacGregor T. Product characteristics and pharmacokinetics of intranasal ipratropium bromide. *J Allergy Clin Immunol.* 1995a;95 Pt 2:1111-1116.
146. Gore RB, Boyle RJ, Gore C, et al. Effect of a novel temperature-controlled laminar airflow device on personal breathing zone aeroallergen exposure. *Indoor Air.* 2015;25:36-44.
147. Boyle RJ, Pedroletti C, Wickman M, et al. Nocturnal temperature controlled laminar airflow for treating atopic asthma: a randomised controlled trial. *Thorax.* 2012;67:215-221.
148. Jeffe JS, Bhushan B, Schroeder JW Jr. Nasal saline irrigation in children: a study of compliance and tolerance. *Int J Pediatr Otorhinolaryngol.* 2012;76:409-413.
149. Chen JR, Jin L, Li XY. The effectiveness of nasal saline irrigation (seawater) in treatment of allergic rhinitis in children. *Int J Pediatr Otorhinolaryngol.* 2014;78:1115-1118.
150. Marchisio P, Varricchio A, Baggi E, et al. Hypertonic saline is more effective than normal saline in seasonal allergic rhinitis in children. *Int J Immunopathol Pharmacol.* 2012;25:721-730.
151. Casale TB, Romero FA, Spierings EL. Intranasal noninhaled carbon dioxide for the symptomatic treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol.* 2008;121:105-109.
152. Casale TB, Korenblat PE, Meltzer EO, Yen K, Bhatnagar A. Nasal carbon dioxide for the symptomatic treatment of perennial allergic rhinitis. *Ann Allergy Asthma Immunol.* 2011;107:364-370.
153. van Cauwenberge PB, Bachert C, Passalacqua G, et al. Consensus statement on the treatment of allergic rhinitis. European Academy of Allergology and Clinical Immunology. *Allergy.* 2000;55:116-134.
154. Shamsi Z, Hindmarch I. Sedation and antihistamines: a review of inter-drug differences using proportional impairment ratios. *Hum Psychopharmacol.* 2000;15S1:S3-S30.
155. Wilson AM, O'Byrne PM, Parameswaran K. Leukotriene receptor antagonists for allergic rhinitis: a systematic review and meta-analysis. *Am J Med.* 2004a;116:338-344.
156. Bachert C, Bousquet J, Canonica GW, et al. Levocetirizine improves quality of life and reduces costs in long-term management of persistent allergic rhinitis. *J Allergy Clin Immunol.* 2004;114:838-844.
157. Pariente PD, LePen C, Los F, Bousquet J. Quality-of-life outcomes and the use of antihistamines in a French national population-based sample of patients with perennial rhinitis. *Pharmacoeconomics.* 1997;12:585-595.
158. Canonica GW, Tarantini F, Compalati E, Penagos M. Efficacy of desloratadine in the treatment of allergic rhinitis: a meta-analysis of randomized, double-blind, controlled trials. *Allergy.* 2007;62:359-366.
159. Ciprandi G, Cirillo I, Vizzaccaro A, Tosca MA. Levocetirizine improves nasal obstruction and modulates cytokine pattern in patients with seasonal allergic rhinitis: a pilot study. *Clin Exp Allergy.* 2004;34:958-964.

160. Ciprandi G, Cosentino C, Milanese M, Mondino C, Canonica GW. Fexofenadine reduces nasal congestion in perennial allergic rhinitis. *Allergy*. 2001;56:1068-1070.
161. Hore I, Georgalas C, Scadding G. Oral antihistamines for the symptom of nasal obstruction in persistent allergic rhinitis—a systematic review of randomized controlled trials. *Clin Exp Allergy*. 2005;35:207-212.
162. Nayak AS, Schenkel E. Desloratadine reduces nasal congestion in patients with intermittent allergic rhinitis. *Allergy*. 2001;56:1077-1080.
163. Patou J, De Smedt H, van Cauwenberge CP, Bachert C. Pathophysiology of nasal obstruction and meta-analysis of early and late effects of levocetirizine. *Clin Exp Allergy*. 2006;36:972-981.
164. van Steekelenburg J, Clement PA, Beel MH. Comparison of five new antihistamines (H1-receptor antagonists) in patients with allergic rhinitis using nasal provocation studies and skin tests. *Allergy*. 2002;57:346-350.
165. Dhand A, Aminoff MJ. The neurology of itch. *Brain*. 2014;137:313-322.
166. Nelson HS. Prospects for antihistamines in the treatment of asthma. *J Allergy Clin Immunol*. 2003;112(4 Suppl):S96-S100.
167. Portnoy JM, Dinakar C. Review of cetirizine hydrochloride for the treatment of allergic disorders. *Expert Opin Pharmacother*. 2004;5:125-135.
168. Schwarzer G, Bassler D, Mitra A, Ducharme FM, Forster J. Ketotifen alone or as additional medication for long-term control of asthma and wheeze in children. *Cochrane Database Syst Rev*. 2004; CD001384.
169. Ciprandi G, Passalacqua G, Mincarini M, Ricca V, Canonica GW. Continuous versus on demand treatment with cetirizine for allergic rhinitis. *Ann Allergy Asthma Immunol*. 1997a;79:507-511.
170. Leurs R, Church MK, Tagliabata M. H1-antihistamines: inverse agonism, anti-inflammatory actions and cardiac effects. *Clin Exp Allergy*. 2002;32:489-498.
171. Walker S, Khan-Wasti S, Fletcher M, Cullinan P, Harris J, Sheikh A. Seasonal allergic rhinitis is associated with a detrimental effect on examination performance in United Kingdom teenagers: case-control study. *J Allergy Clin Immunol*. 2007;120:381-387.
172. Weiler JM, Bloomfield JR, Woodworth GG, et al. Effects of fexofenadine, diphenhydramine, and alcohol on driving performance. A randomized, placebo-controlled trial in the Iowa driving simulator. *Ann Intern Med*. 2000;132:354-363.
173. Gray SL, Anderson ML, Dublin S, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Intern Med*. 2015;175:401-407.
174. Olasinska-Wisniewska A, Olasinski J, Grajek S. Cardiovascular safety of antihistamines. *Postepy Dermatol Alergol*. 2014;31:182-186.
175. Davila I, Sastre J, Bartra J, et al. Effect of H1 antihistamines upon the cardiovascular system. *J Investig Allergol Clin Immunol*. 2006;16 (Suppl 1):13-23.
176. Poluzzi E, Raschi E, Godman B, et al. Pro-arrhythmic potential of oral antihistamines (H1): combining adverse event reports with drug utilization data across Europe. *PLoS One*. 2015;10:e0119551.
177. Picado C. Rupatadine: pharmacological profile and its use in the treatment of allergic disorders. *Expert Opin Pharmacother*. 2006;7:1989-2001.
178. Juniper EF, Kline PA, Hargreave FE, Dolovich J. Comparison of beclomethasone dipropionate aqueous nasal spray, astemizole, and the combination in the prophylactic treatment of ragweed pollen-induced rhinoconjunctivitis. *J Allergy Clin Immunol*. 1989;83:627-633.
179. Ratner PH, van Bavel JH, Martin BG, et al. A comparison of the efficacy of fluticasone propionate aqueous nasal spray and loratadine, alone and in combination, for the treatment of seasonal allergic rhinitis. *J Fam Pract*. 1998;47:118-125.
180. Simpson RJ. Budesonide and terfenadine, separately and in combination, in the treatment of hay fever. *Ann Allergy*. 1994;73:497-502.
181. Takahashi G, Tanaka H, Higuchi N, Ikeda M, Inagaki N, Shichijo M. The potential role of prostaglandin D2 in nasal congestion observed in a guinea pig model of allergic rhinitis. *Int Arch Allergy Immunol*. 2012;158:359-368.
182. Lee TA, Pickard AS. Meta-analysis of azelastine nasal spray for the treatment of allergic rhinitis. *Pharmacotherapy*. 2007;27:852-859.
183. Horak F. Effectiveness of twice daily azelastine nasal spray in patients with seasonal allergic rhinitis. *Ther Clin Risk Manag*. 2008;4:1009-1022.
184. Lieberman P, Kaliner MA, Wheeler WJ. Open-label evaluation of azelastine nasal spray in patients with seasonal allergic rhinitis and nonallergic vasomotor rhinitis. *Curr Med Res Opin*. 2005;21:611-618.
185. Horak F, Zieglmayer UP, Zieglmayer R, et al. Azelastine nasal spray and desloratadine tablets in pollen-induced seasonal allergic rhinitis: a pharmacodynamic study of onset of action and efficacy. *Curr Med Res Opin*. 2006;22:151-157.
186. Ciprandi G, Ricca V, Passalacqua G, et al. Seasonal rhinitis and azelastine: long- or short-term treatment? *J Allergy Clin Immunol*. 1997b;99:301-307.
187. LaForce CF, Corren J, Wheeler WJ, Berger WE. Efficacy of azelastine nasal spray in seasonal allergic rhinitis patients who remain symptomatic after treatment with fexofenadine. *Ann Allergy Asthma Immunol*. 2004;93:154-159.
188. Yanez A, Rodrigo GJ. Intranasal corticosteroids versus topical H1 receptor antagonists for the treatment of allergic rhinitis: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol*. 2002;89:479-484.
189. Bielory B, Bielory L. Over-the-counter migration of steroid use: impact on the eye. *Curr Opin Allergy Clin Immunol*. 2014;14:471-476.
190. Hong J, Bielory B, Rosenberg JL, Bielory L. Efficacy of intranasal corticosteroids for the ocular symptoms of allergic rhinitis: a systematic review. *Allergy Asthma Proc*. 2011;32:22-35.
191. Keith PK, Scadding GK. Are intranasal corticosteroids all equally consistent in managing ocular symptoms of seasonal allergic rhinitis? *Curr Med Res Opin*. 2009;25:2021-2041.
192. Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. *BMJ*. 1998;317:1624-1629.
193. Graft D, Aaronson D, Chervinsky P, et al. A placebo- and active-controlled randomized trial of prophylactic treatment of seasonal allergic rhinitis with mometasone furoate aqueous nasal spray. *J Allergy Clin Immunol*. 1996;98:724-731.
194. Derendorf H, Meltzer EO. Molecular and clinical pharmacology of intranasal corticosteroids: clinical and therapeutic implications. *Allergy*. 2008;63:1292-1300.
195. Homer JJ, Gazis TG. Cushing's syndrome induced by betamethasone nose drops. In rhinological disease betamethasone should be regarded as systemic corticosteroid. *BMJ*. 1999;318:1355.
196. McMahon C, Darby Y, Ryan R, Scadding G. Immediate and short-term effects of benzalkonium chloride on the human nasal mucosa in vivo. *Clin Otolaryngol Allied Sci*. 1997;22:318-322.
197. Allen DB. Systemic effects of intranasal steroids: an endocrinologist's perspective. *J Allergy Clin Immunol*. 2000;106(4 Suppl):S179-S190.
198. Bui CM, Chen H, Shyr Y, Joos KM. Discontinuing nasal steroids might lower intraocular pressure in glaucoma. *J Allergy Clin Immunol*. 2005;116:1042-1047.
199. Pullerits T, Praks L, Ristioja V, Lotvall J. Comparison of a nasal glucocorticoid, antileukotriene, and a combination of antileukotriene

- and antihistamine in the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol*. 2002a;109:949-955.
200. Wilson AM, Orr LC, Sims EJ, Lipworth BJ. Effects of monotherapy with intra-nasal corticosteroid or combined oral histamine and leukotriene receptor antagonists in seasonal allergic rhinitis. *Clin Exp Allergy*. 2001b;31:61-68.
  201. Carr W, Bernstein J, Lieberman P, et al. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. *J Allergy Clin Immunol*. 2012a;129:1282-1289.
  202. Meltzer EO, LaForce C, Ratner P, Price D, Ginsberg D, Carr W. MP29-02 (a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate) in the treatment of seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial of efficacy and safety. *Allergy Asthma Proc*. 2012;33:324-332.
  203. Price D, Shah S, Bhatia S, et al. A new therapy (MP29-02) is effective for the long-term treatment of chronic rhinitis. *J Investig Allergol Clin Immunol*. 2013a;23:495-503.
  204. Aasbjerg K, Torp-Pedersen C, Vaag A, Backer V. Treating allergic rhinitis with depot-steroid injections increase risk of osteoporosis and diabetes. *Respir Med*. 2013;107:1852-1858.
  205. Nasser SM, Ewan PW. Lesson of the week: depot corticosteroid treatment for hay fever causing avascular necrosis of both hips. *BMJ*. 2001;322:1589-1591.
  206. Barnes ML, Bialosterski BT, Gray RD, Fardon TC, Lipworth BJ. Decongestant effects of nasal xylometazoline and mometasone furoate in persistent allergic rhinitis. *Rhinology*. 2005;43:291-295.
  207. Baroody FM, Brown D, Gavanescu L, DeTineo M, Naclerio RM. Oxymetazoline adds to the effectiveness of fluticasone furoate in the treatment of perennial allergic rhinitis. *J Allergy Clin Immunol*. 2011a;127:927-934.
  208. Scadding GK. Rhinitis medicamentosa. *Clin Exp Allergy*. 1995;25:391-394.
  209. Morris S, Eccles R, Martez SJ, Riker DK, Witek TJ. An evaluation of nasal response following different treatment regimes of oxymetazoline with reference to rebound congestion. *Am J Rhinol*. 1997;11:109-115.
  210. Yoo JK, Seikaly H, Calhoun KH. Extended use of topical nasal decongestants. *Laryngoscope*. 1997;107:40-43.
  211. Baroody FM, Naclerio RM. Nasal-ocular reflexes and their role in the management of allergic rhinoconjunctivitis with intranasal steroids. *World Allergy Organ J*. 2011;4(1 Suppl):S1-S5.
  212. Malm L. Pharmacological background to decongesting and anti-inflammatory treatment of rhinitis and sinusitis. *Acta Otolaryngol Suppl*. 1994;515:53-55.
  213. Naclerio RM. Optimizing treatment options. *Clin Exp Allergy*. 1998;28(Suppl 6):54-59.
  214. Philip G, Malmstrom K, Hampel FC, et al. Montelukast for treating seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial performed in the spring. *Clin Exp Allergy*. 2002;32:1020-1028.
  215. Pullerits T, Praks L, Skoogh BE, Ani R, Lotvall J. Randomized placebo-controlled study comparing a leukotriene receptor antagonist and a nasal glucocorticoid in seasonal allergic rhinitis. *Am J Respir Crit Care Med*. 1999;159:1814-1818.
  216. Ratner PH, Howland WC III, Arastu R, et al. Fluticasone propionate aqueous nasal spray provided significantly greater improvement in daytime and nighttime nasal symptoms of seasonal allergic rhinitis compared with montelukast. *Ann Allergy Asthma Immunol*. 2003;90:536-542.
  217. Wilson AM, Dempsey OJ, Sims EJ, Lipworth BJ. A comparison of topical budesonide and oral montelukast in seasonal allergic rhinitis and asthma. *Clin Exp Allergy*. 2001a;31:616-624.
  218. Fowler SJ, Hall IP, Wilson AM, Wheatley AP, Lipworth BJ. 5-Lipoxygenase polymorphism and in-vivo response to leukotriene receptor antagonists. *Eur J Clin Pharmacol*. 2002;58:187-190.
  219. Mastalerz L, Nizankowska E, Sanak M, et al. Clinical and genetic features underlying the response of patients with bronchial asthma to treatment with a leukotriene receptor antagonist. *Eur J Clin Invest*. 2002;32:949-955.
  220. Sampson AP, Siddiqui S, Buchanan D, et al. Variant LTC(4) synthase allele modifies cysteinyl leukotriene synthesis in eosinophils and predicts clinical response to zafirlukast. *Thorax*. 2000;55(Suppl 2):S28-S31.
  221. Meltzer EO, Malmstrom K, Lu S, et al. Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: a randomized, placebo-controlled clinical trial. *J Allergy Clin Immunol*. 2000;105:917-922.
  222. Nayak AS, Philip G, Lu S, Malice MP, Reiss TF. Efficacy and tolerability of montelukast alone or in combination with loratadine in seasonal allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial performed in the fall. *Ann Allergy Asthma Immunol*. 2002;88:592-600.
  223. Wilson AM, Orr LC, Coutie WJ, Sims EJ, Lipworth BJ. A comparison of once daily fexofenadine versus the combination of montelukast plus loratadine on domiciliary nasal peak flow and symptoms in seasonal allergic rhinitis. *Clin Exp Allergy*. 2002;32:126-132.
  224. Wilson AM, White PS, Gardiner Q, Nassif R, Lipworth BJ. Effects of leukotriene receptor antagonist therapy in patients with chronic rhinosinusitis in a real life rhinology clinic setting. *Rhinology*. 2001c;39:142-146.
  225. Di Lorenzo G, Pacor ML, Pellitteri ME, et al. Randomized placebo-controlled trial comparing fluticasone aqueous nasal spray in monotherapy, fluticasone plus cetirizine, fluticasone plus montelukast and cetirizine plus montelukast for seasonal allergic rhinitis. *Clin Exp Allergy*. 2004;34:259-267.
  226. Philip G, Nayak AS, Berger WE, et al. The effect of montelukast on rhinitis symptoms in patients with asthma and seasonal allergic rhinitis. *Curr Med Res Opin*. 2004;20:1549-1558.
  227. Hauser T, Mahr A, Metzler C, et al. The leukotriene receptor antagonist montelukast and the risk of Churg-Strauss syndrome: a case-crossover study. *Thorax*. 2008;63:677-682.
  228. Nathani N, Little MA, Kunst H, Wilson D, Thickett DR. Churg-Strauss syndrome and leukotriene antagonist use: a respiratory perspective. *Thorax*. 2008;63:883-888.
  229. Grossman J, Banov C, Boggs P, et al. Use of ipratropium bromide nasal spray in chronic treatment of nonallergic perennial rhinitis, alone and in combination with other perennial rhinitis medications. *J Allergy Clin Immunol*. 1995a;95 Pt 2:1123-1127.
  230. Kaiser HB, Findlay SR, Georgitis JW, et al. The anticholinergic agent, ipratropium bromide, is useful in the treatment of rhinorrhea associated with perennial allergic rhinitis. *Allergy Asthma Proc*. 1998;19:23-29.
  231. Meltzer EO, Orgel HA, Bronsky EA, et al. Ipratropium bromide aqueous nasal spray for patients with perennial allergic rhinitis: a study of its effect on their symptoms, quality of life, and nasal cytology. *J Allergy Clin Immunol*. 1992;90:242-249.
  232. Dockhorn R, Aaronson D, Bronsky E, et al. Ipratropium bromide nasal spray 0.03% and beclomethasone nasal spray alone and in combination for the treatment of rhinorrhea in perennial rhinitis. *Ann Allergy Asthma Immunol*. 1999;82:349-359.
  233. Pras E, Stienlauf S, Pinkhas J, Sidi Y. Urinary retention associated with ipratropium bromide. *DICP*. 1991;25:939-940.
  234. Bronsky EA, Druce H, Findlay SR, et al. A clinical trial of ipratropium bromide nasal spray in patients with perennial nonallergic rhinitis. *J Allergy Clin Immunol*. 1995a;95:1117-1122.
  235. Ratner PH, Ehrlich PM, Fineman SM, Meltzer EO, Skoner DP. Use of intranasal cromolyn sodium for allergic rhinitis. *Mayo Clin Proc*. 2002;77:350-354.

236. James IG, Campbell LM, Harrison JM, Fell PJ, Ellers-Lenz B, Petzold U. Comparison of the efficacy and tolerability of topically administered azelastine, sodium cromoglycate and placebo in the treatment of seasonal allergic conjunctivitis and rhino-conjunctivitis. *Curr Med Res Opin.* 2003;19:313-320.
237. Meltzer EO. Efficacy and patient satisfaction with cromolyn sodium nasal solution in the treatment of seasonal allergic rhinitis: a placebo-controlled study. *Clin Ther.* 2002;24:942-952.
238. Hadley JA. Cost-effective pharmacotherapy for inhalant allergic rhinitis. *Otolaryngol Clin North Am.* 2003;36:825-836.
239. Owen CG, Shah A, Henshaw K, Smeeth L, Sheikh A. Topical treatments for seasonal allergic conjunctivitis: systematic review and meta-analysis of efficacy and effectiveness. *Br J Gen Pract.* 2004;54:451-456.
240. Glacy J, Putnam K, Godfrey S, et al. Treatment for Seasonal Allergic Rhinitis. Rockville, MD: AHRQ Publication No. 13-EHC098-EF – Agency for Healthcare Research and Quality; Report nr 120; 2013.
241. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. *J Allergy Clin Immunol.* 1998;1:558-562.
242. Canonica GW, Cox L, Pawankar R, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. *World Allergy Organ J.* 2014;7:6.
243. Passalacqua G, Durham SR. Allergic rhinitis and its impact on asthma update: allergen immunotherapy. *J Allergy Clin Immunol.* 2007;119:881-891.
244. Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev.* 2007;CD001936.
245. Eifan AO, Calderon MA, Durham SR. Allergen immunotherapy for house dust mite: clinical efficacy and immunological mechanisms in allergic rhinitis and asthma. *Expert Opin Biol Ther.* 2013;13:1543-1556.
246. Alvarez-Cuesta E, Cuesta-Herranz J, Puyana-Ruiz J, Cuesta-Herranz C, Blanco-Quiros A. Monoclonal antibody-standardized cat extract immunotherapy: risk-benefit effects from a double-blind placebo study. *J Allergy Clin Immunol.* 1994;93:556-566.
247. Varney VA, Edwards J, Tabbah K, Brewster H, Mavroleon G, Frew AJ. Clinical efficacy of specific immunotherapy to cat dander: a double-blind placebo-controlled trial. *Clin Exp Allergy.* 1997;27:860-867.
248. Alvarez-Cuesta O, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E. Standards for practical allergen-specific immunotherapy. *Allergy.* 2006;61(Suppl 82):1-20.
249. Radulovic S, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev.* 2010;CD002893.
250. Bufe A, Eberle P, Franke-Beckmann E, et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol.* 2009;123:167-173.
251. Cox LS, Casale TB, Nayak AS, et al. Clinical efficacy of 300IR 5-grass pollen sublingual tablet in a US study: the importance of allergen-specific serum IgE. *J Allergy Clin Immunol.* 2012;130:1327-1334.
252. Dahl R, Kapp A, Colombo G, et al. Sublingual grass allergen tablet immunotherapy provides sustained clinical benefit with progressive immunologic changes over 2 years. *J Allergy Clin Immunol.* 2008;121:512-518.
253. Didier A, Malling HJ, Worm M, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol.* 2007;120:1338-1345.
254. Halcken S, Agertoft L, Seidenberg J, et al. Five-grass pollen 300IR SLIT tablets: efficacy and safety in children and adolescents. *Pediatr Allergy Immunol.* 2010;21:970-976.
255. Maloney J, Bernstein DI, Nelson H, et al. Efficacy and safety of grass sublingual immunotherapy tablet, MK-7243: a large randomized controlled trial. *Ann Allergy Asthma Immunol.* 2014;112:146-153.
256. Creticos PS, Esch RE, Couroux P, et al. Randomized, double-blind, placebo-controlled trial of standardized ragweed sublingual-liquid immunotherapy for allergic rhinoconjunctivitis. *J Allergy Clin Immunol.* 2014;133:751-758.
257. Creticos PS, Maloney J, Bernstein DI, et al. Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European adults. *J Allergy Clin Immunol.* 2013;131:1342-1349.
258. Calderon MA, Linneberg A, Kleine-Tebbe J, et al. Respiratory allergy caused by house dust mites: what do we really know? *J Allergy Clin Immunol.* 2015;136:38-48.
259. Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med.* 1999;341:468-475.
260. Didier A, Malling HJ, Worm M, et al. Post-treatment efficacy of discontinuous treatment with 300IR 5-grass pollen sublingual tablet in adults with grass pollen-induced allergic rhinoconjunctivitis. *Clin Exp Allergy.* 2013;43:568-577.
261. Durham SR, Emminger W, Kapp A, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol.* 2012;129:717-725.
262. Jacobsen L, Niggemann B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy.* 2007;62:943-948.
263. Des RA, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol.* 1997;99:450-453.
264. Pajno GB, Barberio G, De LF, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *Clin Exp Allergy.* 2001;31:1392-1397.
265. Walker SM, Durham SR, Till SJ, et al. Immunotherapy for allergic rhinitis. *Clin Exp Allergy.* 2011;41:1177-1200.
266. Becker B, Borum S, Nielsen K, Mygind N, Borum P. A time-dose study of the effect of topical ipratropium bromide on methacholine-induced rhinorrhoea in patients with perennial non-allergic rhinitis. *Clin Otolaryngol Allied Sci.* 1997;22:132-134.
267. Bonadonna P, Senna G, Zanon P, et al. Cold-induced rhinitis in skiers—clinical aspects and treatment with ipratropium bromide nasal spray: a randomized controlled trial. *Am J Rhinol.* 2001;15:297-301.
268. Dolovich J, Kennedy L, Vickerson F, Kazim F. Control of the hypersecretion of vasomotor rhinitis by topical ipratropium bromide. *J Allergy Clin Immunol.* 1987;80:274-278.
269. Druce HM, Spector SL, Fireman P, et al. Double-blind study of intranasal ipratropium bromide in nonallergic perennial rhinitis. *Ann Allergy.* 1992;69:53-60.
270. Georgitis JW, Banov C, Boggs PB, et al. Ipratropium bromide nasal spray in non-allergic rhinitis: efficacy, nasal cytological response and patient evaluation on quality of life. *Clin Exp Allergy.* 1994;24:1049-1055.
271. Jessen M, Bylander A. Treatment of non-allergic nasal hypersecretion with ipratropium and beclomethasone. *Rhinology.* 1990;28:77-81.
272. Jokinen K, Sipila P. Intranasal ipratropium in the treatment of vasomotor rhinitis. *Rhinology.* 1983;21:341-345.
273. Kirkegaard J, Mygind N, Molgaard F, et al. Ordinary and high-dose ipratropium in perennial nonallergic rhinitis. *J Allergy Clin Immunol.* 1987;79:585-590.

274. O'Dwyer TP, Lee RJ, Kaye J, Fennell G. Ipratropium bromide in the treatment of the 'rhinorrhoea syndrome'. *J Laryngol Otol*. 1988;102:799-801.
275. Purello-D'Ambrosio F, Isola S, Ricciardi L, Gangemi S, Barresi L, Baginato GF. A controlled study on the effectiveness of loratadine in combination with flunisolide in the treatment of nonallergic rhinitis with eosinophilia (NARES). *Clin Exp Allergy*. 1999;29:1143-1147.
276. Sanwikarja S, Schmitz PI, Dieges PH. The effect of locally applied ipratropium aerosol on the nasal methacholine challenge in patients with allergic and non-allergic rhinitis. *Ann Allergy*. 1986;56:162-166.
277. Sapci T, Yazici S, Evcimik MF, et al. Investigation of the effects of intranasal botulinum toxin type A and ipratropium bromide nasal spray on nasal hypersecretion in idiopathic rhinitis without eosinophilia. *Rhinology*. 2008;46:45-51.
278. Sjogren I, Jonsson L, Koling A, Jansson C, Osterman K, Hakansson B. The effect of ipratropium bromide on nasal hypersecretion induced by methacholine in patients with vasomotor rhinitis. A double-blind, cross-over, placebo-controlled and randomized dose-response study. *Acta Otolaryngol*. 1988;106:453-459.
279. Blom HM, van Rijswijk JB, Garrelds IM, Mulder PG, Timmermans T, Gerth van WR. Intranasal capsaicin is efficacious in non-allergic, non-infectious perennial rhinitis. A placebo-controlled study. *Clin Exp Allergy*. 1997b;27:796-801.
280. Ciabatti PG, D'Ascanio L. Intranasal Capsicum spray in idiopathic rhinitis: a randomized prospective application regimen trial. *Acta Otolaryngol*. 2009;129:367-371.
281. van Rijswijk JB, Boeke EL, Keizer JM, Mulder PG, Blom HM, Fokkens WJ. Intranasal capsaicin reduces nasal hyperreactivity in idiopathic rhinitis: a double-blind randomized application regimen study. *Allergy*. 2003;58:754-761.
282. Blom HM, Godthelp T, Fokkens WJ, Kleinjan A, Mulder PG, Rijntjes E. The effect of nasal steroid aqueous spray on nasal complaint scores and cellular infiltrates in the nasal mucosa of patients with nonallergic, noninfectious perennial rhinitis. *J Allergy Clin Immunol*. 1997a;100:739-747.
283. Jacobs R, Lieberman P, Kent E, Silvey M, Locantore N, Philpot EE. Weather/temperature-sensitive vasomotor rhinitis may be refractory to intranasal corticosteroid treatment. *Allergy Asthma Proc*. 2009;30:120-127.
284. Lofkvist T, Svensson G. Treatment of vasomotor rhinitis with intranasal beclomethasone dipropionate (Becotide). Results from a double-blind cross-over study. *Acta Allergol*. 1976;31:227-238.
285. Lundblad L, Sipila P, Farstad T, Drozdiewicz D. Mometasone furoate nasal spray in the treatment of perennial non-allergic rhinitis: a nordic, multicenter, randomized, double-blind, placebo-controlled study. *Acta Otolaryngol*. 2001;121:505-509.
286. Varricchio A, Capasso M, De Lucia A, et al. Intranasal flunisolide treatment in patients with non-allergic rhinitis. *Int J Immunopathol Pharmacol*. 2011;24:401-409.
287. Tantilipikorn P, Thanaviratnanich S, Chusakul S, et al. Efficacy and Safety of Once Daily Fluticasone Furoate Nasal Spray for Treatment of Irritant (Non-allergic) Rhinitis. *Open Respir Med J*. 2010;4:92-99.
288. Banov CH, Lieberman P. Efficacy of azelastine nasal spray in the treatment of vasomotor (perennial nonallergic) rhinitis. *Ann Allergy Asthma Immunol*. 2001;86:28-35.
289. Gehanno P, Deschamps E, Garay E, Baehre M, Garay RP. Vasomotor rhinitis: clinical efficacy of azelastine nasal spray in comparison with placebo. *ORL J Otorhinolaryngol Relat Spec*. 2001;63:76-81.
290. Kalpaklioglu AF, Kavut AB. Comparison of azelastine versus triamcinolone nasal spray in allergic and nonallergic rhinitis. *Am J Rhinol Allergy*. 2010;24:29-33.
291. Lieberman P, Meltzer EO, LaForce CF, Darter AL, Tort MJ. Two-week comparison study of olopatadine hydrochloride nasal spray 0.6% versus azelastine hydrochloride nasal spray 0.1% in patients with vasomotor rhinitis. *Allergy Asthma Proc*. 2011;32:151-158.
292. Murdoch RD, Bareille P, Denyer J, et al. TRPV1 inhibition does not prevent cold dry air-elicited symptoms in non-allergic rhinitis. *Int J Clin Pharmacol Ther*. 2014;52:267-276.
293. Holland C, van Drunen DC, Denyer J, et al. Inhibition of capsaicin-driven nasal hyper-reactivity by SB-705498, a TRPV1 antagonist. *Br J Clin Pharmacol*. 2014;77:777-788.
294. Fruth K, Pogorzelski B, Schmidtmann I, et al. Low-dose aspirin desensitization in individuals with aspirin-exacerbated respiratory disease. *Allergy*. 2013;68:659-665.
295. Howe R, Mirakian RM, Pillai P, Gane S, Darby YC, Scadding GK. Audit of nasal lysine aspirin therapy in recalcitrant aspirin exacerbated respiratory disease. *World Allergy Organ J*. 2014;7:18.
296. Miller B, Mirakian R, Gane S, et al. Nasal lysine aspirin challenge in the diagnosis of aspirin - exacerbated respiratory disease: asthma and rhinitis. *Clin Exp Allergy*. 2013;43:874-880.
297. Xu JJ, Sowerby L, Rotenberg BW. Aspirin desensitization for aspirin-exacerbated respiratory disease (Samter's Triad): a systematic review of the literature. *Int Forum Allergy Rhinol*. 2013;3:915-920.
298. Passali D, Passali FM, Damiani V, Passali GC, Bellussi L. Treatment of inferior turbinate hypertrophy: a randomized clinical trial. *Ann Otol Rhinol Laryngol*. 2003;112:683-688.
299. Lavinsky-Wolff M, Camargo HL Jr, Barone CR, et al. Effect of turbinate surgery in rhinoseptoplasty on quality-of-life and acoustic rhinometry outcomes: a randomized clinical trial. *Laryngoscope*. 2013;123:82-89.
300. Nogueira-Silva L, Martins SV, Cruz-Correia R, et al. Control of allergic rhinitis and asthma test—a formal approach to the development of a measuring tool. *Respir Res*. 2009;10:52.
301. Nathan RA, Dalal AA, Stanford RH, et al. Qualitative Development of the Rhinitis Control Assessment Test (RCAT), an Instrument for Evaluating Rhinitis Symptom Control. *Patient*. 2010;3:91-99.
302. Schatz M, Meltzer EO, Nathan R, et al. Psychometric validation of the rhinitis control assessment test: a brief patient-completed instrument for evaluating rhinitis symptom control. *Ann Allergy Asthma Immunol*. 2010;104:118-124.
303. Demoly P, Jankowski R, Chassany O, Bessah Y, Allaert FA. Validation of a self-questionnaire for assessing the control of allergic rhinitis. *Clin Exp Allergy*. 2011;41:860-868.
304. Bousquet J, Schunemann HJ, Fonseca J, et al. MACVIA-ARIA Sentinel Network for allergic rhinitis (MASK-rhinitis): the new generation guideline implementation. *Allergy*. 2015;70:1372-1392.
305. Bousquet J, Bachert C, Canonica GW, et al. Unmet needs in severe chronic upper airway disease (SCUAD). *J Allergy Clin Immunol*. 2009;124:428-433.
306. Christensen AJ. *Patient adherence to medical treatment regimens: challenges for behavioral science and biomedicine*. New Haven: Yale University Press; 2004.
307. Passalacqua G, Baiardini I, Senna G, Canonica GW. Adherence to pharmacological treatment and specific immunotherapy in allergic rhinitis. *Clin Exp Allergy*. 2013;43:22-28.
308. Vita D, Caminiti L, Ruggeri P, Pajno GB. Sublingual immunotherapy: adherence based on timing and monitoring control visits. *Allergy*. 2010;65:668-669.
309. Incorvaia C, Rapetti A, Scurati S, Puccinelli P, Capece M, Frati F. Importance of patient's education in favouring compliance with sublingual immunotherapy. *Allergy*. 2010;65:1341-1342.
310. Dzieciolowska-Baran E, Teul-Swiniarska I, Gawlikowska-Sroka A, Poziomkowska-Gesicka I, Zietek Z. Rhinitis as a cause of respiratory disorders during pregnancy. *Adv Exp Med Biol*. 2013;755:213-220.
311. Keles N. Treatment of allergic rhinitis during pregnancy. *Am J Rhinol*. 2004;18:23-28.

312. Ellegard EK. The etiology and management of pregnancy rhinitis. *Am J Respir Med.* 2003;2:469-475.
313. Incaudo GA. Diagnosis and treatment of allergic rhinitis and sinusitis during pregnancy and lactation. *Clin Rev Allergy Immunol.* 2004;27:159-177.
314. Gilbey P, McGruthers L, Morency AM, Shrim A. Rhinosinusitis-related quality of life during pregnancy. *Am J Rhinol Allergy.* 2012;26:283-286.
315. Indirani B, Raman R, Omar SZ. Hormonal changes causing rhinitis in pregnancy among Malaysian women. *J Laryngol Otol.* 2013;127:876-881.
316. Shinohara M, Wakiguchi H, Saito H, Matsumoto K. Symptoms of allergic rhinitis in women during early pregnancy are associated with higher prevalence of allergic rhinitis in their offspring. *Allergol Int.* 2007;56:411-417.
317. Gani F, Braid A, Lombardi C, Del GA, Senna GE, Passalacqua G. Rhinitis in pregnancy. *Allerg Immunol (Paris).* 2003;35:306-313.
318. Garavello W, Somigliana E, Acaia B, Gaini L, Pignataro L, Gaini RM. Nasal lavage in pregnant women with seasonal allergic rhinitis: a randomized study. *Int Arch Allergy Immunol.* 2010;151:137-141.
319. Demoly P, Piette V, Daures JP. Treatment of allergic rhinitis during pregnancy. *Drugs.* 2003b;63:1813-1820.
320. Ellegard EK, Hellgren M, Karlsson NG. Fluticasone propionate aqueous nasal spray in pregnancy rhinitis. *Clin Otolaryngol Allied Sci.* 2001;26:394-400.
321. Mazzotta P, Loebstein R, Koren G. Treating allergic rhinitis in pregnancy. *Safety considerations. Drug Saf.* 1999;20:361-375.
322. Diav-Citrin O, Shechtman S, Aharonovich A, et al. Pregnancy outcome after gestational exposure to loratadine or antihistamines: a prospective controlled cohort study. *J Allergy Clin Immunol.* 2003;111:1239-1243.
323. Moretti ME, Caprara D, Coutinho CJ, et al. Fetal safety of loratadine use in the first trimester of pregnancy: a multicenter study. *J Allergy Clin Immunol.* 2003;111:479-483.
324. Hilbert J, Radwanski E, Affrime MB, Perentesis G, Symchowicz S, Zampaglione N. Excretion of loratadine in human breast milk. *J Clin Pharmacol.* 1988;28:234-239.
325. Briggs GG, Freeman RK, Jaffe SJ. *Drugs in Pregnancy and Lactation*, 6th edn. Philadelphia: Lippincott Williams & Wilkins; 2001.
326. RCPCH. Manual of childhood infections;2016:373.
327. Kurukulaaratchy RJ, Karmaus W, Raza A, Matthews S, Roberts G, Arshad SH. The influence of gender and atopy on the natural history of rhinitis in the first 18 years of life. *Clin Exp Allergy.* 2011;41:851-859.
328. Burgess JA, Walters EH, Byrnes GB, et al. Childhood allergic rhinitis predicts asthma incidence and persistence to middle age: a longitudinal study. *J Allergy Clin Immunol.* 2007;120:863-869.
329. Rochat MK, Illi S, Ege MJ, et al. Allergic rhinitis as a predictor for wheezing onset in school-aged children. *J Allergy Clin Immunol.* 2010;126:1170-1175.
330. Roberts G, Xatzipsalti M, Borrego LM, et al. Paediatric rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. *Allergy.* 2013;68:1102-1116.
331. Forester JP, Calabria CW. Local production of IgE in the respiratory mucosa and the concept of entopy: does allergy exist in nonallergic rhinitis? *Ann Allergy Asthma Immunol.* 2010;105:249-255.
332. Payne SC. Empty nose syndrome: what are we really talking about? *Otolaryngol Clin North Am.* 2009;42:331-337, ix-x.
333. Payne SC, Chen PG, Borish L. Local class switching in nonallergic rhinitis. *Curr Opin Otolaryngol Head Neck Surg.* 2011;19:193-198.
334. Garavello W, Romagnoli M, Sordo L, Gaini RM, Di BC, Angrisano A. Hypersaline nasal irrigation in children with symptomatic seasonal allergic rhinitis: a randomized study. *Pediatr Allergy Immunol.* 2003;14:140-143.
335. Allen DB, Meltzer EO, Lemanske RF Jr, et al. No growth suppression in children treated with the maximum recommended dose of fluticasone propionate aqueous nasal spray for one year. *Allergy Asthma Proc.* 2002;23:407-413.
336. Schenkel EJ, Skoner DP, Bronsky EA, et al. Absence of growth retardation in children with perennial allergic rhinitis after one year of treatment with mometasone furoate aqueous nasal spray. *Pediatrics.* 2000;105:E22.
337. Moller C, Dreborg S, Ferdousi HA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol.* 2002; 109:251-256.
338. Niggemann B, Jacobsen L, Dreborg S, et al. Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. *Allergy.* 2006;61:855-859.
339. Indradat S, Jirapongsananuruk O, Visitsunthorn N. Evaluation of animated cartoon-aided teaching of intranasal corticosteroid administration technique among Thai children with allergic rhinitis. *Asian Pac J Allergy Immunol.* 2014;32:166-170.
340. Scadding GK, Darby YC, Jansz AJ, et al. Double-blind, placebo controlled randomised trial of medical therapy in otitis media with effusion. *Adv Life Sci Health.* 2014;1:58-68.
341. Carr WW, Ratner P, Munzel U, et al. Comparison of intranasal azelastine to intranasal fluticasone propionate for symptom control in moderate-to-severe seasonal allergic rhinitis. *Allergy Asthma Proc.* 2012b;33:450-458.
342. Baroody FM, Logothetis H, Vishwanath S, Bashir M, DeTineo M, Naclerio RM. Effect of intranasal fluticasone furoate and intraocular olopatadine on nasal and ocular allergen-induced symptoms. *Am J Rhinol Allergy.* 2013;27:48-53.
343. Bernstein DI, Teper A, Gopalan G, Gates D. Effects of intranasal mometasone furoate on itchy ear and palate in patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol.* 2012;108:359-362.
344. Meltzer EO, Bernstein DI, Prenner BM, Berger WE, Shekar T, Teper AA. Mometasone furoate nasal spray plus oxymetazoline nasal spray: short-term efficacy and safety in seasonal allergic rhinitis. *Am J Rhinol Allergy.* 2013;27:102-108.

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## APPENDIX A1

### Levels of evidence<sup>12</sup>

Level of evidence	Definition
1++	High quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studiesHigh quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2–	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, for example case reports, case series
4	Expert opinion



## APPENDIX A2

## Evidence table—recent combination therapy for rhinitis

Bibliographic citation	Study type	Evidence level	No. patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Has the study provided answers to the original question?	Weakness/limitations	Cited Y/N
Carr W 2012 JACI <sup>341</sup>	Meta-Analysis	1+ (Grade A)	3398	12 or above. Mod-Sev SAR	Dymista	Az/FP/PI	14 days	Primary rTNSS change Time to response	Minus 5.7 mean r TNSS	MEDA	Yes-combination Az/FP better than individual drugs alone	None	Y
Carr W 2012 Allergy Asthma Proc	Double-blind placebo-control	2+ (Grade C)	610	12 or above. Mod-Sev SAR	Az vs FP	vs PI	14 days	Primary rTNSS change. Secondary r T O S S		MEDA	Az as good as FP overall in treating nose and eye. FP better for rhinorrhoea. At 14 days more volunteers eyes improved in Az group than FP	Post hoc analysis from previous study on Dymista vs AZ/FP/PL	Y
Meltzer EO 2012 Allergy Asthma Proc	Double-blind placebo-control	2+ (Grade C)	779	12 or above. Mod-Sev SAR	Dymista	Az/FP/PI	14 days	Primary rTNSS change. Secondary r T O S S Time to onset of action and 12 hour r individual nasal symptom scores Eye QOL		MEDA	Yes Time to onset action 30 minutes vs placebo. Dymista particularly decreased nasal congestion compared to FP and Az used alone. Dymista overall better at treating eyes than FP alone and possibly just better than Az alone.	None	Y
Baroodi F Am J Rhinol Allergy <sup>342</sup>	Double-blind placebo-control 4 way X-over	2- (Grade C)	21	18-50 yrs NAC out of season in SAR	FF+OP vs FF/PL vs PL/OP vs PL/PL	4 way x over	Pre-Rx groups 1 week and then NACX2	Symptoms nose and eye and nasal histamine and tryptase		GSK	FF/OL no better than FF/PL. Suggests treating the nose with an INS is best for treating the nasal ocular reflex. BUT if done in SAR will OL drops in eye act on effects of pollen in the conjunctiva	Small numbers NAC out of season is artificial	Y
Bernstein D Ann Allergy Asthma Immunol 2012 <sup>343</sup>	Pooled data from 4 DBPC studies	2+ (Grade C)	962	12 or above. Mod-Sev SAR subgroup	MF-only looked at.	Placebo	15 days	Ear and palate itch		MSD	Yes. Decreases itch mouth and ears	Post hoc analysis from previous studies. Confined only to MF	Y

(Continues)

## APPENDIX A2 (Continued)

Bibliographic citation	Study type	Evidence level	No. patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding	Has the study provided answers to the original question?	Weakness/limitations	Cited Y/N
Baroody F JACI 2011	Double-blind placebo-control 4 group parallel	2+ (Grade C)	60	PAR	Oxy vs Oxy/FF vs FF vs PI	Parallel 4 groups	Rx 4 weeks + 2 weeks FU	TNSS and Acoustic Rhinometry		GSK	FF/Oxy better than Oxy or FF alone or placebo in decreasing TNSS including congestion score. AR shows FF/oxy better than Oxy alone. Oxy adds to FF effects on nose.	Small numbers	Y
Meltzer EO 2013 Am J Rhinol <sup>344</sup>	Unblinded, single dummy for MF, placebo control for MF NOT Oxy	2+ (Grade C)	705	SAR	MF + OXY different doses vs MF vs Oxy vs Placebo	vs baseline TNSS		TNSS		MSD	MF/OXY (both doses) same efficacy and better than Oxy or placebo alone. Faster onset of action than just MF alone (MF still as good for relieving TNSS to same level as MF/OXY combinations)	Blinding/Placebo/single dummy	Y
Price D 2013	Open-label, parallel group study, randomised	2+ (Grade C)	Total, 612 with 424 PAR and 188 NAR	Patients aged 12 years and over	Novel Dymista (MP29-02)	PAR and NAR with MP29-02 vs FP	52 weeks	TNSS			Yes, (MP29-02) is more of an effective treatment for chronic rhinitis in PAR and NAR patients compared to FP over 52 weeks	Blinding/placebo	Y