Eur Ann Allergy Clin Immunol Vol 41, N 3, 67-79, 2009

B. Farabollini†, M.C. Braschi, F. Bonifazi

Allergic rhinitis and associated pathologies: the rationale for steroid options

Allergy Unit, Department of Internal Medicine, Immuno-Allergic and Respiratory Deseases, Azienda Ospedaliero-Universitaria "Ospedali Riuniti" di Ancona, Ancona, Italy

Key words

Upper airway inflammation, atopy and sleep disorder, nasal polyps, upper viral infection

Summary

The aim of this review article is to provide greater insight into the relationship between allergic rhinitis and the three most frequently diagnosed conditions of exacerbating viral infections, chronic rhinosinusitis with polyps and obstructive sleep apnoea syndrome. The alleged physiopathological effects of steroids are also investigated within the scope of this paper. Regarding the exacerbating viral infections, seems to establish a dynamic and counter relationship between the load and nature of the viral infection on one hand and widespread and pre-existing allergic inflammation on the other. If chronic rhinosinusitis with polyps and allergic rhinitis present overlapping picture of inflammatory cell and cytokine, the etyiological relationship between the two conditions appears to be influenced by the type of antigenic stimulus. Allergic rhinitis can influence the presence of OSAS through both obstructive and inflammatory mechanical factors. Topical corticosteroid therapy is a promising candidate as a new therapeutic tool able to improve symptoms and quality of life in patient with chronic rhinosinusitis with polyps and obstructive sleep apnoea syndrome. Other study are necessary to elucidate relationship between corticosteroids therapy and hypothetical benefit effect on viral infection when concomitant atopy in patient.

Introduction

The ARIA guidelines were the first ever to recognise the association of allergic rhinitis and its risk factors with the onset and severity of bronchial asthma, involving the upper and lower airways as a single entity, though they present distinct organ symptoms and are treated differently (1). Similarly, other conditions (e.g. chronic rhinosinusitis with and without nasal polyps, vocal cord dysfunction, secretory otitis media and viral infections) have been identified as co-morbidities in subjects with allergic rhinitis.

The aim of this paper is to provide greater insight into the relationship between allergic rhinitis and the three most frequently diagnosed conditions of exacerbating viral infections, chronic rhinosinusitis with polyps and obstructive sleep apnoea syndrome. The alleged physiopathological effects of steroids are also investigated within the scope of this paper.

It has long since been established that allergic reactions occur in two separate phases, the first of which is triggered within a few minutes of exposure to allergen-induced histamine release with arachidonic acid metabolites (leukotrienes, prostaglandins and thromboxanes) progressing into a late stage reaction developing 6-12 hours once exposed to mast cells, T-lymphocytes, basophils and eosinophils.

Activation of these cells produces Th2 cytokines which in turn are responsible for activating endothelials and epithelials, thereby inducing endothelial adhesion molecules like ICAM-1 to be expressed along with vascular cell adhesion molecules, such as VCAM-1. ICAM-1 is a surface glycoprotein which normally directs leukocyte traffic and regulates its accumulation into the inflamed site through the cell-surface ligand of the lymphocyte function-associated antigen (LFA)-1 and macrophage-1 antigen (MAC)-1. Epithelial activation is associated with the production and release of numerous immunoregulatory cytokines which include RANTES, macrophage proteins, inflammatory (MIP)-1·, monocyte chemotactic proteins (MCP)-1, IL-8, and eotaxin (2).

The inflammatory mechanisms described above are activated and detectable in viral infection-mediated exacerbations of the upper airways, in chronic rhinosinusitis with polyps and in nocturnal apnoea syndrome, leading to the hypothesis of a set of mechanisms common to allergic rhinitis and the aforementioned conditions.

The corticosteroid molecules routinely used in the local treatment of allergic rhinitis with good clinical outcomes (1) include beclometasone propionate, flunisolide, budesonide, triamcinolone acetomide, fluticasone propionate, mometasone furoate and more recently fluticasone furoate. Topical corticosteroids provide elevated selectivity for the glucocorticoid receptor and low oral bioavailability (3-5). The effectiveness of fluticasone furoate appears interesting also on ocular symptoms, widening the therapeutic spectrum of this drug class to the naso-lacrimal duct (3,6-8).The mechanism of action of corticosteroids involves changes in DNA molecule which results in a down regulation of transcription, of pro-inflammatory proteins, in an enhanced production of anti-inflammatory proteins, which limits recruitment and action of inflammatory cells, as well as in a reduced secretion of pro-inflammatory mediators during the late phase allergic response (2,9-11).

Allergic rhinitis and viral exacerbations

Airway viruses are powerful stimulants of chemokine and cytokine production. These, rather than the cytopathic impact of the virus itself, are the real culprits of the pro-inflammatory effects of respiratory viral infections (12).

In one study on spontaneously virally infected airway mucosa the majority of the documented cases were caused by rhinoviruses followed by coronaviruses, flu B virus, and respiratory syncytial virus (12) (Fig. 1).

For the most part, the data in the literature come from experimental nasal and/or bronchial inoculations. In worsening asthma, rhinovirus was the most frequent causative pathogen with hospitalisations correlating with the seasonal peak of the infection (14).

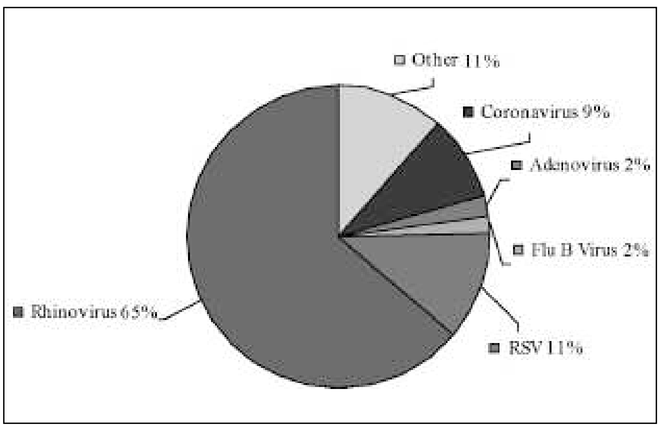
More than 90% of rhinovirus serotypes (15,16) are utilized the ICAM-1 adhesion molecule that trought cell receptors and ligands enable the virus to penetrate a host cell and insert its DNA into the host's genome eventually leading to infection (17). Rhinovirus infection induces ICAM-1 expression, thereby making epithelia susceptible to further viral spread (18).

Rhinovirus infection typically causes common cold symptoms which include rhinorrhoea, nasal congestion, sneezing, sore throat, coughing and headache.

Experimentally infected samples of bronchial epithelial cells along with slight cellular damage reveal a pattern of immunological responses, showing that rhinovirus acts by causing clinical worsening through mechanisms not associated with cell damage (19).

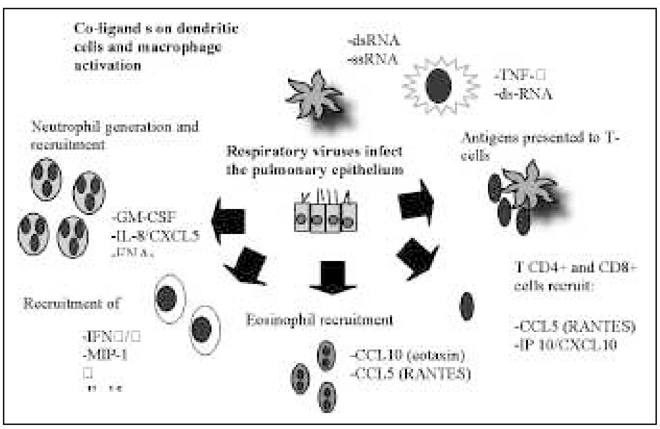
Studies based on genetic expression performed using infected epithelial cells suggest that viral replication induces cytokine and chemokine production which are required for recruiting inflammatory cells for the antiviral response: IL-1, IL-6, IL-8, GM-CSF, eotaxin and RANTES (19-22). The secretion of these mediators can

Figure 1 - Adapted from Edwards MR et al. New treatment regimes for virus-induced exacerbations of asthma. Pulmonary Pharmacology & Therapeutics 2006; 19: 320–334 (13)



contribute to virus-induced activation mechanisms and inflammatory cell recruitment (Fig. 2).
This not only means that the epithelial cells are a target for a potential virus reservoir, but also the site and source of a preliminary inflammatory response.
The cellular response to rhinovirus which takes place in this way is both innate and adaptive. T-cell recruitment (adaptive response) can contribute to the clearance of the virus through Th1 cytokine production, including IFN-γ e IL-12. Indeed, the production of RANTES and protein inducing IFN-γ (IP-10) promotes chemotaxis of Th1 cells (23). IFN-γ plays a crucial role in the protection of the host by promoting inflammation which acts as a chemotactic factor towards eosinophils (24) and perhaps by increasing basophil and mast cell histamine release (25).
Besides the production of specific IgA, IgM, IgG, in experimental models, the B lymphocyte response to viral inoculation induces a rapid increase in total IgE sera in subjects with allergic rhinitis with no evident increase in specific IgE (26).
Apart from histamine release (27), leukotriene C_4 is another mediator whose levels are elevated in nasal lavage mucus and debris during rhinovirus infection (28).
The influence which atopic status and specific sensitisations have on the airway responses to viral infections is still under investigation.
There are important differences in the immunological mechanisms which are activated in atopic and non-atopic individuals. Atopic individuals show elevated histamine release and reduced levels of IL-10 during the acute phase, and higher inflammatory cytokine levels of IL-1β, IL-6, RANTES and ICAM-1 along with the prolonged eosinophilis of the airways during the convalescence phase (12). The reduced concentration of IL-10, a powerful anti-inflammatory cytokine which inhibits the synthesis of both Th1 and Th2 would enhance a Th2 anti-inflammatory response (29).

Figure 2 - Adapted from Edwards MR et al. New treatment regimes for virus-induced exacerbations of asthma. Pulmonary Pharmacology & Therapeutics 2006; 19: 320–334 (13)



According to the premise that the mechanisms which are the basis for the link between viral infection and atopy for rhinitis and allergic asthma are similar (30), it is clear that a typical Th1 anti-viral immune response in atopic individuals can be inhibited by a pre-existing Th2 (31) environment, thereby favouring the persistence of viral inflammation. Indeed, compelling clinical evidence demonstrates the inverse relationship between IFN-γ production and synthesis of Th2 cytokines like IL-4 and IL-5 (30,32).
Additionally, an IgE increase towards airborne allergens has been considered to be a marker of a greater risk factor for the worsening of both the upper and lower airways during an inflammatory response to viral infections (33). On this point, the analysis of experimentally induced rhinovirus infection in adults with mild asthma reveals that a subset of patients whose total IgE is greater than 300 UI/mL present a significant increase in symptoms involving the upper and lower airways compared to healthy controls (33).
One possible explanation of this evidence could lie in the demonstration that IL-13 and other Th2-like cytokines are able to increase ICAM-1 expression on *in vitro* rhinovirus-infected epithelial cell lines (EC line) (34) and that in epithelial cells harvested from nasal brushing in atopic individuals ICAM-1 expression is higher than in healthy subjects; this increase can be ascribed to the exposure to an allergen of an atopic subjects (35).
On one side exposure to an allergen in sensitised subjects can favour viral infections thereby increasing ICAM-1 expression, while as regards the adaptive immune response, the clinical outcome to the respiratory viral infection in allergic subjects depends on how the individual immune response balances the load and type of virus as well as the severity of the pre-existing atopic inflammation. (30) (Tab.1).
Some *in vitro* studies have shown that glucocorticosteroids can block virus-induced pro-inflammatory mechanisms in the airways at an epithelial level by means of corticosteroid-induced down-regulation of ICAM-1 expression by epithelial cells. Indeed, treatment with corticosteroids can inhibit the up-regulation of rhinovirus-induced ICAM-1 (37-40).

Other data show that glucocorticoids can reduce basic ICAM-1 expression and its subsequent induction on exposure to allergens (40).

Similarly, corticosteroids inhaled *in vivo* are able to reduce ICAM-1 expression in bronchoalveolar lavage cells in mild asthmatics (41-44).

Hence, corticosteroids limit the inflammatory action of rhinovirus, not only by inhibiting ICAM-1, but also by reducing cytokine production (Fig.3).

Corticosteroids indeed interfere with the inflammatory process by binding to specific cytoplasmic receptors which: 1) interfere directly with the nuclear -kB factor (NF-kB) and preventing this molecule from attaching itself to DNA and subsequently leading to the release of pro-inflammatory molecules and 2) repress the transcription gene of pro-inflammatory molecules through glucocorticoid-responsive elements, or induce the activation of anti-inflammatory molecules.

For example, pre-treatment with corticosteroids reduces rhinovirus-induced IL-6 production by bronchial epithelials (46), through suppression of the IL-6 gene promoter sequence or reduces IL-8 production through a trans-repression mechanism, inhibiting activator protein-1 (AP-1) and nuclear-kB factor (NF-kB) translocation inside the nucleus, which is required for IL-8 production (41-44).

Interestingly, however, in virus-induced exacerbations of asthma inhaled corticosteroid therapy produces a poorer clinical response, suggesting that mechanisms of steroid resistance develop during worsening,. This circumstance could be related to the increase in nuclear activation factors like the virus-induced activator protein-1 (AP-1) and nuclear-kB factor (NF-kB) (51).

Papi et al. (45) demonstrated that high corticosteroid concentrations do not affect rhinovirus replication or the ability to infect cell lines, which supports the hypothesis that corticosteroids negatively influence rhinovirus replication.

Likewise, Farr et al (52) investigated the role of prednisone (30 mg twice daily) or intranasal beclometasone (168 mg twice daily) administered 3-4 days prior to the rhinovirus challenge which was repeated on 5 successive days. Treatment successfully reduced congestion, rhinorrheoa and kinin production for up to 48 hours after virus inoculation, though any improvement ceased after stopping steroid therapy, suggesting the drug's lack of carry-over effect. The limited amount of experimental data on viral infections of the upper airways and on the clinical effectiveness of topical steroids available to date does not t provide a definitively clear picture of the associated risks and of the efficacy of the treatment (18,53,54).

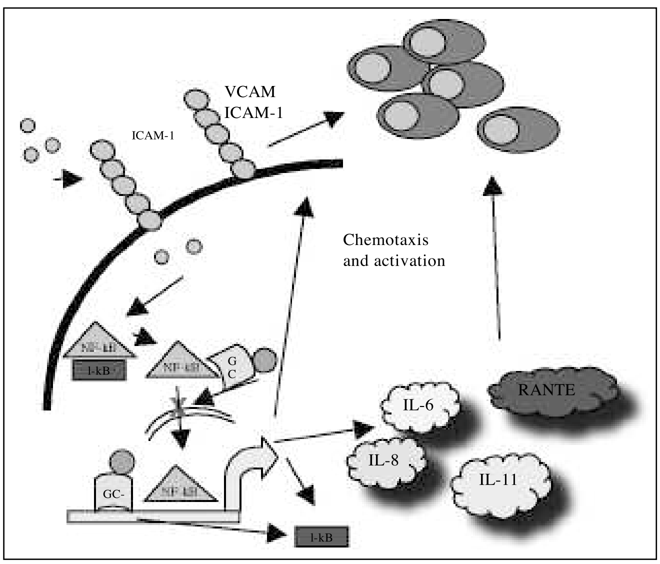
Allergic rhinitis and chronic rhinosinusitis with polyps

In the general population, the prevalence of chronic rhinosinusitis is 15.5% (55), while that of nasal poliposys ranges

Table 1 - Cellular mechanism of susceptibility to the effects of rhinovirus infection (RV) in asthmatics

	Control	Asthmatics
RV ligand:		
ICAM-1 expression	Low	High
Epithelium integrity	Intact	Altered
Post-RV ligand		
IFN-β response	Early,	Deficit
Cellular lysis VS apoptosis	good	Apoptosis damaged Increase in cellular lysis
Release of inflammatory mediators	Present	Increased (?)
Immune response		
Neutrophil recriutment	Present	Increased
Thl response	Poor (IFN-γ)	Lacking (IFN-γ)

Figure 3 - Adapted from Papi A., Nikolaos G. Papadopoulos, Degitz K, Holgate S. T., Johnston S. L. Corticosteroids inhibit rhinovirus -induced intercellular adhesion molecule- 1 up-regulation and promoter activation on respiratory epithelial cells. J Allergy Clin Immunol 2000;105:318-26 (45)



between 1-4%, with a probable multi-factor inflammatory mechanisms which is still being studied (56-62).

Chronic rhinosinusitis with nasal polyps currently presents as a chronic inflammatory disease of the paranasal sinuses, associated with Th2 inflammation, increased numbers of eosinophils (63), presence of mast cells in polyps which are often degranulated (64,65), and local production of polyclonal IgE which often does not correlate with the patient's allergic status (66).

Unlike chronic rhinosinusitus without nasal polyps which in immunological terms presents with a prevalent Th1 profile with elevated levels of interferon-γ (IFN-γ) and transforming growth factor-β (TGF-β), nasal polyps are characterised by eosinophil inflammation (55) with elevated concentrations of eosinophil cationic protein (ECP), with eotaxin cellular activation markers and IL-5 cooperating in eosinophil recruitment and activation. The activated eosinophils infiltrate the nasal polyps producing toxic mediators as well as a variety of chemokines, cytokines and growth factors whose action probably reduces apoptosis and favours increased tissue infiltration through an autocrine mechanism.

It is widely accepted that eosinophils are one of the markers of allergic inflammation.

In patients with nasal polyps and concomitant allergic rhinitis, eosinophils seem mainly attracted by the release of IL-5. In contrast, in the absence of allergy, recruitment appears to correlate with GM-CSF release (67). Nevertheless, the eventual eosinophil influx seems to be identical for both atopic and non-atopic subjects.

Factors associated with chronic rhinosinusitis with polyps are aspirin intolerance (68-73) where 36-96% of sufferers have polyposis, asthma (26-42% of asthmatic with nasal polypolsis) (59), genetically pre-disposed to chronic rhinosinusitis with nasal polyps and environmental factors, especially cigarette smoke (74-77).

When an allergy clinic medical records of almost 5,000 patients were re-examined, the prevalence of nasal polyposis was 4.2% (78), highest among asthmatics (6,7%).

The aetiology of polyposis has been ascribed to to allergy, but this has never been definitely established (79). Between 0.5% and 4.5% of subjects with allergic rhinitis present with nasal polyposis (78,79), a prevalenche that matches that of general population (80). In children, the prevalence of chronic rhinosinusitis with polyps shows a wide variability ranging between 0.1% (78) and 25.6%. (81) of cases.

On the other hand the prevalence of allergic sensitisation in patients with nasal polyposis varies between 10% and 64% (79-84).

If subjects with nasal polyposis and controls with chronic rhinosinusitis are compared for allergic sensitisation a major prevalence of sensitisation to perennial allergens emerges in the former and seasonal allergens in the latter (85).

Though nasal polyposis is classified as showing two different histopathological subtypes, showing a predominance eosinophils and neutrophils, respectively, atopic status did not significantly differ between the 2 subsets, being 62.7% and 81.8% respectively (86).

In contrast with studies reporting that atopy is more frequent in patients with nasal polyposis other studies have not been able to confirm this finding (87-89). In a recent paper, Bachert et al. (56) demonstrated that the presence of atopy, based on allergy testing with airborne allergens, does not correlate with total IgE or IgE antibodies present in nasal polyp tissue and that atopy has no impact on IL-5, IL-4, eotaxin, LTC4/D4/E4, ECP levels nor on the number of eosinophils in nasal polyp tissue. Moreover, Wagenmann et al. (90) demonstrated that Th1 and Th2 cytokines increased esinophils in nasal polyps irrespective of allergic test results. This finding was confirmed by the observation that IL-5 concentration in nasal polyps, which is significantly higher than in controls, correlates independently with atopic status (55). By contrast, Hamilos et al (91) identified different cytokine content in polyp tissues samples collected from allergic and non-allergic subjects.

Although the relationship between allergy and nasal polyps is not clear, from clinical point of wiev the sympton score does not have increase effect.

Indeed, it has been demonstrated in atopic subjects with nasal polyposis that allergen exposure does not correlate with sectioned polyps, clinical scores and the frequency of worsenings (92,93).

The histological findings of a chronic inflammatory infiltrate made up of lymphocytes, plasma cells, eosinophils and respective cytokines suggest a chronic inflammatory type mechanism. Research is underway to isolate the agents responsible for inducing and/or favouring persistent inflammation of paranasal sinuses.

Several micro organisms have been investigated to determine their causal role in chronic rhinosinusitis with polyps. Ponikau et al (94) reported that fungi were present in 96% of 210 patients evaluated for rhinosinusitis. Braun et al. (95) found a comparably high incidence of fungal colonisation in chronic rhinosinusitis sufferers (91%), but together with Ragab et al. they demonstrated that the colonisation occurs frequently in healthy controls (91-100%) (96).

Other pathogens frequently seen in mucus from patients with nasal polyposis are bacteria, especially Staphylococcus aureus (66,97,98).
Van Zele et al. documented that Staphylococcus aureus colonises the centre of middle meatus prevalently in patients with nasal polyposis (64%) compared to those with chronic rhinosinusitis (27%) and healthy controls (33%) (97). Colonisation by Staphylococcus aureus is paralleled by IgE specific for Staphylococcus aureus-derived enterotoxin. The tissue concentration of specific IgE towards Staphylococcical enterotoxinin the nasal polyposis is associated with asthma and aspirin intollerance. Similarly, elevated levels of eosinophils infiltrating nasal polyps and IgE production were detected in this group of patients.
This IgE production appears to be polyclonal, indicating that the S.aureus-derived enterotoxin can behave as a superantigen and activate large subpopulations of T-lymphocytes (56). Besides the enterotoxin, these bacteria express a number of surface proteins like Protein A (SpA) which have the potential to interfere with host defence mechanisms (99,100).
A recent study revealed (101) different temporal and immunological stimulations by various S.aureus-derived products: while staphylococcal enterotoxin is activated through the release of several immunoregolatory and proinflammatory cytokines in the late stage (after approximately 24 hr) favouring a Th2 type pattern, Protein A (SpA) induces the release of mast cell mediators, namely histamines, the leukotrienes LTC4/D4/E4 and prostaglandin PGD2 after only 30 minutes. These data highlight the influence of S.aureus-derived products on nasal polyposis inflammation inducing mast cell degranulation and T-cell activation.
Another extremely interesting chapter in understanding the natural history of chronic allergic rhinitis and rhinosinusitis with and without nasal polyposis is the remodelling in the upper airways (102).
Similarly to bronchial asthma, chronic rhinosinusitis with polyps shows epithelial damage, basement membrane thickening and oedema, at times, with extensive fibrotic tissue (103). A recent study evaluated the presence of MMP-7, MMP-8, MMP-9 and tissue inhibitor of metalloproteinases (TIMP) in chronic rhinosinusitis with polyps, suggesting the role of an imbalance between metalloproteinases and their natural inhibitors (104,105).
By stereologically testing the vascular surface and the density of nasal tissue volume in rhinitic and non-rhinitic subjects, some authors have demonstrated a lack of vascular remodelling in the mucous membrane of allergic subjects (106, 107), whereas others hypothesise increased angiogenesis at a nasal level (108,109).
All authors agree, however, that limited damage to nasal allergic rhinitis mucosa is indicative of extensive remodelling of bronchial mucosa in asthmatics (104).
In the extensive review of the literature on the treatment of nasal polyposis, the European Position Paper on Rhinosinusitis and Nasal Polyposis (55) stresses the importance of disease management recommending steroid therapy as the mainstay of treatment for this condition. Substantial evidence exists supporting the efficacy of topical corticosteroids in reducing the size of nasal polyps (110,111). However, certain patients are either poor responders to steroid therapy or develop resilience to it.
Consistent with studies of the lower airways which demonstrate that glucocorticoid-insensitive asthma is associated with a significantly elevated level of $GR\beta^{+}$inflammatory cells (112-114), the same mechanism has been hypothesised for nasal polyps as well. Hamilos et al. underline an association between $GR\beta$ expression and glucocorticoid insensitivity in nasal polyposis and in particular in patients with aspirin intolerance. Specifically, the authors report an inverse correlation between $GR\beta$ basal expression and post-corticosteroid therapy reduction of eosinophils, T-lymphocytes and the expression of VCAM-1 and mRNA cells positive to IL-4 (115). However, other authors having failed to determine the role of $GR\alpha$ and $GR\beta$ as markers of corticosteroid-insensitivity in nasal polyposis cannot confirm this finding (112), ultimately leading to the conclusion that neither the $GR\alpha$ receptor, nor $GR\beta$ are responsible for glucocorticoid sensitivity in nasal polyposis.
Based on the data above, further studies will be necessary to clarify the various degrees of sensitivity to topical steroids and for a better comprehension the therapeutic effect should be valuated differentiating allergy sufferers with eosinophil polyposis and allergy sufferers without eosinophil polyposis (92,93,116).

Allergic rhinitis and obstructive sleep apnoea syndrome

Obstructive sleep apnoea syndrome (OSAS) is a clinical condition characterised by recurrent nocturnal episodes of apnoea ed hypopnoea, experienced by 4-10% of men and 2-4% of women (117,118).
The physiopathological mechanisms underlying OSAS are complex and have yet to be fully understood (119).
There are two types of relationships that can occur be-

tween allergic rhinitis and OSAS: purely mechanical or inflammatory, both local and systemic.

Interaction between nasal and oral resistance could be implicated in the physiopathology of this disorder. Indeed, the upper airways are described as a Starling resistor which resembles an empty tube partially occluded at the start of the nose area and partly collapsed at the section below it corresponding to the oropharynx (120). The clinical significance of the properties of the resistor imply that changes in pressure and intraluminal resistance and/or the collapsibility of the airways influence patency, so that high inspiratory pressure will reduce airflow (121,122).

Among the factors that influence maximal airflow in the collapsible section of the airways (122) besides increased intranasal pressure, which occurs during therapy (CPAP, BiPAP), or greater collapsibilty due to an anatomical predisposition of the intermediate region of the resistor (oropharynx), a possible third factor is upper airway resistance, particularly in the nose (123).

In the presence of nasal obstruction, the ability of the section below to collapse increases (119) in that a Bernoulli-type effect occurs due to increased negative pressure at the oropharyngeal level during inspiration (124).

The Starling resistor theory therefore hypothesises that nasal obstruction plays an important role in the physiopathology of OSAS (119), though the success rate of corrective nasal surgery is poor, only rarely substantially reducing the frequency of apnoea/hypopnoea attacks (125).

On this point, data is largely controversial regarding nasal obstruction as a risk factor for OSAS. On the one hand studies done using objective parameters of nasal resistance in snorers have been unable to produce a correlation between increased resistance to airflow in the nasal fossa and OSAS (126-128), while on the other, a subsequent study performed on a large snorer population who underwent posterior rhinomanometry successfully found that nocturnal nasal obstruction is an independent risk factor for OSAS (124).

The authors who used multiple regression analysis demonstrated that nasal obstruction contributes to the development of OSAS in 2.3% of cases, while other noted risk factors such as the distance between the hyoid bone and mandibular plane, BMI, male sex and age contribute 6.2 %, 4.6%, 3% and 1.3% respectively to the variation (124).

In addition, a stronger correlation was found between an increase in nasal resistance when supine and OSAS (129,130). Indeed, nasal congestion increases in the supine body position and worsens during sleep, especially in the case of allergic rhinitis when inflammatory mediators peak in the early hours of the morning which combine with a reduced sympathetic nocturnal tone inducing a corresponding increase in parasympathetic tone which is associated with nasal congestion (131).

Several studies have investigated the relationship between nasal obstruction in allergic subjects and respiratory changes during sleep. In their cohort study of 911 subjects who were given a polysomnograph Young et al. (128) reported substantial respiratory changes during sleep in subjects with symptomatic allergic rhinitis compared to those without nasal symptoms. However, the same authors found no linear correlation between reduced upper airways airflow and the severity of breathing changes during sleep.

As allergic rhinitis produces various types of nasal obstruction it has been the subject of study: micro-awakening associated with breathing disorders in sleep are far more frequent in subjects with seasonal allergic rhinitis than in healthy controls (132,133).

One case control study by Canova et al (134) aimed to evaluate whether atopy to perennial allergens and subsequent allergic rhinitis were risk factors for OSAS. The authors concluded that the prevalence of allergic rhinitis was higher in OSAS subjects than in COPD controls. Therefore the author hypothesized that allergic rhinitis to perennial allergens is a risk factor for OSAS and that treatment of this comorbidity is important in reducing OSAS morbility (134). This is the first study to identify the link between OSAS and perennial allergic rhinitis (134). To support this paper's case we cite the study by McNicholas et al. (132) which documents that seasonal allergic rhinitis patients have a higher apnoea/hypopnoea index (AHI) and more protracted seizures of sleep apnoea in the pollen season. More recently, the same author (135) evaluated the efficacy of intranasal steroid therapy in subjects with OSAS and allergic rhinitis by applying the parameters of nocturnal apnoea severity, sleep quality, snoring and daytime symptoms. The OSAS was found to improve, as indicated by a fall in the apnoea/hypopnoea index, with no snoring improvement, leading to the author's conclusion that steroid therapy could benefit selected groups of patients with OSAS.

Subsequent studies reported significant associations between breathing disorders during sleep and nasal obstruction of diverse origins (134,136,137).

As for inflammatory factors in OSAS, it has recently been reported that the presence of systemic inflammation is associated with daytime sleepiness and an increased risk for

cardiovascular complications or metabolic syndrome in these patients (138).
The underlying inflammation of OSAS has been attributed to a mechanical change in airways tissue induced by repeated trauma from snoring and the hypoxia-normoxia cycle of the disorder (138).
Systemic inflammation in OSAS is characterised by an increase in TNF-α, IL-6, PCR, IL-1, and the ICAM-1 adhesion molecule plasma values (139, 140). Intermittent hypoxemia can also stimulate transition factors like nuclear factor-kB and increase cytokine production (141).
A comparison of nasal lavage in OSAS and normal subjects yields a higher number of neutrophils and, concentrations of bradykinins and VIP in the former (142).
The evaluation of inflammation through analysis of induced sputum confirms the high percentage of neutrophils and reduced number of macrophages in OSAS sufferers, while other cell populations do not appear to present any differences from those of healthy controls (143). IL-6 and 8-isopentane values measured in exhaled breath condensate were elevated in OSAS patients compared to those of obese and control subjects (144).
These data demonstrate that similarly to systemic inflammation in OSAS patients, the airways are also characterised by local inflammation and oxidative stress (138).
As previously mentioned, through the hypothetical resistor model the mechanics of the upper airways determines the significant role of nasal obstruction (119). A recent editorial by (119) McNicholas et al. makes the assumption that variable nasal obstruction plays a more important role in the physiopathology of OSAS than anatomical obstruction in the nasal cavities. This is a partially biased point of view which bases itself on the hypothesis that in subjects with fixed nasal obstruction an oral respiration adaptive response develops which limits the impact of the pathogenesis of nasal obstruction OSAS. The response does not seen to occur in intermittent nasal obstruction, whose relationship is more closely linked with automatic nasal respiration.
In children, the prevalence of OSAS is 2-3% (145) of which the highest incidence is between 2-8 year olds. Though anatomical and neuromuscular abnormalities can contribute to the development of OSAS its severity is especially related to adenoid and palatine tonsil size (146, 147) to such an extent that the choice treatment is an adenotonsillectomy (148).
Adenotonsillar hypertrophy is frequent in children with allergic rhinitis (149,150). A study of 28 children with seasonal allergic rhinitis revealed a significant increase in adenoid size in 71% of cases with an associated decrease of the nasopharyngeal cavity in 93% of subjects during the pollen season (151). These changes subside in 90% of the subjects after the pollen season ends.
As a result, in children, snoring and OSAS are associated with adenotonsillar hypertrophy and chronic rhinitis, and allergic rhinitis increases the risk for OSAS especially in children with habitual snoring (152).
The combination of steroid therapy and adenoidectomy is a key competitor in the treatment of paediatric populations (153). However, in the management of OSAS the benefits of oral corticosteroid therapy do not appear to be diminished when compared to the outcome of an adenoidectomy (153), practised by general consensus in the last decade to reduce the size of upper airways lymphoid tissue (154-158).
More recent studies (159) have demonstrated that the upper airways lymphoid tissue in children with OSAS presents a large number of glucocorticoid receptors α, and hypothesise that the better topical steroid therapy response is linked to this circumstance.
In one study (145) of 62 children polysomnographically diagnosed with mild OSAS, the administration of intranasal corticosteroids seemed to reduce the severity of OSAS and the size of the underlying adenoid hypertrophy, which lasted eight weeks after discontinuing therapy. Moreover, in a previous study, after six weeks of topical fluticasone treatment, the steriod improved the apnoea/hypopnoea index (AHI) in children with OSAS (155), which was confirmed by a fall in the number of episodes of haemoglobin desaturation, activation of the respiratory muscles and night time awakenings.

Conclusions

Though allergic rhinitis, viral exacerbations, chronic rhinitis with polyps and OSAS have many inflammatory mechanisms in common, further studies will be necessary to investigate the most controversial hypotheses.
Viral exacerbations in particular belong to this category, where a dynamic relationship and counter relationship seem to develop between the load and nature of the viral infection on one hand and widespread and pre-existing allergic inflammation on the other. That being so dynamism related therapy, Any data remains necessarily undefined regarding the effects of steroid therapy, when there is a concomitant viral inflammatory response of the airway mucus.

Once again, if chronic rhinosinusitis with polyps and allergic rhinitis present an inflammatory cell and cytokine in pictures which match, the etyiological relationship between the two conditions appears to be influenced by the type of antigenic stimulus, which is more powerful in the case of the Staphylococcus aureus super antigens and mycophytes but less for dust mites, pollens and animal dander.

No one questions the efficacy of topical nasal steroids for the treatment of allergic rhinitis especially when obstructive and of eosinophilic chronic rhinitis with polyps.

Data from the literature seem to indicate that nasal obstruction is probably a smaller risk factor for OSAS that other already detected risk factors, and that allergic rhinitis can influence the presence of OSAS through both obstructive and inflammatory mechanical factors. It seems probable that OSAS itself can contribute to the severity of allergic rhinitis. Topical corticosteroid therapy, even in paediatric age is a promising candidate as a new therapeutic tool able to improve symptoms and quality of life in patients with obstructive allergic rhinitis and OSAS

References

1. Bousquet J, Van Cauwenberge P, Khaltaev N. ARIA Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 2001; 108: S147-S334.
2. Howarth PH. A comparison of the anti-inflammatory properties of intranasale corticosteroids and antihistamines in allergic rhinitis. Allergy 2000; 62:6-11.
3. Mc Cormack P, Scott LJ. Fluticasone furoate –Intranasal Use in Allergy Rhinitis. Drugs 2007; 67(13):1905-15.
4. Salter M et al. Pharmacological properties of the enhanced-affinity glucocorticoid fluticasone furoate in vitro and an in vivo model of respiratory inflammatory disease. Am J Physiol Lung Cell Mol Physiol 2007; 293: L6660-L667.
5. Biggadike K et al. X-ray crystal structure of the novel enhanced-affinity glucocorticoid agonist fluticasone furoate in the glucocorticoid receptor-ligand binding domain. J Med Chem. 2008;51:3349-52.
6. Fokkens WJ et al. Once daily fluticasone furoate nasal spray is effective in seasonal allergic rhinitis caused by grass pollen. Allergy 2007; 62:1078-84.
7. Maspero JF et al. Safety and efficacy of fluticasone furoate in pediatric patients with allergic rhinitis. Otolaryngol Head Neck Surg. 2008;138:30-7.
8. Vasar M et al. Fluticasone furoate nasal spray: effective monotherapy for symptoms of perennial allergic rhinitis in adult/adolescents. Allergy Asthma Proc 2008;29:313-21.
9. Derendorf H, Meltzer EO. Molecular and clinical pharmacology of intranasal corticosteroids: clinical and therapy implications. Allergy 2008: 63:1292-300.
10. Onrust SV, Lamb HM. Mometasone furoate. A review of its intranasal use in allergic rhinitis. Drugs 1998;56:725-45.
11. Naclerio RM. Allergic rhinitis. N Eng J Med 1991;325:860-9.
12. Jonathan M. Corne, Laurie Lau, Stephen J. Scott, Rhys Davies, Sebastian L. Johnston, Peter H. Howarth. The Relationship between Atopic Status and IL-10 Nasal Lavage Levels in the Acute and Persistent Inflammatory Response to Upper Respiratory Tract Infection. Am J Respir Crit Care Med 2001;163:1101–7.
13. Edwards MR et al. New treatment regimes for virus-induced exacerbations of asthma. Pulmonary Pharmacology & Therapeutics 2006; 19: 320–34.
14. Johnston SL, Pattemore PK, Sanderson G, Smith S, Campbell MJ, Josephs LK, et al. The relationship between upper respiratory infections and hospital admissions for asthma: a time-trend analysis. Am J Respir Crit Care Med 1996;154: 654-60.
15. Greve JM, Davis G, Meyer AM, Forte CP, Yost SC, Marlor CW, et al. The major human rhinovirus receptor is ICAM-1. Cell 1989;56:839-47.
16. Hofer F, Gruenberger M, Kowalski H, Machat H, Huettinger M, Kuechler E, et al. Members of the low density lipoprotein receptor family mediate cell entry of a minor-group common cold virus. Proc Natl Acad Sci U S A 1994;91:1839-42.
17. Smith CW, Marlin SD, Rothlein R, Toman C, Anderson DC. Cooperative interactions of LFA-1 and Mac-1 with intercellular adhesion molecule-1 in facilitating adherence and transendothelial migration of human neutrophils in vitro. J Clin Invest 1989;83:2008-17.
18. Papi A, Johnston SL. Rhinovirus infection induces expression of its own receptor intercellular adhesion molecule 1 (ICAM-1) via increased NF-kappaB-mediated transcription. J Biol Chem 1999;274:9707-20.
19. Schroth MK, Grimm E, Frindt P, Galagan DM, Konno SI, Love R, et al. Rhinovirus replication causes RANTES production in primary bronchial epithelial cells. Am J Respir Cell Mol Biol 1999;20:1220-8.
20. Papadopoulos NG, Papi A, Meyer J, Stanciu LA, Salvi S, Holgate ST, et al. Rhinovirus infection up-regulates eotaxin and eotaxin-2 expression in bronchial epithelial cells. Clin Exp Allergy 2001;31:1060-6.
21. Zhu Z, Tang W, Gwaltney JM Jr, Wu Y, Elias JA. Rhinovirus stimulation of interleukin-8 in vivo and in vitro: role of NF-kappaB. Am J Physiol 1997;273: L814-24.
22. Terajima M, Yamaya M, Sekizawa K, Okinaga S, Suzuki T, Yamada N, et al. Rhinovirus infection of primary cultures of human tracheal epithelium: role of ICAM-1 and IL-1beta. Am J Physiol 1997;273:L749-59.
23. Wark PA, Bucchieri F, Johnston SL, Gibson PG, Hamilton L, Mimica J, et al. IFN-gamma-induced protein 10 is a novel biomarker of rhinovirus-induced asthma exacerbations. J Allergy Clin Immunol 2007;120:586-93.
24. Chen Y, Hamati E, Lee PK, Lee WM, Wachi S, Schnurr D, et al. Rhinovirus induces airway epithelial gene expression through double-stranded RNA and IFNdependent pathways. Am J Respir Cell Mol Biol 2006;34:192-203.
25. Ida S, Hooks JJ, Siraganian RP, Notkins AL. Enhancement of IgE mediated histamine release from human basophils by viruses: role of interferon. J Exp Med 1977;145:892–906.
26. Skoner DP, Doyle WJ, Tanner EP, Kiss J, Fireman P. Effect of

rhinovirus 39 (RV- 39) infection on immune and inflammatory parameters in allergic and non-allergic subjects. Clin Exp Allergy 1995;25:561-7.
27. Chonmaitree T, Left-Brown MA, Tsong Y, Goldman AS, Baron S. Role of interferon in leukocyte histamine release caused by common respiratory viruses. J Infect Dis 1988;157:127–132.
28. Gentile DA, Fireman P, Skoner DP. Elevations of local leukotriene C4 levels durino viral upper respiratory tract infections. Ann Allergy Asthma Immunol 2003; 91:270-4.
29. Del Prete G, DeCarli M, Almerigogna F, Giudizi MG, Biagiotti R, Romagnani S. Human IL-10 is produced by both type 1 helper (Th1) and type 2 helper (Th2) T cell clones and inhibits their antigen-specific proliferation and cytokine production. J Immunol 1993;150:353–60.
30. Gern JE, Vrtis R, Grindle KA, Swenson C, Busse WW. Relationship of upper and lower airway cytokines to outcome of experimental rhinovirus infection. Am J Respir Crit Care Med 2000;162:2226-31.
31. Patrick Mallia, Sebastian L. Johnston, How Viral Infections Cause Exacerbation of Airway Diseases CHEST 2006; 130:1203–10.
32. Papadopoulos NG, Stanciu LA, Papi A, et al. A defective type 1 response to rhinovirus in atopic asthma. Thorax 2002; 57:328–32
33. John T. Kelly, William W. Busse. Host immune responses to rhinovirus: Mechanisms in asthma. J Allergy Clin Immunol 2008;122:671-82.
34. Bianco A, Sethi SK, Allen JT, Knight RA, Spiteri MA. Th2 cytokines exert a dominant influence on epithelial cell expression of the major group human rhinovirus receptor, ICAM-1. Eur Respir J 1998;12:619-26.
35. Bianco A, Whiteman SC, Sethi SK, Allen JT, Knight RA, Spiteri MA. Expression of intercellular adhesion molecule-1 (ICAM-1) in nasal epithelial cells of atopic subjects: a mechanism for increased rhinovirus infection? Clin Exp Immunol 2000;121:339-45.
36. P A B Wark and P G Gibson Asthma exacerbations · 3: Pathogenesis Thorax 2006;61;909-15.
37. Rennard SI, Aalbers R, Bleecker E, Klech H, Rosenwasser L, Olivieri D et al. Bronchoalveolar lavage: performance, sampling procedure, processing and assessment. Eur Respir J Suppl 1998;26:13S-15S.
38. Gern JE, Dick EC, Lee WM, Murray S, Meyer K, Handzel ZT et al. Rhinovirus enters but does not replicate inside monocytes and airway macrophages. J Immunol 1996;156:621–7.
39. Johnston SL, Papi A, Monick MM, Hunninghake GW. Rhinoviruses induce interleukin-8 mRNA and protein production in human monocytes. J Infect Dis 1997;175:323–9.
40. Donninger H, Glashoff R, Haitchi HM, Syce JA, Ghildyal R, van Rensburg E et al. Rhinovirus induction of the CXC chemokine epithelial-neutrophil activating peptide-78 in bronchial epithelium.J Infect Dis 2003;187:1809–17.
41. van de Stolpe A, Caldenhoven E, Raaijmakers JA, van der Saag PT, Koenderman L. Glucocorticoid-mediated repression of intercellular adhesion molecule-1 expression in human monocytic and bronchial epithelial cell lines. Am J Respir Cell Mol Biol 1993;8:340-7.
42. Barnes PJ. Mechanisms of action of glucocorticoids in asthma. Am J Respir Crit Care Med 1996;154:S21-6.
43. Brinkmann V, Kristofic C. Regulation by corticosteroids of Th1 and Th2 cytokine production in human CD4+ effector T cells generated from CD45RO- and CD45RO+ subsets. J Immunol 1995;155:3322-8.
44. Olivieri D, Chetta A, Del Donno M, et al. Effect of short-term treatment with low-dose inhaled fluticasone propionate on airway inflammation and remodeling in mild asthma: a placebo-controlled study. Am J Respir Crit Care Med 1997;155:1864-71.
45. Papi A., Nikolaos G. Papadopoulos, Degitz K, Holgate S. T., Johnston S. L. Corticosteroids inhibit rhinovirusinduced intercellular adhesion molecule- 1 up-regulation and promoter activation on respiratory epithelial cells. J Allergy Clin Immunol 2000;105:318-26.
46. Edwards MR, Haas J, Panettieri RA Jr, Johnson M, Johnston SL. Corticosteroids and beta2 agonists differentially regulate rhinovirus-induced interleukin-6 via distinct Cis-acting elements. J Biol Chem 2007;282:15366-75.
47. Pelaia G, Vatrella A, Cuda G, Maselli R, Marsico SA. Molecular mechanisms of corticosteroid actions in chronic inflammatory airway diseases. Life Sci 2003;72: 1549-61.
48. Pelaia G, Cuda G, Vatrella A, Grembiale RD, De Sarro G, Maselli R, et al. Effects of glucocorticoids on activation of c-jun N-terminal, extracellular signal-regulated, and p38 MAP kinases in human pulmonary endothelial cells. Biochem Pharmacol 2001;62:1719-24.
49. Auphan N, DiDonato JA, Rosette C, Helmberg A, Karin M. Immunosuppression by glucocorticoids: inhibition of NF-kappa B activity through induction of I kappa B synthesis. Science 1995;270:286-90.
50. Edwards MR, Mukaida N, Johnson M, Johnston SL. IL-1beta induces IL-8 in bronchial cells via NF-kappaB and NF-IL6 transcription factors and can be suppressed by glucocorticoids. Pulm Pharmacol Ther 2005;18:337-45.
51. N. G. Papadopoulos, P. Xepapadaki, P. Mallia, G. Brusselle, J.-B. Watelet, M. Xatzipsalti, G. Foteinos, C. M. van Drunen, W. J. Fokkens, C. D'Ambrosio, S. Bonini, A. Bossios, Jan Lçtvall, P. van Cauwenberge, S. T. Holgate, G. W. Canonica, A. Szczeklik, G. Rohde, J. Kimpen, A. Pitk_ranta, M. Mäkelä, P. Chanez, J. Ring, S. L. Johnston. Mechanisms of virus-induced asthma exacerbations: state-of-theart. A GA2LEN and InterAirways document Allergy 2007: 62: 457–70.
52. Farr BM, Gwaltney Jr JM, Hendley JO, Hayden FG, Naclerio RM, McBride T, et al. A randomized controlled trial of glucocorticoid prophylaxis against experimental rhinovirus infection. J Infect Dis 1990;162(5):1173–7.
53. Wark PA, Johnston SL, Bucchieri F, et al. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. J Exp Med 2005; 201:937–47.
54. Wang J, Zhu Z, Nolfo R, Elias JA. Dexamethasone regulation of lung epithelial cell and fibroblast interleukin-11 production. Am J Physiol 1999;276(1, part 1):L175–85.
55. Wytske Fokkens, Valerie Lund, Joaquim Mullol, on behalf of the European Position Paper on Rhinosinusitis and Nasal Polyps group. European Position Paper on Rhinosinusitis and Nasal Polyps. Rhinology 2007; 45; suppl. 20: 1-139.
56. Bachert C, Gevaert P, Holtappels G, Johansson SG, van Cauwenberge P. Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. J Allergy Clin Immunol

2001;107:607-14.
57. Kirsch JP, White JA. Nasal polyposis. J La State Med Soc 1990;142:11-4.
58. Johansson L, Akerlund A, Holmberg K, Melen I, Bende M. Prevalence of nasal polyps in adults: the Skovde populationbased study. Ann Otol Rhinol Laryngol. 2003;112(7):625-9.
59. Hedman J, Kaprio J, Poussa T, Nieminen MM. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. Int J Epidemiol. 1999;28(4):717-22.
60. Klossek JM, Neukirch F, Pribil C, Jankowski R, Serrano E, Chanal I, et al. Prevalence of nasal polyposis in France: A cross-sectional, case-control study. Allergy. 2005;60(2):233-7.
61. Larsen PL, Tos M. Origin of nasal polyps. Laryngoscope. 1991;101(3):305-12.
62. Larsen PL, Tos M. Site of origin of nasal polyps. Transcranially removed naso-ethmoidal blocks as a screening method for nasal polyps in autopsy material. Rhinology. 1995;33(4):185-8.
63. Van Zele T, Claeys S, Gevaert P, Van Maele G, Holtappels G, Van Cauwenberge P, et al. Differentiation of chronic sinus diseases by measurement of inflammatory mediators. Allergy 2006;61:1280-9.
64. Kawabori S, Denburg JA, Schwartz LB, Irani AA, Wong D, Jordana G, et al. Histochemical and immunohistochemical characteristics of mast cells in nasal polyps. Am J Respir Cell Mol Biol 1992;6:37-43.
65. Sasaki Y. Distribution of the degranulated and non-degranulated mast cells in nasal polyp. Acta Otolaryngol 1986;430(Suppl):34-8.
66. Gevaert P, Holtappels G, Johansson SG, Cuvelier C, Cauwenberge P, Bachert C. Organization of secondary lymphoid tissue and local IgE formation to Staphylococcus aureus enterotoxins in nasal polyp tissue. Allergy 2005;60:71-9.
67. Hamilos DL, Leung DY, Huston DP, Kamil A, Wood R, Hamid Q. GM-CSF, IL-5 and RANTES immunoreactivity and mRNA expression in chronic hyperplastic sinusitis with nasal polyposis (NP). Clin Exp Allergy 1998;28:1145–52.
68. Settipane GA, Chafee FH, Klein DE. Aspirin intolerance. II. A prospective study in an atopic and normal population. J Allergy Clin Immunol. 1974;53(4):200-4.
69. Chafee F, Settipane GA. Aspirin intolerance. I. Frequency in an allergic population. J Allergy Clin Immunol. 1974;53:193-9.
70. Weber RW, Hoffman M, Raine DA, Jr., Nelson HS. Incidence of bronchoconstriction due to aspirin, azo dyes, non-azo dyes, and preservatives in a population of perennial asthmatics. J Allergy Clin Immunol. 1979;64(1):32-7.
71. Szczeklik A, Gryglewski RJ, Czerniawska-Mysik G. Clinical patterns of hypersensitivity to nonsteroidal anti-inflammatory drugs and their pathogenesis. J Allergy Clin Immunol. 1977;60(5):276-84.
72. Spector SL, Wangaard CH, Farr RS. Aspirin and concomitant idiosyncrasies in adult asthmatic patients. J Allergy Clin Immunol. 1979;64(6 Pt 1):500-6.
73. Ogino S, Harada T, Okawachi I, Irifune M, Matsunaga T, Nagano T. Aspirin-induced asthma and nasal polyps. Acta Otolaryngol Suppl. 1986;430:21-7.
74. Rugina M, Serrano E, Klossek JM, Crampette L, Stoll D, Bebear JP, et al. Epidemiological and clinical aspects of nasal polyposis in France; the ORLI group experience. Rhinology. 2002;40(2):75-9.
75. Luxenberger W, Posch U, Berghold A, Hofmann T, Lang-Loidolt D. HLA patterns in patients with nasal polyposis. Eur Arch Otorhinolaryngol. 2000;257(3):137-9.
76. Molnar-Gabor E, Endreffy E, Rozsasi A. HLA-DRB1, -DQA1, and -DQB1 genotypes in patients with nasal polyposis. Laryngoscope. 2000;110(3 Pt 1):422-5.
77. Liu Z, Kim J, Sypek JP, Wang IM, Horton H, Oppenheim FG, et al. Gene expression profiles in human nasal polyp tissues studied by means of DNA microarray. Journal of Allergy & Clinical Immunology. 2004;114(4):783-90.
78. Settipane GA, Chafee, F.H. Nasal polyps in asthma and rhinitis. J Allergy Clin Immunol. 1977;59:17-21.
79. Caplin I, Haynes JT, Spahn J. Are nasal polyps an allergic phenomenon? Ann Allergy 1971;29:631–4.
80. Drake-Lee A. Nasal polyps. In: Mygind N, Naclerio RM, editor. Allergic and non-allergic rhinitis. Copenhagen: Munksgaard; 1993.
81. Kern R, Schenck H-P. Allergy: a constant factor in the etiology of so-called mucous nasal polyps. J Allergy. 1993;4:483.
82. Delaney JC. Aspirin idiosyncrasy in patients admitted for nasal polypectomy. Clin Otolaryngol. 1976;1(1):27-30.
83. Blumstein GI, Tuft Ll. Allergy treatment in recurrent nasal polyposis: its importance and value. Am J Med Sci. 1957;234(3):269-80.
84. English G. Nasal polyposis. In: GM E, editor. Otolaryngology. Philadelphia: Harper and Row; 1985. p. 1-30.
85. Asero R, Bottazzi G. Nasal polyposis: a study of its association with airborne allergen hypersensitivity. Ann Allergy Asthma Immunol. 2001 Mar;86(3):283-5.
86. Kirtsreesakul V. Nasal polyps : the relationship to allergy, sinonasal infection and histopathological type. J Med Assoc Thai 2004; 87(3): 277-82.
87. Pepys J, Duveen GE. Negative skin tests in allergic rhinitis and nasal polyposis. Int Arch Allergy Immunol. 1951;2:147-60.
88. Drake-Lee AB. Histamine and its release from nasal polyps: preliminary communication. J R Soc Med. 1984;77(2):120-4.
89. Liu CM, Shun CT, Hsu MM. Lymphocyte subsets and antigen-specific IgE antibody in nasal polyps. Ann Allergy. 1994;72(1):19-24.
90. Wagenmann M G-AM, Helmig P. Increased production of type-2 and type-1 cytokines in nasal polyps. J Allergy Clin Immunol. 2000;105(Supplement):S210.
91. Hamilos DL, Leung DY, Wood R, Cunningham L, Bean DK, Yasruel Z, et al. Evidence for distinct cytokine expression in allergic versus nonallergic chronic sinusitis. J Allergy Clin Immunol. 1995;96(4):537-44.
92. Keith PK, Conway M, Evans S, Wong DA, Jordana G, Pengelly D, Dolovich J. Nasal polyps: effects of seasonal allergen exposure.J Allergy Clin Immunol. 1994 Mar;93(3):567-74.
93. Erbek SS, Erbek S, Topal O, Cakmak O, The role of allergy in the severità of nasal polyposis. Am J Rhinol 2007; 21(6): 686-90
94. Ponikau JU, Sherris DA, Kern EB, Homburger HA, Frigas E, Gaffey TA et al. The diagnosis and incidence of allergic fungal sinusitis. Mayo Clin Proc 1999;74:877–84.
95. Braun H, Buzina W, Freudenschuss K, Beham A, Stammberger H. Eosinophilic fungal rhinosinusitis: a common disorder in Europe? Laryngoscope 2003;113:264–9.
96. Ragab A, Clement P, Vincken W, Nolard N, Simones F. Fungal cultures of different parts of the upper and lower airways in chronic rhinosinusitis. Rhinology 2006;44:19–25.

97. Van Zele T, Gevaert P, Watelet JB, Claeys G, Holtappels G, Claeys C et al. Staphylococcus aureus colonization and IgE antibody formation to enterotoxins is increased in nasal polyposis. J Allergy Clin Immunol 2004;114:981–3.
98. Zhang N, Gevaert P, Van ZT, Perez-Novo C, Patou J, Holtappels G et al. An update on the impact of Staphylococcus aureus enterotoxins in chronic sinusitis with nasal polyposis. Rhinology 2005;43:162–8.
99. Marone G, Poto S, Petracca R, Triggiani M, de Lutio di Castelguidone E, Condorelli M. Activation of human basophils by staphylococcal protein A, I: the role of cyclic AMP, arachidonic acid metabolites, microtubules and microfilaments. Clin Exp Immunol 1982;50:661-8.
100. Genovese A, Bouvet JP, Florio G, Lamparter-Schummert B, Bjorck L, Marone G. Bacterial immunoglobulin superantigen proteins A and L activate human heart mast cells by interacting with immunoglobulin E. Infect Immun 2000;68:5517-24.
101. Joke Patou, Philippe Gevaert, Thibaut Van Zele, Gabriele Holtappels, Paul van Cauwenberge, Claus Bachert Staphylococcus aureus enterotoxin B, protein A, and lipoteichoic acid stimulations in nasal polyps. J Allergy Clin Immunol 2008;121:110-5.
102. Laprise C, Sladek R, Ponton A, Bernier MC, Hudson TJ, Laviolette M. Functional classes of bronchial mucosa genes that are differentially expressed in asthma. BMC Genomics 2004;23:21–31.
103. J.-B. Watelet, T. Van Zele, M. Gjomarkaj, G. W. Canonica, S.-E. Dahlen, W. Fokkens, V. J. Lund, G. K. Scadding, J. Mullol, N. Papadopoulos, S. Bonini, M. L. Kowalski, P. Van Cauwenberge, J. Bousquet and GA2LEN workpackage members. Tissue remodelling in upper airways: where is the link with lower airway remodelling? Allergy 2006: 61: 1249–58.
104. Pawankar R, Nonaka M. Inflammatory mechanisms and remodeling in chronic rhinosinusitis and nasal polyps. Curr Allergy Asthma Rep. 2007 Jun;7(3):202-8.
105. Sanai A, Nagata H, Konno A. Estensive interstitial collagen deposition on the basement membrane zone in allergic nasal mucosa. Acta Otolaryngol 1999;119:473–8.
106. Abrams DC, Toynton SC, Dore C, Emson MA, Taylor P, Springall DR et al. Stereological estimation of blood vessel surface and volume densities in human normal and rhinitic nasal mucosa. Rhinology 1997;35:22–7.
107. Chanez P, Vignola AM, Vic P, Guddo F, Bonsignore G, Godard P et al. Comparison between nasal and bronchial inflammation in asthmatic and control subjects. Am J Respir Crit Care Med 1999;159:588–95.
108. Kirmaz C, Ozbilgin K, Yuksel H, Bayrak P, Unlu H, Giray G et al. Expression of angiogenic markers in patients with seasonal allergic rhinitis.Eur Cytokine Netw 2004;15:317–22.
109. Kang HJ, Kang JS, Lee SH, Hwang SJ, Chae SW, Woo JS et al. Upregulation of oncostatin m in allergic rhinitis. Laryngoscope 2005;115:2213–6.
110. Ruhno J, Andersson B, Denburg J, Anderson M, Hitch D, Lapp P et al. A double-blind comparison of intranasal budesonide with placebo for nasal polyposis. J Allergy Clin Immunol 1990;86(6 Pt 1):946–53.
111. Rowe-Jones JM, Medcalf M, Durham SR, Richards DH, Mackay IS. Functional endoscopic sinus surgery: 5 year follow up and results of a prospective, randomised, stratified, double-blind, placebo controlled study of postoperative fluticasone propionate aqueous nasal spray. Rhinology 2005;43:2–10.
112. Pujols L, Alobin I, Benitez P, Martinez-Anton A, Roca-Ferrer J, Fokkens WJ, Mullol J, Picado C. Regulation of glucocorticoid receptor in nasal polyps by systemic and intranasal glucocorticoids. Allergy 2008; 63: 1377-86.
113. Leung DY, Hamid Q, Vottero A, Szefler SJ, Surs W, Minshall E et al. Association of glucocorticoid insensitivity with increased expression of glucocorticoid receptor beta. J Exp Med 1997;186:1567–74.
114. Christodoulopoulos P, Leung DY, Elliott MW, Hogg JC, Muro S, TodaM et al. Increased number of glucocorticoid receptor-beta-expressing cells in the airways in fatal asthma. J Allergy Clin Immunol 2000;106:479–84.
115. Hamilos DL, Leung DY, Muro S, Kahn AM, Hamilos SS, Thawley SE et al. GRbeta expression in nasal polyp inflammatory cells and its relationship to the anti-inflammatory effects of intranasal fluticasone. J Allergy Clin Immunol 2001;108:59–68.
116. Kirtsreesakul V. Atchariyasathian V. Nasal polyposis: role of allergy on therapeutic response of eosinophil-and non eosinophil-dominated inflammation. Am J Rhinol 2006; 20(1): 95-100.
117. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S: The occurence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230–5.
118. Kripke DF, Ancoli-Israel S, Klauber MR, Wingard DL, Mason WJ, Mullaney DJ: Prevalence of sleep-disordered breathing in ages 40–64 years: A population-based suvey. Sleep 1997; 20:65–76.
119. McNicholas WT. The nose and OSA: variable nasal obstruction may be more important in pathophysiology than fixed obstruction. Eur Respir J 2008; 32: 3–8.
120. Park SS. Flow-regulatory function of upper airway in health and disease: a unified pathogenetic view of sleepdisordered breathing. Lung 1993; 171: 311–33.
121. Gleeson K, Zwillich CW, Bendrick TW, White DP. Effect of inspiratory nasal loading on pharyngeal resistance. J Appl Physiol 1986;60:1882-6.
122. Schwartz AR, Smith PL, Gold AR, Wise RA, Permutt S. Induction of upper airway occlusion in sleeping individual with subatmospheric nasal pressure. J Appl Physiol 1989;66:1626-34.
123. Veasey SC. Molecular and physiologic basic of obstructive sleep apnea. Clin Chest Med 2003; 24: 179-93.
124. Lofaso F, Coste A, d'Ortho MP, Zerah-Lancner F, Delclaux C, Goldenberg F, Harf A. Nasal obstruction as a risk factor for sleep apnoea syndrome. Eur Respir J 2000; 16: 639-43.
125. Verse T, Maurer JT, Pirsig W. Effect of nasal surgery on sleep-related breathing disorders. Laryngology 2002;112:64-9.
126. Miljeteig H, Hoffstein P, Cole P. The effects of unilateral and bilateral nasal obstruction on snoring and sleep apnea. Laryngoscope 1992; 102: 1150-2.
127. Atkins M, Tashkar V, Clayton N, Stone P, Woodcock A. Nasal resistance in obstructive sleep apnea. Chest 1994; 105: 1133-5.
128. Young T, Finn L, Kim H. Nasal obstruction as a risk factor for sleep disordered breathing. J Allergy Clin Immunol 1997; 99(2): S757-S762.
129. Shepard JW Jr, Burger CD. Nasal and oral flow–volume loops

in normal subjects and patients with obstructive sleep apnea. Am Rev Respir Dis 1990; 142: 1288–93.
130. Virkkula P, Maasilta P, Hyto¨nen M, Salmi T, Malmberg H. Nasal obstruction and sleep-disordered breathing: the effect of supine body position on nasal measurements in snorers. Acta Otolaryngol 2003; 123: 648–54.
131. Storms W. Allergic rhinitis-induced nasal congestion: its impact on sleep quality. Primary Care Respiratory Journal 2008; 17(1):7-18.
132. McNicholas WT, Tarlo S, Cole P, et al. Obstructive apneas during sleep in patients with seasonal allergic rhinitis. Am Rev Respir Dis 1982; 126: 625–8.
133. Lavie P, Gertner R, Zomer J, Podoshin L. Breathing disorders in sleep associated with "microarousals" in patients with allergic rhinitis. Acta Otolaryngol 1981; 92: 529–33.
134. Canova CR, Downs SH, Knoblauch A, Andersson M, Tamm M, Leuppi JD. Increased Prevalence of Perennial Allergic Rhinitis in Patients with Obstructive Sleep Apnea. Respiration 2004;71:138–43.
135. J L Kiely, P Nolan, W T McNicholas. Intranasal corticosteroid therapy for obstructive sleep apnoea in patients with co-existing rhinitis. Thorax 2004;59:50–5.
136. Young T, Finn L, Palta M. Chronic nasal congestion at night is a risk factor for snoring in a population-based cohort study. Arch Intern Med 2001; 161: 1514–9.
137. Udaka T, Suzuki H, Fujimura T, et al. Relationships between nasal obstruction, observed apnea, and daytime sleepiness. Otolaryngol Head Neck Surg 2007; 137: 669–73.
138. Bergeron C, Kimoff J, Hamid Q. Obstuctive sleep apnea syndrome and inflammation. J Allergy Clin Immunol. 2005; 116: 1393-6.
139. Hatipoglu U, Rubinstein I. Inflammation and obstructive sleep apnea sindrome pathogenesis: a working hypotesis. Respiration 2003;70:665-71.
140. Lavie L. Obstructive sleep apnea sindrome – an oxidative stress disorder. Sleep Med Rev 2003;7:35-51.
141. Semenza GL. Hypoxia-inducible factor I: control of oxygen homeostasis in health and disease. Pediatr Res 2001; 49: 614-7.
142. Rubinstein I. Nasal inflammation in patients with obstructive sleep apnea. Laryngoscope 1995; 105: 175-7.
143. Salerno FG, Carpagnano E, Guido P, Bonsignore MR, Roberti A, Aliani M, et al. Airway inflammation in patients affected by obstructive sleep apnea sindrome. Resp Med 2004; 98: 25-8.
144. Carpagnano GE, Kharitonov SA, Resta O, Foschino-Barbato MP, Gramiccioni E, Barnes PJ. Increased 8-isoprostane and interleukin-6 in breath condensato of obstructive sleep apnea patients. Chest 2002;122:1162-7.
145. Kheirandish-Gozal L, Gozal D. Intranasal Budesonide Treatment for Children With Mild Obstructive Sleep Apnea Syndrome. Pediatrics 2008;122:e149–e155.
146. Brooks LJ, Stephens B, Bacevice AM. Adenoid size is related to severity but not the number of episodes of obstructive apnea in children. J Pediatr. 1998;132(4):682–6.
147. Li AM, Wong E, Kew J, Hui S, Fok TF. Use of tonsil size in the evaluation of obstructive sleep apnoea. Arch Dis Child. 2002; 87(2):156–9.
148. Schechter MS; American Academy of Pediatrics, Section on Pediatrics Pulmonology, Subcommittee on Obstructive Sleep Apnea Syndrome. Technical report: diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics. 2002;109(4).
149. Lack G. Pediatric allergic rhinitis and comorbid disorders. J Allerg Clin Immunol 2001;108:S9-15.
150. Modrzynski M, Zawisza E. An analysis of the incidence of adenoid hypertrophy in allergic children. Int J Pediatr Otorhinolaryngol 2007;71:713-9.
151. Modrzynski M, Zawisza E. The influence of birch pollination on adenoid size in children with intermittent allergic rhinitis. Int J Pediatr Otorhinolaryngol 2007;71:1017-23.
152. McColley SA, Carrol JL, Curtis S, Loughlin GM, Sampson HA. High prevalence of allergic sensitization in children with habitual snoring and obstructive sleep apnea. Chest 1997; 111: 170-3.
153. Al-Ghamdi SA, Manoukian JJ, Morielli A, Oudjhane K, Ducharme FM, Brouillette RT. Do systemic corticosteroids effectively treat obstructive sleep apnea secondary to adenotonsillar hypertrophy? Laryngoscope. 1997;107(10):1382–7.
154. Demain JG, Goetz DW. Pediatric adenoidal hypertrophy and nasal airway obstruction: reduction with aqueous nasal beclomethasone. Pediatrics. 1995;95(3):355–64.
155. Brouillette RT, Manoukian JJ, Ducharme FM, et al. Efficacy of fluticasone nasal spray for pediatric obstructive sleep apnea. J Pediatr. 2001;138(6):838–44.
156. Alexopoulos EI, Kaditis AG, Kalampouka E, et al. Nasal corticosteroids for children with snoring. Pediatr Pulmonol. 2004; 38(2):161–6.
157. Mansfield LE, Diaz G, Posey CR, Flores-Neder J. Sleep disordered breathing and daytime quality of life in children with allergic rhinitis during treatment with intranasal budesonide. Ann Allergy Asthma Immunol. 2004;92(2):240-4.
158. Berlucchi M, Salsi D, Valetti L, Parrinello G, Nicolai P. The role of mometasone furoate aqueous nasal spray in the treatment of adenoidal hypertrophy in the pediatric age group: preliminary results of a prospective, randomized study. Pediatrics. 2007; 119(6).
159. Goldbart AD, Veling MC, Goldman JL, Li RC, Brittian KR, Gozal D. Glucocorticoid receptor subunit expression in adenotonsillar tissue of children with obstructive sleep apnea. Pediatr Res. 2005;57(2):232–6.