

Non-allergic rhinitis: diagnosis and management

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Patients in the rhinitis clinic with negative skin prick tests present a challenge. Non-allergic rhinitis consists of a variety of conditions including infection, hormonal changes, drugs and autonomic dysfunction. There is also a range of systemic disorders to be considered. The pathogenesis of many of these are less well understood than that of allergic rhinitis, diagnosis and treatment pathways are also more complex. A detailed accurate history needs to be taken followed by relevant investigations which may include allergen challenge, because skin prick and RAST-negative allergic rhinitis is now recognised. Nitric oxide levels may prove helpful: elevated levels suggest inflammation, very low levels indicate the possibility of primary ciliary dyskinesia or cystic fibrosis. Treatment is of the underlying cause when found: for those without obvious pathology a trial of combined therapy with topical corticosteroids plus antihistamine or plus anti-cholinergic may be worth while. A complex inter-relationship between allergic and infectious rhinitis is becoming apparent. *Curr Opin Allergy Clin Immunol* 1:15–20. © 2001 Lippincott Williams & Wilkins.

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Introduction

The most recent classification and differential diagnosis of rhinitis (rhinosinusitis) is in the ARIA document [1•] (Tables 1 and 2). This review will concentrate on those non-allergic conditions in Table 1, omitting those mentioned in the differential diagnosis. Basically, rhinitis can be divided into 3 major forms: allergic, infectious and a variety of other causes. These are not mutually exclusive, for example allergy and viral infections show a complex inter-relationship (*vide infra*).

Infectious rhinitis

Infectious rhinitis can occur because of infection by a wide variety of organisms, the most common being acute viral rhinosinusitis which affects millions of people annually [2]. Approximately one-third of viral infections are caused by human rhinoviruses (HRV), of which there are at least 100 different sub-types. The pathophysiology of such infections has been reviewed recently [3•]. It has recently become apparent that ICAM-1 is the receptor for the rhinovirus and is also critical for the migration and activation of immune effector cells. ICAM-1 is upregulated in nasal epithelial cells of atopic individuals and is further increased by contact by allergen and by HRV 14 [4•]. It is not known whether this renders allergic individuals more susceptible to viral infections because only one rhinovirus–receptor contact is necessary for an infection to occur. However, reduction of ICAM-1 by 1 year of oral terfenadine in children was associated with a

Table 1. Classification of rhinitis

Infectious
Viral
Bacterial
Other infective agents
Allergic
Intermittent
Persistent
Occupational (allergic/non-allergic)
Intermittent
Persistent
Drug-induced
Aspirin
Other medications
Hormonal
Other Causes
Non-allergic rhinitis with eosinophilia syndrome
Irritants
Food
Emotional
Atrophic
Gastro-oesophageal reflux
Idiopathic

Data from [1•].

Table 2. Differential diagnosis of rhinitis**Polyps****Mechanical Factors**

Deviated septum
Adenoidal hypertrophy
Foreign bodies
Choanal atresia

Tumours

Benign
Malignant

Granulomas

Wegener's Granulomatosis
Sarcoid
Infectious
Malignant – midline destructive granuloma

Ciliary defects**Cerebrospinal rhinorrhoea**

Data from [1••].

50% reduction in visits to the primary care practitioner for upper respiratory tract problems [5•]. Similar effects have been noted with regular nasal beclomethasone (Parikh *et al.*, PAI in press).

Therapy for the common cold is still problematic. A recent randomised double-blind, placebo-controlled trial of zinc acetate lozenges which showed a reduction in symptom duration and severity has revived the issue of zinc treatment [6•]. Five out of 10 placebo-controlled trials have been positive, although doubts have been cast on the validity of the blinding because of the bitter taste of some zinc salts [6•]. Speculations about the possible mechanism of zinc activity include prevention of viral replication [7] or interactions with ICAM-1 [8,9]. It may be relevant that zinc is present in the olfactory receptors which are at the nose–central nervous system interface.

Nitric oxide, which is produced by respiratory epithelial cells and has many actions including vaso-dilatation, neurotransmission, immune regulation, smooth muscle relaxation and anti-microbial activity, has been shown by Sanders and co-workers to inhibit rhinovirus replication and cytokine induction in human respiratory epithelial cells [10]. A nitric oxide donor has similar effects [11•]. Bradykinin is present in nasal secretions during a cold and may be responsible for symptoms such as blockage and discomfort, however topical corticosteroids which reduced bradykinin in nasal washings did not decrease symptoms [12]. Bradykinin beta-2 receptor antagonists have not yet been shown to reduce symptoms.

Secondary effects

Most attacks of asthma, certainly in childhood, are precipitated by viral upper respiratory tract infections [13]. Allergic sensitisation and relevant allergen exposure appear to be synergistic with this [14•]. It is conceivable that similar factors operate in other comorbid associations of rhinitis such as sinusitis and otitis media with effusion.

Approximately 0.5% to 2% of viral upper respiratory tract infections progress to an acute bacterial rhinosinusitis [1••].

Chronic rhinosinusitis is one of the most common chronic conditions of man [15], and is responsible for a reduction in quality of life, work place attendance and productivity [16••]. Overall healthcare expenditures in the USA in 1996 for sinusitis as a primary diagnosis or comorbid condition were \$5.8 billion [16••]. Approximately 14% of the population is thought to be affected, however sinus abnormalities are seen in 30% (adults) and 46% (children) of CT/MRI scans undertaken for other conditions [17•,18]. This affords a reminder that one should treat the patient and not the X-ray. A comparison of CT and MRI scans confirms that CT gives better bony delineation and is more useful for planning endoscopic sinus surgery. There are, however, circumstances under which MRI could be used as the primary diagnostic tool [19•].

Recently, endoscopically guided sinonasal cultures have been shown to identify accurately the predominant bacterial pathogen and to correlate with the cultures from maxillary sinus aspiration in more than 90% of infections [20•], confirming previous observations. Interestingly, endoscopically normal maxillary sinuses are not, as previously thought, sterile [21•]. In-situ hybridisation techniques have also been found to be a useful adjunct to current methods of detecting micro-organisms within chronically infected sinus tissue [22]. The amount of nasal secretion aspirated into the lower airway is not increased during acute sinonasal infection [23•]. The choice of appropriate anti-microbial therapy is important: a recent guide is helpful [24••]. The bacteria commonly responsible for rhinosinusitis are carbohydrate coated, thus reducing phagocytosis. *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae* and *Moraxella catarrhalis* are four common examples. Many of them have been found to secrete molecules which have adverse effects upon muco ciliary clearance. Individuals with primary defects in muco ciliary clearance, such as primary ciliary dyskinesia or cystic fibrosis, have chronic or recurrent upper respiratory tract infections. Interestingly they also have very low levels of nitric oxide (NO) in their airways [25]. Sinus puncture studies [26] have shown that the predominant source of nitric oxide in the upper airways is within the sinuses where levels of 20 ppm to 25 ppm, which are bactericidal, exist. Nasal levels are lower, around 500 to 850 ppb, but are elevated in uncomplicated inflammatory rhinitis. The levels fall with progressive obstruction due to nasal polyposis [27]. Patients with HIV may develop rhinosinusitis which is steroid responsive [28•]. They may also develop otitis media with effusion. Recently the gp120 sub unit of the HIV virus has been shown to induce IgE production by

B-cells via a subversion of T-cells towards IL-4 secretion [29].

The relationship between allergy and sinusitis is unclear with some recent studies [30•] again suggesting that rhinosinusitis is a common complication of allergic rhinitis. Forty per cent of patients with chronic rhinosinusitis suffer from allergy; this figure is 80% in patients with bi-maxillary sinusitis [31]. Two CT studies [32,33] could find no significant difference between allergic and non-allergic adults with chronic rhinosinusitis. Inhaled allergens have not been shown to reach the sinuses [34], the lining of which contains less ICAM-1 than that of the nose [35]. Attempts to treat or prevent chronic rhinosinusitis with topical corticosteroid with or without antibiotic have not shown marked benefits [36,37]. Our recent study showed no acute infective exacerbations in the placebo nor the corticosteroid treated group, suggesting that the douching effect of nasal sprays may be relevant. (A Parikh and GKS Scadding, submitted). A study of douching confirmed benefit on quality of life and endoscopic appearances in chronic rhinosinusitis [38•]. The ability of a nasal aerosol device to deposit aerosol directly in the paranasal sinuses has been studied in five normal healthy individuals, with evidence of some sinus deposition in three [39].

The importance of fungi in nasal disease is under review. Recent suggestions from the Mayo Clinic [40•] have led to the supposition that fungi are responsible for most chronic rhinosinusitis/nasal polyposis. The evidence for this is that fungi can be isolated from the nasal secretions and are found in association with activated eosinophils. However, fungi can be isolated from most noses and there is a group of individuals with rhinosinusitis and eosinophilic mucus who have clinical characteristics quite different from those patients with well defined allergic fungal sinusitis [41••] (Table 3). The medical treatment of allergic fungal sinusitis has recently been reviewed [42•].

Table 3. Comparison of allergic fungal sinusitis and eosinophilic muco rhinosinusitis

	AFS (n = 431)	EMRS (n = 69)	P value
Mean age (years)	30.7	48.0	0.001
Male/Female ratio	1.03:1	1.26:1	N.S.
Asthma (%)	41	93	0.0001
Aspirin-sensitivity (%)	13	54	0.0001
Polyps (%)	100	100	N.S.
Allergic rhinitis (%)	84	63	0.004
Bilateral disease (%)	55	100	0.0001
Mean IgE (mg/dl)	1 941	267	0.001
IgG 1 deficiency	None reported	50%	

Data from [40••]. AFS, allergic fungal sinusitis; EMRS, eosinophilic muco rhinosinusitis.

Drug induced rhinitis

The syndrome of nasal polyposis, eosinophilia and intrinsic asthma which accompany aspirin and non-steroidal anti-inflammatory drug sensitivity has been recently reviewed [43••]. Although COX-1 inhibition is almost certainly relevant to the pathogenesis, there are other interesting factors such as abnormalities of the leukotriene C4 synthase gene promoter region (reviewed by Penrose and Austen [44••]). However, these do not correlate with aspirin sensitivity in patients in the USA [45•]. Eosinophil apoptosis is reduced in nasal polyposis. Leukotriene antagonists have now been shown to reverse survival in eosinophils of asthmatic individuals [46•]. The results of treatment with leukotriene receptor antagonists and leukotriene synthase inhibitors on polyps are being reported with evidence of benefit in some, but not all, aspirin sensitive patients. (S Ragab and GK Scadding, submitted). There appear to be two leukotriene receptors: this may underlie the poor response seen in some patients. Challenges with COX-2 antagonists have revealed that nimesulide and meloxicam are relatively safe in the majority of aspirin-sensitive patients [47,48].

Other drugs which can cause nasal blockage are anti-hypertensives, particularly beta-blockers [1••]. Alpha-agonists can lead to vaso-motor rhinitis if overused, with a chronically blocked and reddened nasal mucosa which is unresponsive to intrinsic or extrinsic alpha stimulation. Exogenous oestrogen can cause rhinitis, as can chlorpromazine.

Hormonal rhinitis

Hormonal rhinitis occurs most commonly with pregnancy, but is sometimes seen at puberty and during the menstrual cycle. Hypothyroidism and acromegaly can also give rise to the chronically blocked nose.

Food-induced rhinitis

Food-induced rhinitis is much rarer than popularly supposed. Food allergy is an unusual cause of isolated rhinitis, although in anaphylaxis rhinitis is often seen. The oral allergy syndrome occurs when a patient sensitive to tree pollens (e.g. birch) exhibits oral allergic reactions to fresh fruits and vegetables such as apples, carrots and celery due to cross-reactive epitopes [49]. Food intolerance can cause nasal symptoms. This is seen with dyes, preservatives and alcohol in some non-allergic patients. The mechanisms are unknown. Spicy foods, such as peppers, cause rhinorrhoea probably via their capsaicin content which stimulates sensory nerve fibres inducing neuropeptide release [50]. Sensitivity to nickel in food has been reported as a cause of rhinitis in two individuals, with improvement on dietary restriction [51•].

Atrophic rhinitis

Atopic rhinitis is characterised by atrophy of the mucosa and underlying bone. The patient presents with a widely patent nose which is crusted and odoriferous. Infection with *Klebsiellae ozaenae* is found [52] but it is uncertain whether this is the primary problem. Secondary atrophy can occur following excessive nasal surgery, radiation trauma or chronic granulomatous disease.

Other causes of rhinitis

Various physical and chemical stimuli cause rhinitis. These include exposure to dry air, spices, air pollutants, occupational irritants. Emotions such as stress and sexual arousal also have a powerful effect on the nose via the autonomic system. Gastro-oesophageal reflux can result in rhinitis especially in small children [53].

Non-eosinophilic non-allergic rhinitis

Patients with no obvious cause for their rhinitis are usually divided into two groups: those with a nasal eosinophilia and those without. In the latter group there does not appear to be any significant immuno-histological change [54]. However, there are significant abnormalities of nasal reflexes [55] including the diving reflex, nasal resistance changes on standing and on axial pressure. Some patients also show abnormal cardiovascular reflexes suggesting that the problem, which is probably one of autonomic dysfunction, is more generalised. The usefulness of nasal ipratropium in reducing watery rhinorrhoea has been known for some time. More recently capsaicin, which inhibits C-fibres, has been found to be effective in non-allergic rhinitis for several months after a few weekly applications. This has now been confirmed in a double-blind, placebo-controlled study [56].

Non-allergic rhinitis with eosinophilia syndrome

The extent of nasal eosinophilia which is necessary for the above syndrome varies from 5% to 25% according to different authors [57–60]. A careful study of full thickness turbinate biopsies from patients with well defined non-allergic rhinitis was compared with allergic rhinitis turbinates and to those from normal control individuals (D Powe, submitted). The epithelium revealed mast cells and IgE positive cells present in both the intrinsic and the allergic groups, but not in the normal individuals. Nasal challenge studies were abnormal in one-half of the intrinsic rhinitis patients with definite positive responses in 27%. These results echo those of Romero *et al.* [61] who examined skin prick test positivity, nasal eosinophilia and nasal allergen challenge results and found that a proportion of skin prick test negative patients show nasal eosinophils and are positive on nasal allergen challenge. This raises the possibility of local IgE production which has been demonstrated by Platts-Mills [62] and Durham [63]. Huggins and Brostoff [64] also showed positive nasal allergen challenges in skin prick test negative patients. Thus the diagnosis of nasal allergy is no longer simple and skin prick test negative patients with nasal eosinophilia may require allergen challenge before they can be reliably ascribed to the non-allergic rhinitis group (Fig. 1).

Occupational rhinitis

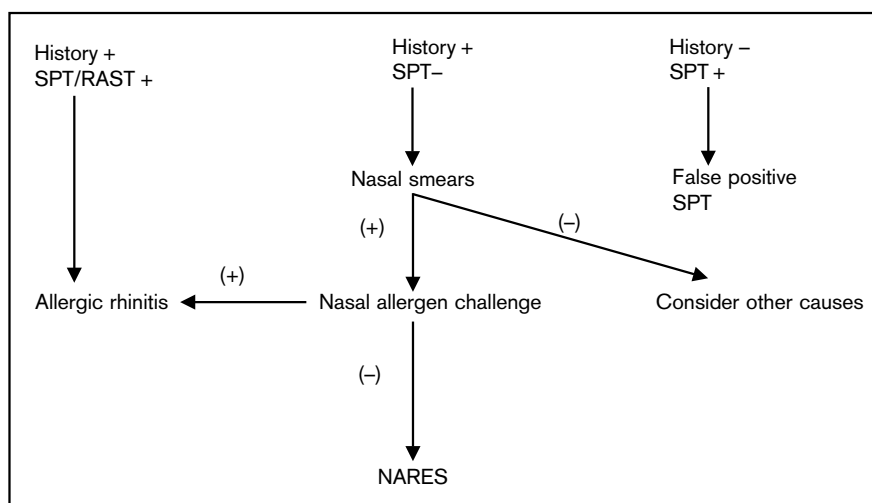
Occupational rhinitis can be allergic or non-allergic and has been reviewed recently [65•].

Treatment

Non-allergic rhinitis tends to be more difficult to treat successfully than allergic rhinitis (personal observation).

Figure 1. Diagnosis of rhinitis

The diagnosis of allergic rhinitis is simple when clinical history and skin prick tests are in accordance. In patients with a history suggestive of allergy, but with negative skin prick tests further tests looking for evidence of local allergy should be undertaken in the form of nasal smears for eosinophils and nasal challenge with likely allergens. The results will categorise the patient into one of three groups: local allergic rhinitis, non-allergic rhinitis with eosinophilia syndrome (nares) or non-allergic rhinitis.



In a recent unpublished survey in our department patients with positive skin prick tests fared better than those without, patients who did best were those with positive skin prick tests who had taken allergen avoidance measures. When a cause, e.g. hypothyroidism or infection, for the rhinitis is found then treatment should obviously be addressed to this. The non-eosinophilic non-allergic rhinitis group may respond to ipratropium or capsaicin. Applications of silver nitrate to the front of the nose have also been advocated [66].

Patients with non-allergic rhinitis with eosinophilia syndrome show some response to topical corticosteroids. Personal experience suggests that combined therapy, e.g. with topical steroid plus topical antihistamine, is often more effective than either alone. Authors of a recent paper support the idea of dual therapy for the combination of topical steroid and ipratropium [67].

Conclusion

Various studies [58,59] report that 37–64% of patients presenting with rhinitis are allergic: therefore between one- and two-thirds of patients are non-allergic and will need to have their rhinitis dissected carefully by means of a careful history [68], thorough examination, investigation and possibly by means of a trial of therapy. Perhaps the most encouraging recent paper is that of Bagenstore and Bernstein [69] which suggests that the treatment of chronic rhinitis by an allergy specialist improves quality of life outcomes.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

- 1 World Health Organisation Initiative. Allergic rhinitis and its impact on Asthma. (ARIA). Bousquet J, van Cauwenberge P. Geneva: WHO; 2000.
- A multi-author, evidence-based document detailing the pathophysiology, diagnosis and treatment of allergic rhinitis, also mentioning other forms of rhinitis plus the evidence of the effect of the upper upon the lower respiratory tract.
- 2 Gwaltney JJ. Acute community-acquired sinusitis. *Clin Infect Dis* 1996; 23:1209–1223; quiz 24–25.
- 3 Van Kempen M, Bachert C, Van Cauwenberge P. An update on the pathophysiology of rhinovirus upper respiratory tract infections. *Rhinology* 1999; 37:97–103.
- Interesting documentation of the extent and effects of rhinoviruses.
- 4 Bianco A, Whiteman SC, Sethi K, et al. Expression of intercellular adhesion molecule-1 (ICAM-1) in nasal epithelial cells of atopic subjects; a mechanism for increased rhinovirus infection? *Clin Immunol* 2000; 121:339–345.
- A mechanism for the interaction between allergy and infection.
- 5 Ciprandi G, Ricca V, Tosca M, et al. Continuous antihistamine treatment controls allergic inflammation and reduces respiratory morbidity in children with mite allergy. *Allergy* 1999; 54:358–365.
- The concept of persistent minimal inflammation and the effect of its long-term treatment.
- 6 Prasad AS, Fitzgerald JT, Bao B, et al. Duration of symptoms and plasma cytokine levels in patients with the common cold treated with zinc acetate. *Ann Int Med* 2000; 133:1–8.
- A well controlled, double-blind trial of therapy for the common cold with a brief review of previous experience with zinc.
- 7 Korant BD, Butterworth BE. Inhibition by zinc of rhinovirus protein cleavage: interaction of zinc with polypeptides. *J. Virol* 1976; 18:298–306.
- 8 Moffat AS. Going back to the future with small synthetic compounds. *Science* 1993; 260:910–912.
- 9 Novick SG, Godfrey JC, Godfrey NJ, Wilder HR. How does zinc modify the common cold? Clinical observation and implications regarding mechanism of action. *Med Hypotheses* 1996; 46:295–302.
- 10 Sanders SP, Siekierski ES, Porter JD, et al. Nitric oxide inhibits rhinovirus-induced cytokine production and viral replication in a human respiratory epithelial cell line. *J Virol* 1998; 72:934–942.
- 11 Sanders SP. Asthma, viruses and nitric oxide. *Proc Soc Exp Biol Med* 1999; 220:123–132.
- Explains some of the multiple and confusing effects of nitric oxide.
- 12 Gustafson LM, Proud D, Hendley JO, et al. Oral prednisone therapy in experimental rhinovirus infections. *J Allergy Clin Immunol* 1996; 97:1009–1014.
- 13 Johnston SL, Bardin PG, Pattemore PK. Viruses as precipitants of asthma symptoms. III Rhinovirus: molecular biology and projects for future intervention. *Exp Allergy* 1993; 23:237–246.
- 14 Stokes I, Peebles R, Hartert TV. Respiratory viruses and asthma. *Curr Opin Pulmonary Med* 2000; 6:1014.
- An excellent overview of the topic.
- 15 Melen I. Chronic sinusitis: clinical and pathophysiological aspects. *Acta Otolaryngol Suppl* 1994; 515:45–48.
- 16 Ray NF, Baranluk JN, Thamer M, et al. Healthcare expenditures for sinusitis in 1996: contributions of asthma, rhinitis, and other airway disorders. *J Allergy Clin Immunol* 1999; 103:409–414.
- The authors of this paper demonstrated the substantial economic impact of diseases leading to and resulting from acute and chronic sinusitis. They explain that upper airway disorders need to be recognised as serious, debilitating, costly diseases that warrant precise diagnosis and effective, specific therapy, and conclude that it is possible that early recognition of sinusitis as a component of allergy in otitis media, eustachian tube dysfunction and asthma, may lead to more comprehensive, but lower cost, outpatient therapy with a reduction in the need for more expensive long-term or hospital care.
- 17 Cotter CS, Stringer S, Rust KR, Mancuso A. The role of computed tomography scans in evaluating sinus disease in paediatric patients. *Int J Paediatr Otorhinolaryngol* 1999; 50:63–68.
- This paper demonstrates the high incidence of mucoperiosteal thickening in the paranasal sinuses of children, being present in 60% of symptomatic and 40% of random CT scans ($P=0.144$). Therefore, decisions regarding the need for sinus surgery should not solely be based on imaging abnormalities.
- 18 Gordt F, Clement PAR, Destryker A, et al. Prevalence of sinusitis signs on MRI in non-ENT polyposis. *Rhinology* 1997; 35:154–157.
- 19 Hahnel S, Ertl-Wagner B, Tasman AJ, et al. Relative value of MR imaging as compared with CT in the diagnosis of inflammatory paranasal sinus disease. *Radiology* 1999; 210:171–176.
- A useful comparison of MRI and CT.
- 20 Vogan JC, Bolger WE, Keyes AS. Endoscopically guided sinonasal cultures: a direct comparison with maxillary sinus aspirate cultures. *Otolaryngol Head Neck Surgery* 2000; 122:370–373.
- The first direct comparison with maxillary sinus aspirate cultures.
- 21 Jiang RS, Liang KL, Jang JW, Hsu CY. Bacteriology of endoscopically normal maxillary sinuses. *J Laryngol Otolaryngol* 1999; 113:825–828.
- A reversal of previous thought on the sterility of maxillary sinuses.
- 22 Hwang PH, Momtane KT, Gannon FH, et al. Applications of in-situ hybridization techniques in the diagnosis of chronic sinusitis. *Am J Rhinology* 1999; 13:335–338.
- 23 Ozagar A, Dede F, Turgut H, Uneri C. Aspiration of nasal secretions into the lungs in patients with acute sinonasal infections. *Laryngoscope* 2000; 110:107–110.
- The authors similarly overturn previous concepts.
- 24 Singh J, Arrieta AC. A guide through the labyrinth of anti-microbial therapy for respiratory tract infections. Of bugs and drugs. *Postgrad Med* 1999; 106:47–54.
- An excellent guide through the labyrinth of anti-microbial therapy for respiratory tract infections.
- 25 Conbry PJ, Jones NS. The nose and nitric oxide: a review. *Clin Otolaryngol Amie Sci* 2000; 25:137.
- 26 Lundberg J, Farkas Szallasi T, Weiteberg E, et al. High nitric oxide production in human paranasal sinuses. Primary nasal origin of exhaled nitric oxide and absence in Kartagener's syndrome. *Eur Resp Journal* 1994; 8:1501–1504.

- 27 Scadding GK, Colantonio D, Brovillet L, Parikh A. Paradoxical low nasal nitric oxide in nasal polyposis. *J Allergy Clin Immunol* 2000; 5206:Abstr 615.
- 28 Porter JP, Patel AA, Dewey CM, Stenart MG. Prevalence of sinonasal symptoms in patients with HIV infection. *Am J Rhinol* 1999; 13:203–208.
A useful reminder that sinonasal symptoms are common in HIV disease.
- 29 Dugas N, Dereuddre-Bosquet N, Goujard C, *et al.* Role of nitric oxide in the promoting effect of HIV type 1 and of gp120 envelope glycoprotein on interleukin 4-induced production by normal human mononuclear cells. *AIDS Res Hum Retroviruses* 2000; 16:251–258.
- 30 Berrettini S, Carabelli A, Sellari-Franceschini S, *et al.* Perennial allergic rhinitis and chronic sinusitis; correlation with rhinologic risk facts. *Allergy* 1999; 54:242–248.
An update on the inter-reaction between allergy and chronic sinusitis.
- 31 Karlsson G, Holmberg K. Does allergic rhinitis predispose to sinusitis? *Acta Otolaryngol* 1994; 515(suppl):26–28; discussion 9.
- 32 Iwens P, Clement PA. Sinusitis in allergic patients. *Rhinology* 1994; 32:65–67.
- 33 Naclerio RM, deTineo ML, Baroody FM. Ragweed allergic rhinitis and the paranasal sinuses. A computed topographic study. *Arch Otolaryngol Head Neck Surg* 1997; 123:193–196.
- 34 Adkins TN, Goodgold HM, Slavin RG. Does inhaled pollen enter the sinus cavities? *Ann Allergy Asthma Immunol* 1998; 81:181–184.
- 35 Demoly P, Sahla M, Campbell AM, *et al.* ICAM-1 expression in upper respiratory mucosa is differentially related to eosinophil and neutrophil inflammation according to the allergic status. *Clin Exp Allergy* 1998; 28:731–738.
- 36 Bertrand B, Eloy P, Rombeaux P. Allergy and sinusitis. *Acta Otorhinol Belg* 1997; 51:227–237.
- 37 Dupont LI, Rochette F, Demedts M, *et al.* Exhaled nitric oxide correlates with airway hyper-responsiveness in steroid-naïve patients with asthma. *Am J Resp Crit Care Med* 1998; 157:894–898.
- 38 Taccariello M, Parikh P, Darby Y, Scadding GK. Nasal douching in chronic rhinosinusitis: a randomised, single-blind study comparing alkaline nasal douche and sterile sea water. *Rhinology* 1999; 37:29–32.
An intensive look at the effects of simple therapy.
- 39 Negley JE, Krause H, Pawar S, Reeves-Hoche MK. RinoFlow nasal wash and sinus system as a mechanism to deliver medications to the paranasal sinuses: results of a radiolabeled pilot study. *ENT Ear Nose Throat J* 1999; 78:550–554.
- 40 Ponikau JJ, Sherris DA, Kern EB, *et al.* The diagnosis and incidence of allergic fungal sinusitis. *Mayo Clinic Proc* 1999; 74:877–884.
A controversial paper.
- 41 Ferguson BJ. Eosinophilic mucin rhinosinusitis: a distinct clinicopathological entity. *Laryngology* 2000; 5:799–813.
Not everything is fungal allergy...
- 42 Kuhn FA, Javer AR. Allergic fungal rhinosinusitis: perioperative management and role of steroids and anti-fungal agents. *Otolaryngol Clin North Am* 2000; 33:419–433.
... but if it is this is what to do.
- 43 Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis and management. *J Allergy Clin Immunol* 1999; 104:5–13.
A good update.
- 44 Penrose JF, Austen KF. The biochemical molecular and genetic aspects of leukotriene C4 synthase. *Prac Assoc Am Physician* 1999; 111:537–546.
Another good update.
- 45 Van Sambeek R, Stevenson DD, Bardasaro M, *et al.* 5ft flanking region polymorphism of the gene involving leukotriene CT synthase does not correlate with the asthma intolerant phenotype in the United States. *J Allergy Clin Immunol* 2000; 106:72–76.
This particular polymorphism does not account for all aspirin sensitivity.
- 46 Lee E, Robertson T, Smith J, Kilfeashen S. Leukotriene receptor antagonists and synthase inhibitors reverse survival in eosinophils of asthmatic individuals. *Am J Clin Immunol* 2000; 161:1881–1886.
One method of increasing eosinophil apoptosis.
- 47 Bavbek S, Celik G, Ediger D, *et al.* The use of nimesulide in patients with acetylsalicylic acid and non-steroidal anti-inflammatory drug intolerance. *J Asthma* 1999; 36:657–663.
- 48 Quarantino D, Romano A, Di Fonson M, *et al.* Tolerability of meloxicam in patients with histories of adverse reactions to non-steroidal anti-inflammatory drug. *Ann Allergy Asthma Immunol* 2000; 84:613–617.
- 49 Kazemi-Shirazi L, Pauli G, Purohit A, *et al.* Quantitative IgE inhibition with purified recombinant allergens indicate pollen-derived allergens as the sensitising agents responsible for many forms of plant allergy. *J Allergy Clin Immunol* 2000; 105:116–125.
- 50 Lacroix JS, Buvelot JM, Polla BS, Lundberg JM. Improvement of symptoms of non-allergic chronic rhinitis by local treatment with capsaicin. *Clin Exp Allergy* 1991; 21:595–600.
- 51 Hassoun S, Sabbah A, Bouchereau JL. Non-allergic rhinitis or intrinsic rhinitis? Unusual features of nickel allergy. *Allergy Immunol* 1999; 3:57–59.
This brief report raised the possibility of an alternative basis for upper respiratory tract sensitisation and reactivity. Further work is needed.
- 52 Henriksen S, Gunderson W. The aetiology of azaena: Actor pathol. *Microbiol Scan* 1959; 47:380–386.
- 53 Halstead LA. Role of gastro-oesophageal reflux in paediatric upper airway disorders. *Otolaryngol Head Neck Surg* 1999; 120:208–214.
- 54 Blom HM, Severijnen LA, Van Rijswijk JB, *et al.* The long-term effects of capsaicin aqueous nasal spray on the nasal mucosa. *Clin Exp Allergy* 1998; 28:1351–1358.
- 55 Jones AS. Autonomic reflexes and non-allergic rhinitis. *Allergy* 1997; 52:14–19.
- 56 Blom HM, Van Rijswijk JV, Garrelts IM, *et al.* Intranasal capsaicin is efficacious in non-allergic, non-infectious perennial rhinitis. A placebo-controlled study. *Clin Exp Allergy* 1997; 27:796–801.
- 57 Mygind N, Dirksen A, Johnsen NJ, Weeke B. Perennial rhinitis; an analysis of skin testing, serum IgE and blood and smear eosinophilia in 201 patients. *Clin Otolaryngol* 1978; 3:189–196.
- 58 Mullarkey MF, Hill JS, Web DR. Allergic and non-allergic rhinitis; their characterisation with attention to the meaning of nasal eosinophilia. *J Allergy Clin Immunol* 1980; 65:122–126.
- 59 Settiane GA, Klein DE. Non-allergic rhinitis: demography of eosinophils in nasal smears, blood eosinophil counts and IgE levels. *Allergy Prac* 1985; 6:363–366.
- 60 Crobach M, Hermans J, Kaptein A, *et al.* Nasal smear eosinophilia for the diagnosis of allergic rhinitis and eosinophilic non-allergic rhinitis. *Scan Journal Prim Health Care* 1996; 14:116–121.
- 61 Romero JN, Scadding GK. Eosinophilia in nasal secretions compared to skin prick test and nasal challenge test in the diagnosis of nasal allergy. *Rhinology* 1992; 30:169–175.
- 62 Platts-Mills TA. Local production of IgG, IgA and IgE antibodies in grass pollen hayfever. *J Immunol* 1979; 122:2218–2225.
- 63 Durham SR, Gould HJ, Hamid QA. Local IgE production in nasal allergy. *Int Arch Allergy Immunol* 1997; 113:128–130.
- 64 Huggins KG, Brostoff J. Local production of specific IgE antibodies in allergic-rhinitis patients with negative skin prick tests. *Lancet* 1976; 7926:148–150.
- 65 Slavin RG. Occupational rhinitis. *Ann Allergy Asthma Immunol*. 1999; 83:597–601.
A useful introduction to a largely overlooked topic.
- 66 Erhan E, Kulahji I, Kandemir O, *et al.* Comparison of topical silver nitrate and flunisolide treatment in patients with idiopathic non-allergic rhinitis. *Tokai J Exp Med* 1995; 21:103–111.
- 67 Dockhorn R, Aaronson D, Bronsky E, *et al.* Ipratropium bromide nasal spray 0.03% and beclomethasone spray alone and in combination for the treatment of rhinitis and perennial rhinitis. *Ann Allergy Asthma Immunol* 1999; 82:349–359.
- 68 Togias A. Age relationships and clinical features of non-allergic rhinitis. *J Allergy Clin Immunol* 1990; 85:182.
- 69 Bagenstore SE, Bernstein JA. Treatment of chronic rhinitis by an allergy specialist improves quality of life outcomes. *Ann Allergy Asthma Immunol* 1999; 83:524–528.
Encouragement to those of us working in this field.