Allergic Rhinitis: Changing Perspectives on Pathophysiology and Management — A J Morris

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Curriculum vitae

Adrian Morris graduated from UCT Medical School in 1983. After his housemanship at Groote Schuur Hospital, his SHO posts included paediatrics at Red Cross Childrens' Hospital and emergency medicine at Groote Schuur Hospital. He then completed GP Vocational training in Surrey, (England) before returning to Cape Town in 1988, to join a group family practice in Newlands. He obtained the DCH(SA) in 1989 and the MFGP(SA) in 1990. Allergy and clinical immunology are his special interests. He is a member of the British Society for Allergy and Clinical Immunology, and was a delegate at their 1991 and 1992 annual conferences. While in England, he attended the BSACI GP training course in Allergy. He was elected onto the executive committee of the Allergy Society of South Africa in 1992.

Summary

Allergic rhinitis has shown a dramatic increase in prevalence over the last two decades. Seasonal allergic rhinitis and perennial allergic rhinitis present as two clinically distinct entities. The pathophysiology of the nasal allergic reaction can be divided into the immediate "histaminic" reaction and the late phase "eosinophilic" reaction. Nasal hypersensitivity following adjuvant and allergen priming may account for the as yet ill-defined entity of chronic rhinitis. Management of allergic rhinitis should attempt to include allergen avoidance measures, as well as pharmacotherapeutic, immunotherapeutic and local nasal surgical considerations when indicated.

S Afr Fam Pract 1993; 14:55-61.

KEYWORDS:
Physicians, Family; Allergy and Immunology; Rhinitis, Allergic; Physiology

The nose is an effective filter of aero-allergens, it is therefore the site of more allergic symptoms than any other organ.

The prevalence of allergic rhinitis has increased four fold in the last twenty-five years, occurring predominantly in the 15 to 25 year age group and affecting more than 15% of the adult population.[1]

Seasonal allergic rhino-conjunctivitis (Hayfever) occurs in spring and early summer and is precipitated by tree, grass and weed pollen as well as fungal spores. Unmistakable symptoms include watery rhinorrhoea, serial sneezing, nasal itch and congestion, conjunctivitis and itching of the palate, eyes and ears.[2]

Perennial allergic rhinitis occurs as a result of atopy to allergens present throughout the year. These allergens include the house-dust mites (Dermatophagoides pteronyssinus and D farinae), animal dander and saliva (especially of dogs and cats), mould spores, cockroach protein and also in countries like South Africa with a very long grass season, grass pollens.[3] Symptoms are less clear cut, but include chronic nasal obstruction, early morning sneezing, sleep disturbance, mouth breathing, headaches, cough, anosmia and associated sinusitis or otitis media.[4]

The typical allergic facies of atopic individuals include "allergic shiners", the bluish hue to their puffy lower eyelids, a nasal "salute" and prominent nasal crease, a high-arched palate, persistent mouth breathing with resultant dental crowding, Dennie-Morgan infra-orbital folds and swollen pale blue nasal turbinates.[5]

Pathophysiology

Until the mid-17th century, physicians believed that rhinorrhoea was due to fluid collecting in the ventricles of the brain and oozing into the nostrils via the cribriform plate or into the palate by the pituitary gland – the so-called cerebral catarrhs of Hippocrates and Galen. More recent research has indicated, however, that the nasal mucosa should rather be compared to that of a bronchus without smooth muscle.[6]

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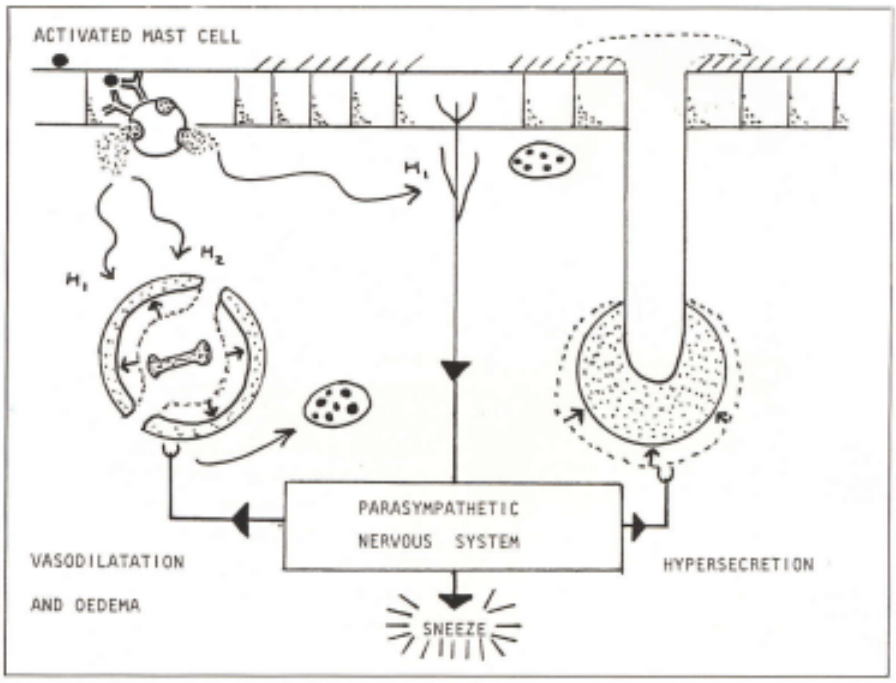
Studies have also shown that neural regulation of the nasal venous sinusoids in the turbinates and anterior nasal septum results in the so called "nasal cycle" which lasts from 2 to 4 hours. At any one point in this cycle, one nostril is more patent than the other.

The allergic reaction in the nose involves a complex interaction between allergen and multiple effector cells. An allergen will act on specific IgE bound to mast cells near the epithelial surface, resulting in histamine release. This is termed the *Immediate Nasal Reaction*. Other mast cell mediators include tryptase, kinins and prostaglandin D_2. Histamine has a direct effect on vascular H_1 and H_2 receptors causing oedema and nasal obstruction. It also has a reflex effect via sensory parasympathetic nerve pathways causing sneezing, itching and hypersecretion, as well as increasing epithelial permeability to further allergen penetration. This triggers sequential sneezing, followed by discharge and finally nasal blockage.[2]



Pathogenesis of Allergic Rhinitis

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Subsequent nasal symptoms that develop between 3 and 10 hours after allergen challenge are due to the *Late Phase Reaction*. This is associated with further inflammatory mediator production in the mucosa (Prostaglandins and Leukotrienes) and eosinophil plus basophil infiltration with increased nasal blockage.[4]

Nasal Hypersensitivity occurs when non-specific irritants or adjuvants such as dust, tobacco smoke, radon, ozone, sulphur dioxide, nitrogen dioxide, cold air and other environmental pollutants or allergens result in increased mucosal permeability, increased nerve ending excitability, eosinophil infiltrates and more superficial distribution of mast cells. These factors lead to enhanced nasal responsiveness to negligable aero-allergen and histamine challenge and amplify the nasal inflammatory reaction.[6]

Nasal hypersensitivity may account for the hitherto ill-defined condition of non-allergic non-infectious rhinitis (NANIR) – a "wastebasket" diagnosis due to the lack of understanding of its pathogenesis, and which includes vasomotor rhinitis, hyperplastic rhinitis and nasal polyposis.[7]

Continuous use of vasoconstrictor sprays may also lead to rebound nasal congestion (so called rhinitis medicamentosa) which might be another manifestation of nasal hypersensitivity. Some antihypertensive medication such as reserpine, methyldopa and alpha-adrenoceptor blockers as well as hormone replacement therapy appear to cause nasal obstruction. Interestingly, pregnancy is also

A dramatic increase over the last 2 decades

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associated with rhinitis in the last trimester, while Aspirin sensitive individuals will often present with rhinitis, sinusitis and nasal polyposis.

One of the more controversial areas in medicine concerns the adverse respiratory reactions to food. There is disagreement on the incidence and prevalence as well as likely pathogenic mechanisms of food allergy, particularly as it relates to the upper respiratory tract. Some investigators have detected significantly raised IgG antibody levels directed against cow's milk protein, wheat, hen egg white and peanuts in serous otitis media prone infants and children.[8]

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Investigating the Allergic Rhinitic

The following tests can be used in allergy diagnosis:

a) Rhinoscopy may demonstrate pale bluish swollen turbinates and mucosa, mucoid discharge and occasionally, evidence of polyposis.

b) Skin Prick Tests (SPT) for inhalant allergens are very useful in confirming the cause of symptoms, so that effective avoidance measures can be implemented. They are specific and cheaper than RAST or Phadiatop tests. Skin-prick testing is the cornerstone of allergy diagnosis according to the eminent allergist Niels Mygind. Available inhalant allergen extracts include housedust mite, dog and cat danders, grass pollen mixes, tree pollens, mould extracts and feather mixes. These are used in conjunction with histamine and saline controls. Food allergen extracts such as cow's milk, hen egg white, wheat and peanut can also be used for skin tests, but results are largely unreliable.

c) Nasal mucus staining with Hansels stain will reveal sheets of eosinophils in the atopic rhinitic.[9]

d) Total serum IgE may not be elevated unless there is associated asthma and/or atopic dermatitis. Interestingly, cigarette smoking as well as helminthic infections will elevate IgE levels in both atopic and non-atopic individuals. The use of cord serum IgE has been shown to be an insensitive method for predicting atopy in neonates, and can no longer be recommended.[10]

e) Nasal endoscopy using the new rigid fibreoptic endoscopes has markedly improved visualisation of the septum, turbinates and osteo-meatal complex of the paranasal sinuses.

More research orientated investigations include:

1) Nasal lavage to measure inflammatory mediators such as histamine, tryptase and eosinophil derived proteins (MBP, ECP and EPO).

2) Nasal provocation tests using specific antigens and histamine.

3) Rhinomanometry and measurement of peak nasal inspiratory flow rates using a modified mini peak flow meter, can objectively assess nasal airway patency.

Allergen avoidance

Allergen avoidance measures should be implemented before prescribing therapeutic drugs.

Risk factors for developing allergic rhinitis include a family history of atopy; the month of birth in relation to seasonal allergens; maternal smoking during pregnancy; viral respiratory tract infections and atmospheric exhaust pollution.

The housedust mite (Dermato-phagoides pteronyssinus) is approximately 300um long and feeds on human skin scales. It is attracted to warm humid habitats, has a 6 to 10 week life cycle, and the females lay up to 80 eggs during this period. Its main allergens are Der p 1 and Der p 11 which are derived from the mite faecal pellets and body material respectively. Their optimal environmental temperature is 25 to 30°C and they require a relative humidity of 70 to 80% – as a result of these factors, it tends to thrive in coastal areas.[11]

Seasonal allergic rhinitis is a clinically distinct entity to perennial allergic rhinitis

To be effective, housedust mite avoidance measures need to reduce mite allergen Der p 1 levels to below 10ug per gram of dust. These measures should endeavour to prepare a mite "free" bedroom

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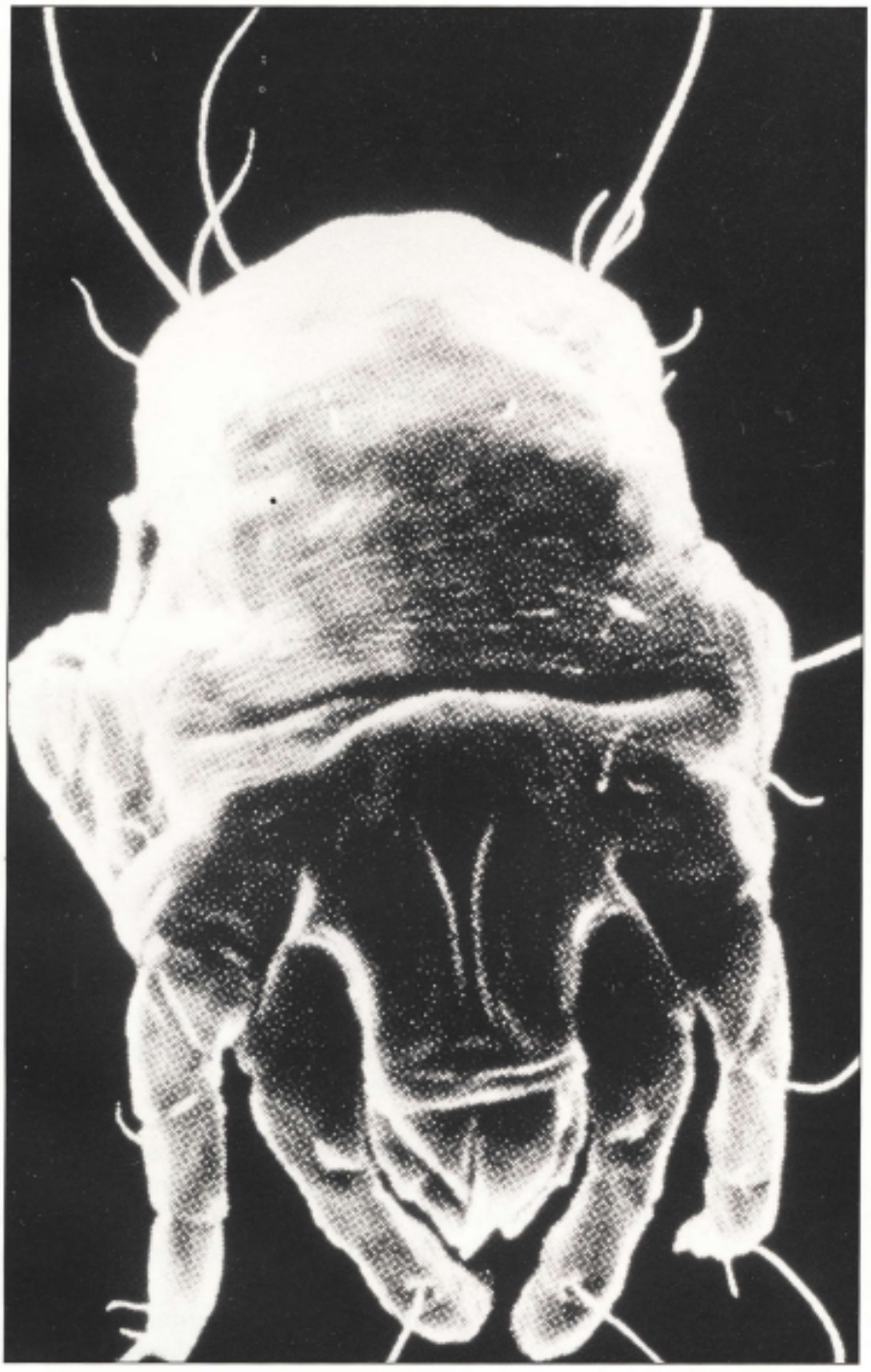

Housedust Mite: Courtesy Janssen Pharmaceutica

environment; by covering the mattress with plastic or a microporous material, replacing fitted carpets with vinyl or tiles, removing dust trapping soft toys and washing bedding and curtains regularly at temperatures in excess of 55°C. Vacuum cleaning should be performed using special mite trapping filters, all bedroom surfaces should be damp dusted, while bedding can also be aired in sunlight to kill mites. Bedroom humidity must be reduced to below 50% and the room should

Nasal hypersensitivity may account for the condition known as non-allergic non-infectious rhinitis

be well ventilated. Electric blankets provide a means of raising the bed temperature to levels above that at which mites survive. Specific acarosides including benzyl benzoate (Acarosan), tannic acid and liquid nitrogen may be of benefit, but have to be used frequently in conjunction with thorough post-treatment vacuum cleaning.

The Acarex test (a guanine assay) is a useful indicator of housedust mite concentrations in bedding, carpets and furniture.[11]

For animal dander allergic rhinitis, pets, if present in the home, should be washed regularly to reduce allergen levels. Animals should not be permitted to enter the bedrooms and living area, nor sleep on bedding.

The major cat allergen Fel d 1 is found in the saliva and sebaceous glands and the fur becomes coated with Fel d 1 during grooming.

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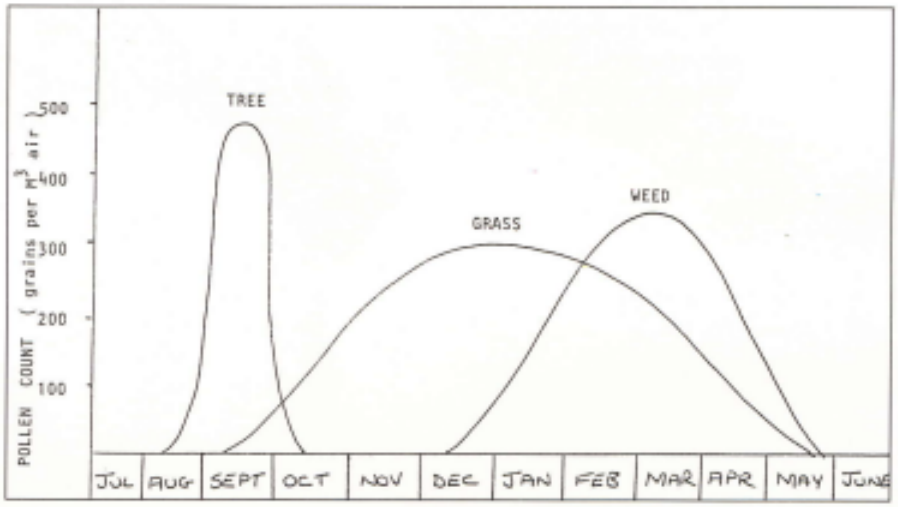
The major dog allergen Can f 1 is found in dander, hair and saliva. It is also common for patients to describe sensitivity to specific breeds of dogs.

Avoiding non-specific irritants or adjuvants such as cigarette smoke, sprays and gases will help reduce nasal hypersensitivity. There is no scientific evidence as yet in favour of the use of ionisers.

Seasonal Variation of Pollen Types

In seasonal rhinitis, allergen avoidance (pollens and moulds) is much more difficult, if not impossible. Sufferers should be advised not to be present during grass cutting and to avoid areas where rotting vegetation is plentiful. Contrary to popular opinion, the pollens of the Port Jackson Willow or Wattle and the Jacaranda tree are not significant allergens as they are too heavy and too sticky to be windborne.



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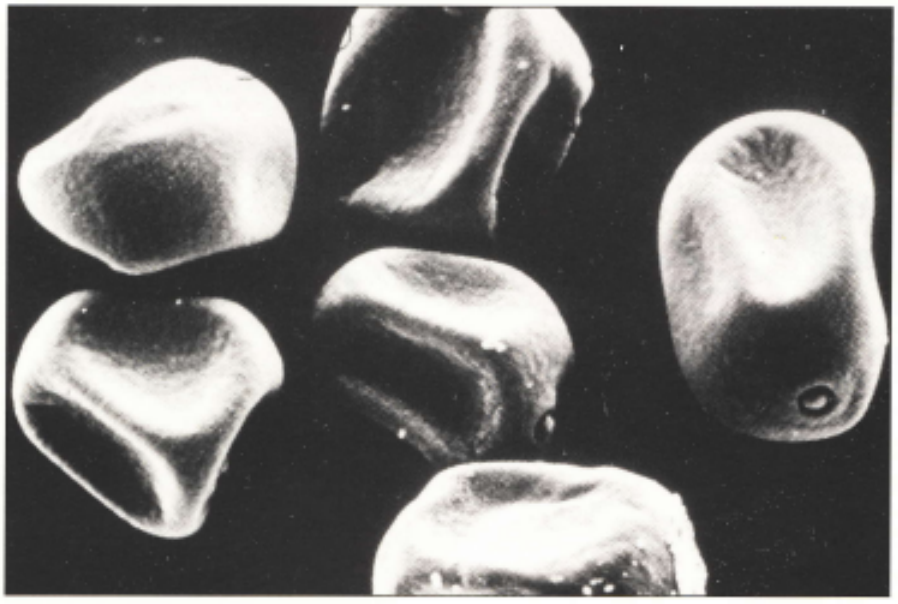

Pollen Grains: Courtesy of Janssen Pharmaceutica

Pharmaco-Therapeutics

1) *Antihistamines* remain the cornerstone of treatment in allergic rhinitis. This is especially so with the advent of the newer non-sedating H_1 receptor antagonists, such as Cetirizine (Zyrtec), Astemizole (Hismanal), Loratadine (Clarityne) and Terfenadine (Triludan). Older antihistamines such as Promethazine (Phenergan) and Chlorpheniramine (Polaramine) have unpleasant sedative and antimuscarinic side effects including dry mouth, urinary retention, blurred vision and gastro-intestinal disturbances. Antihistamines are effective against sneezing, itching and rhinorrhoea but not against the nasal obstruction itself. Cetirizine seems to have additional suppressive effects on the Late Phase Reaction by inhibiting

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eosinophil adherance and migration to inflamed tissues. H_2 blockers such as cimetidine and ranitidine may have supplementary roles in treatment, but so far results have been disappointing. Ketotifen (Zaditen) also an antihistamine, seems to be a good prophylactic agent especially in the paediatric age group.

2) *Vaso-Constrictors* such as alpha-adrenergic agonists-xylometazoline (Otrivin) and oxymetazoline (Iliaden), and noradrenalin releasers such as ephedrine give symptomatic relief of problematic nasal congestion in perennial allergic rhinitis but should only be used for short periods as prolonged use may lead to rebound rhinitis medicamentosa.

3) *Mast cell stabilisers* include Sodium Chromoglycate (Rynacrom) which has anti-inflammatory action and is a useful preventative treatment especially in seasonal allergic rhinoconjunctivitis. It has no notable side-effects,but has to be used at least 4 times per day. It is however, less effective than topical cortico-steroids. Nedocromil sodium (Tilade) is also a mast cell stabiliser with more anti-inflammatory activity and seems better suited to adult patients.

4) *Corticosteroids*, when used regularly as topical preparations, are effective in relieving itch, rhinorrhoea and nasal congestion. They also suppress mucosal mast cell numbers and eosinophil activation. Topical steroids should be used with great caution in allergic conjunctivitis. It has been suggested that Budesonide (Rhinocort) has fewer systemic side-effects than Beclomethasone diproprionate (Beconase or Clenil) when used in very high topical dosages. Fluticasone (Flixonase) – a new topical corticosteroid – seems to be very effective when used once daily. All the above products are useful in treating seasonal and perennial allergic rhinitis as well as nasal hypersensitivity. Oral steroids may be used for short periods when prompt symptomatic relief is sought at examination time or other special occasions. Longer acting depot steroid preparations (Depo Medrol, Celestone Soluspan) are cheap, effective and safe if given as "once only" treatments during the pollen season. They are not recommended as regular treatment for perennial allergic rhinitis.

Continuous use of vasoconstrictor sprays may also lead to rebound nasal congestion

5) *Anticholinergic sprays* such as Ipratropium bromide (Atrovent nasal spray), can be used topically to reduce nasal discharge considerably in the more resistant cases of water rhinorrhoea.

Immunotherapy

Immunotherapy or desensitisation injections are widely used in Europe and in the United States. In South Africa it is used most successfully in grass pollen allergy where symptom control is difficult and allergen avoidance is impossible.

There has been renewed interest in this form of therapy in both seasonal and perennial rhinitis especially as more standardised allergen extracts become available. However, treatment and maintenance therapy have to be continued at 6 weekly intervals for 3 to 5 years. Further studies should include comparisons between immunotherapy, the best available current treatment and "add on" studies where immunotherapy is continued with current treatments.[12]

Surgery in Chronic Rhinitis

Surgical options in chronic nasal congestion include sub-mucosal resection of the septum, and turbinate reduction to relieve the obstruction.

The minimally invasive functional endoscopic sinus surgery ("FESS") is an important advance in the treatment of nasal polyposis and disease of the osteo-meatal complex which are associated with sinusitis.[12]

Although the above treatment modalities are extremely effective, in the underfunded public health sector a more pragmatic approach has to be adopted. The older cheaper antihistamines and oral corticosteroids still have an important role to play and are cost effective.

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