

Introduction to nasal and pulmonary allergy cascade

The early phase of an IgE-dependent allergic reaction is followed by the activation of a complex network of inflammatory phenomena – T lymphocytes, cytokines, mediators, and adhesion molecules – that mediate late and ongoing allergic symptoms. The kinetics of respiratory inflammation following allergen exposure involve the migration of inflammatory cells to the mucosa within about 30 min, increased inflammatory infiltration over the following hours, and then slow subsidence. A relationship between asthma and allergic rhinitis is supported by epidemiological, histological, physiological, and immunopathological data, and by the response of asthma symptoms in rhinitic patients to intranasal corticosteroids and antihistamines. For example, there is no morphological difference between the bronchial inflammatory response following allergen-specific challenge in patients suffering from asthma alone or rhinitis alone. It is the allergen dose that makes the difference in the airway response to allergen in allergic rhinitis and asthma. Recognition of the relationship between asthma and allergic rhinitis has led to the introduction of new diagnostic terminology and treatment recommendations: 1) patients with persistent rhinitis should be evaluated for asthma; 2) patients with persistent asthma should be evaluated for rhinitis; and 3) a strategy should combine the treatment of upper and lower airways in terms of efficacy and safety.

G. W. Canonica

Allergy and Respiratory Diseases, Department of Internal Medicine, Genoa University, Genova, Italy

Key words: allergic, allergy cascade, asthma, hay fever, rhinitis

G. Walter Canonica, MD
Allergy and Respiratory Diseases
Department of Internal Medicine
Genoa University
L.go R. Benzi
10-16132 Genova
Italy

Since the early 1990s, understanding of the complexities of the IgE-dependent allergy cascade has increased dramatically, leading to clarification of the relationship between nasal and pulmonary allergy. It has become evident that respiratory allergy is a disorder of the entire respiratory tract, with different manifestations in the specific target organs of the nose and lungs. This article briefly reviews the current understanding of the IgE-dependent allergy cascade and examines the relationship between nasal and pulmonary respiratory allergy.

The IgE-dependent allergy cascade

An IgE-dependent allergic reaction is characterized by an early-phase and a late-phase reaction (Fig. 1). The early-phase reaction involves the release of histamine and other proinflammatory mediators. In the airways these lead, within seconds or minutes, to vasodilatation, increased permeability, and symptoms of nasal discharge, sneezing, and bronchoconstriction (1). During the early-phase reaction, mast cells release histamine and other preformed elements such as enzymes, hydrolases, and proteoglycans, and also release proinflammatory mediators such as prostaglandins (e.g. PGD₂), leukotrienes, platelet-activating factor, bradykinin, and cytokines

(e.g. tumour necrosis factor- α and interleukins IL-4, IL-5, IL-6, IL-10, and IL-13) (2). Proinflammatory mediators initiate a complex network of inflammatory phenomena involving adhesion molecules, Th2 T lymphocytes (which mainly release IL-4, IL-5, and IL-13), cytokines, and mediators (Fig. 2). These result in the late and ongoing allergic symptoms of nasal congestion, asthma, and urticaria. For an exhaustive review of the IgE-dependent allergy cascade, the reader is referred to the recent publication of the Allergic Rhinitis and Its Impact on Asthma (ARIA) Workshop Group (2).

One of the earliest and most important actions of proinflammatory effects caused by mast cells is to up-regulate or cause the *de novo* expression of adhesion molecules on the surface of endothelial cells (selectins) and epithelial cells (integrins). Adhesion molecules are involved in the recruitment of inflammatory cells (eosinophils, basophils, and neutrophils) from the circulation to the site of the inflammatory reaction. Specific adhesion molecules favour the tether/roll of inflammatory cells towards the epithelium (e.g. vascular cellular adhesion molecule-1 (VCAM-1), P-selectin, and L-selectin), the firm arrest of inflammatory cells to the epithelium (e.g. CD18 integrin, intercellular adhesion molecule-1 (ICAM-1), and VCAM-1), and

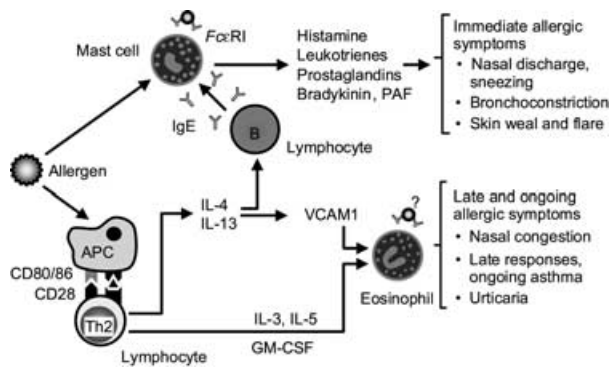


Figure 1 The IgE-dependent allergy cascade. APC, antigen-presenting cell; B, B lymphocyte; FcεRI, high-affinity receptor for IgE; GM-CSF, granulocyte monocyte colony-stimulating factor; IL, interleukin; PAF, platelet-activating factor; Th2, Th2 T lymphocyte; VCAM-1, vascular cellular adhesion molecule-1.

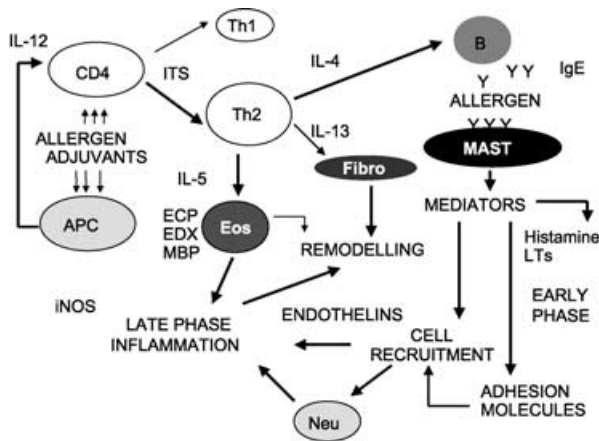


Figure 2 The allergic reaction. APC, antigen-presenting cell; B, B lymphocyte; Eos, eosinophil; ECP, eosinophil cationic protein; EDX, eosinophil-derived neurotoxin; Fibro, fibroblast; IL, interleukin; iNOS, inducible nitric oxide synthase; ITS, specific immunotherapy; LT, leukotriene; MBP, major basic protein; Neu, neutrophil; Th1, Th1 T lymphocyte; Th2, Th2 T lymphocyte; VCAM-1, vascular cellular adhesion molecule-1.

diapedesis (migration) through the epithelium (3). Experimental nasal, conjunctival, and bronchial data indicate that inflammatory cells begin to migrate to the mucosa approximately 30 min after specific challenge, continue to increase during the following 24 h, and then slowly subside (4–7). However, up-regulation of expression of the ICAM-1 molecule is evident on the conjunctival and nasal epithelium of allergic patients, even when they are asymptomatic (8).

Persistent up-regulation of ICAM-1 expression offers a theoretical mechanism for the minimal persistent inflammation that continues in the absence of symptoms when a subthreshold exposure to the allergen persists (8,9). It also suggests a mechanism for the exacerbation of asthma in

children during upper respiratory viral infection (10,11); the ICAM-1 molecule is the major receptor for human rhinoviruses (12), which in turn is the main cause of upper respiratory tract viral infections in children.

Comorbid association between nasal and pulmonary allergy

The relationship between asthma and allergic rhinitis is supported by epidemiological studies; by histological, physiological, and immunopathological characteristics; and by the positive effect of intranasal corticosteroids and antihistamines on asthma symptoms in rhinitic patients.

Epidemiological evidence

Early clinical observations showing an association between asthma and allergic rhinitis were confirmed in cross-sectional epidemiological studies (13), as reviewed by Annaesi-Maesano (14). For example, among young Italian men assessed in the mid-1990s, allergic rhinitis was present in 77% of those with asthma (15).

Large longitudinal studies revealed that allergic rhinitis usually precedes the onset of asthma (16–18). Although such results have been interpreted to define allergic rhinitis as a risk factor for the development of asthma, rhinitis appears to be an early stage of combined allergic airways disease. Disease extension probably occurs both upward and downward through the airways. In a recent survey conducted at Genoa University, 99 patients were followed for up to 10 years after the initial diagnosis of allergic rhinitis, allergic asthma, or both (19). During the 10-year follow-up, 32% of rhinitic patients developed asthma and 50% of patients with asthma alone developed rhinitis. A family history for atopy was associated with development of disease, but gender, age, smoking, and skin sensitization were not.

Functional considerations

The structural differences of the upper and lower airways result in different responses to allergic stimuli: rhinorrhoea/blockage in the rigid nose and sinuses, but mucus secretion/bronchoconstriction in the elastic tissues of the lung. Histological similarities and physiological relationships suggest that the respiratory tract is a single morphofunctional entity. The respiratory epithelium (ciliate epithelium and mucinous glands) extends from the smaller bronchi to the upper tract; bronchial/mucosal-associated lymphoid tissues (BALT or MALT) are present in both the upper and lower

airways (20). The upper respiratory tract functions as a physical filter, resonator, heat exchanger, and humidifier for inhaled air, the failure of which may compromise the homeostasis of the lower airways (21).

Immunological evidence

The underlying allergic processes are similar in the upper and lower airways (22). Allergic rhinitis and asthma are connected via an immunological response to airborne allergens that is evident throughout the entire body and through bronchial reaction to intranasal challenge.

The body-wide immunological response to airborne allergens is evident by the presence of antigen-specific responses of peripheral blood mononuclear cells (PBMCs), resulting in increased IL-4 production and reduced interferon (IFN)- γ production (23), and by the presence of eosinophilia systemically as well as in secretions from the nose and sputum (22). The specific communication between the upper and lower airways and the bone marrow leading to up-regulation is not yet known, but the bone marrow appears to provide an ongoing source of differentiating inflammatory cells (eosinophils, basophils, and mast cells) to the entire airway (24).

The lower airway response to nasal challenge is demonstrated by morphological changes and by bronchoconstriction. Thickening of the reticular basement membrane is characteristic of airway remodelling in asthma, but similar degrees of thickening are seen in patients with perennial rhinitis and those with perennial allergic asthma (25). There is no morphological difference between the bronchial inflammatory response (cell influx and basement membrane thickening) following allergen-specific challenge in patients suffering from asthma alone or rhinitis alone (Fig. 3) (25,26). Allergen-specific challenge of rhinitic patients also causes a contractile response or increased responsiveness of bronchi

(nasobronchial reflex) (20). This may be mediated via cytokine release of mast cells, which are abundantly present throughout the respiratory mucosa (27). The important difference between asthma and rhinitis is that a greater dose of allergen is necessary to cause bronchoconstriction in rhinitic patients (28).

Indirect evidence: outcomes of therapy

β_2 -adrenergic agonists dilate the elastic lower airways, but are ineffective in the rigid upper airways. In contrast, the structural differences between the upper and lower airways are not a barrier to system-wide effects of other treatment options, such as intranasal corticosteroids and systemic antihistamines. For example, the use of intranasal corticosteroids (e.g. beclomethasone and fluticasone propionate) for rhinitis symptoms significantly reduces bronchial hyperresponsiveness to methacholine and has been shown to improve asthma symptoms (29–31). In a double-blind, double-dummy, placebo-controlled study of rhinitic patients with documented carbachol-induced bronchial hyperresponsiveness, beclomethasone 100 μ g given intranasally four times daily – but not by inhalation – reduced bronchial hyperresponsiveness (32). Several studies have documented the efficacy of antihistamine therapy in reducing symptoms of asthma in people with seasonal allergic rhinitis when given alone (33), or in combination with a decongestant (34) or an antileukotriene (35,36). Furthermore, the Early Treatment of Atopic Child (ETAC) study showed that the onset of asthma was prevented by continuous antihistamine treatment in a defined subset of patients (37).

Discussion and conclusions

Increased understanding of the nasal and pulmonary allergy cascade has furthered the appreciation of allergy as a systemic disease, and the role of systemic

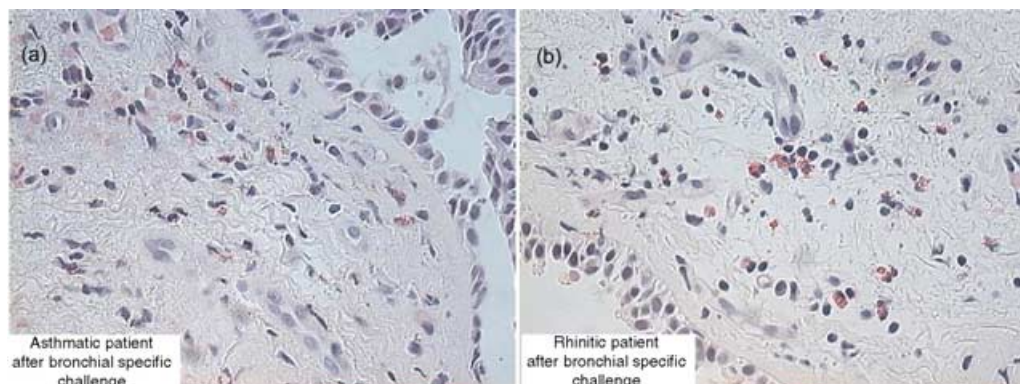


Figure 3 Bronchial biopsies obtained after allergen-specific bronchial challenge; the inflammatory changes are superimposable.

intervention. This has prompted investigation and development of new therapeutic interventions for respiratory allergy.

Recognizing the comorbid association of nasal and pulmonary allergy (and its related and concurrent manifestation as allergic rhinitis and asthma, respectively) is a major development in the field of allergic respiratory disease. It has led to the introduction of several new terms, including *allergic rhinobronchitis* (22) and *united airways disease* (20). However, *combined allergic rhinitis and asthma syndrome* (CARAS) was recently chosen as most appropriate by the global membership of the World Allergy Organization (38). It has also changed the management of allergy. As recommended by the evidence-based document Allergic Rhinitis and Its Impact on Asthma, written in

collaboration with the World Health Organization: 1) patients with persistent rhinitis should be evaluated for asthma; 2) patients with persistent asthma should be evaluated for rhinitis; and 3) a strategy should combine the treatment of upper and lower airways in terms of efficacy and safety (2).

Major international research efforts, such as the International Study of Asthma and Allergies in Childhood (ISAAC), have revealed substantial worldwide variations in the prevalence and labelling of symptoms of allergic rhinoconjunctivitis (39). New points of intervention in the treatment of respiratory allergy, the systemic nature of allergy (manifested as chronic idiopathic urticaria), and changes in the management of allergy are among the topics addressed in other articles in this Supplement to *Allergy*.

References

1. BACHERT C, VAN KEMPEN M, VAN CAUWENBERGE P. Regulation of proinflammatory cytokines in seasonal allergic rhinitis. *Int Arch Allergy Immunol* 1999;**118**: 375–379.
2. BOUSQUET J, VAN CAUWENBERGE P, KHALTAEV N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;**108** (Suppl. 5):S147–S334.
3. KANWAR S, JOHNSTON B, KUBES P. Leukotriene C4/D4 induces P-selectin and sialyl Lewis (x)-dependent alterations in leukocyte kinetics in vivo. *Circ Res* 1995;**77**:879–887.
4. CIPRANDI G, PRONZATO C, RICCA V, PASSALACQUA G, BAGNASCO M, CANONICA GW. Allergen-specific challenge induces intercellular adhesion molecule-1 (ICAM-1 or CD54) on nasal epithelial cells in allergic subjects. Relationships with early and late inflammatory phenomena. *Am J Respir Crit Care Med* 1994;**150**:1653–1659.
5. VIGNOLA AM, CAMPBELL A, CHANEZ P et al. HLA DR and ICAM 1 expression in asthma and chronic bronchitis. *Am Rev Respir Dis* 1993;**148**:689–694.
6. BEASLEY R, ROCHE WR, ROBERTS JA, HOLGATE ST. Cellular events in the bronchi in mild asthma after bronchial provocation. *Am Rev Respir Dis* 1989;**139**: 806–817.
7. JEFFERY PK, WARDLAW AJ, NELSON FC et al. Bronchial biopsies in asthma. An ultrastructural quantitative study and correlation with hyperreactivity. *Am Rev Respir Dis* 1989;**140**:1745–1753.
8. CIPRANDI G, BUSCAGLIA S, PESCE G et al. Minimal persistent inflammation is present at mucosal level in patients with asymptomatic rhinitis and mite allergy. *J Allergy Clin Immunol* 1995;**96**: 971–979.
9. RICCA V, LANDI M, FERRERO E et al. Minimal persistent inflammation is also present in patients with pollen allergy. *J Allergy Clin Immunol* 2000;**105**:54–63.
10. JOHNSTONE SL, PATTERMORE PD, SANDERSON G et al. A longitudinal study on the role of viral infections in exacerbations of asthma in school children in the community. *Br Med J* 1995;**310**:1225–1229.
11. JOHNSTONE SL, PATTERMORE PD, SANDERSON G 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**:154–660.
12. GREVE JM, DAVIS G, MEYER AM et al. The major human rhinovirus receptor is ICAM-1. *Cell* 1989;**56**:839–847.
13. JOHNSTONE D, DUTTON A. The value of hyposensitization therapy for bronchial asthma in children: a 14-year study. *Pediatr* 1968;**42**: 793–797.
14. ANNAESI-MAESANI I. Epidemiological evidence of the occurrence of rhinitis and sinusitis in asthma. *Allergy* 1999;**54** (Suppl. 57):7–13.
15. CIPRANDI G, VIZZACCARO A, CIRILLO I, CRIMI P, CANONICA G. Increase of asthma and allergic rhinitis prevalence in young Italian men. *Int Arch Allergy Immunol* 1996;**111**:279–283.
16. SETTIPANE G, SETTIPANE RJ, HAGY GW. Long term risk factors for developing asthma and allergic rhinitis: a 23-year follow up study of college students. *Allergy Proc* 1994;**15**:21–25.
17. ANDERSON HR, POTTIER AC, STRACHAN DP. Asthma from birth to age 23: incidence and relationship to prior and concurrent atopic status. *Thorax* 1992;**47**: 537–542.
18. JENKINS MA, HOPPER JL, FLANDER LB et al. The associations between childhood asthma, and atopy, and parental asthma, hay fever and smoking. *Paediatr Perinat Epidemiol* 1993;**7**:67–76.
19. LOMBARDI C, PASSALACQUA G, GARGIONI S et al. The natural history of respiratory allergy: a follow-up study of 99 patients up to 10 years. *Respir Med* 2001;**95**:9–12.
20. PASSALACQUA G, CIPRANDI G, CANONICA GW. The nose–lung interaction in allergic rhinitis and asthma: united airways disease. *Curr Opin Allergy Clin Immunol* 2001;**1**:7–13.
21. FONTANARI P, BURNET H, ZATERA-HARTMANN C, JAMMES Y. Changes in airway resistance induced by nasal inhalation of cold, dry or moist air in normal individuals. *J Appl Physiol* 1996;**81**: 1739–1743.
22. SIMONS FE. Allergic rhinobronchitis: the asthma–allergic rhinitis link. *J Allergy Clin Immunol* 1999;**104**:534–540.
23. IMADA M, SIMONS FER, JAY FT, HAYGLASS KT. Antigen-mediated and polyclonal stimulation of human cytokine production elicit qualitatively different patterns

- of cytokine gene expression. *Int Immunol* 1995;**7**:229–237.
24. DENBURG J. Asthma and rhinitis: a systemic disease. In: NEFFEN H, FABBRI L, HOLGATE ST, O'BYRNE P, BAENA-CAGNANI C, editors. *Asthma: A Link Between Environment, Immunology, and the Airways*. Seattle, WA: Hogrefe and Huber, 1999, 162–166.
25. MILANESE M, CRIMI E, SCORDAMAGLIA A et al. On the functional consequences of bronchial basement membrane thickening. *J Appl Physiol* 2001;**91**:1035–1040.
26. CRIMI E, MILANESE M, ODDERA S et al. Inflammatory and mechanical factors of allergen-induced bronchoconstriction in mild asthma and rhinitis. *J Appl Physiol* 2001;**91**:1029–1034.
27. OKUDA M. Functional heterogeneity of airways mast cells. *Allergy* 1999;**54**(Suppl. 57):50–62.
28. BONAVIA M, CRIMI E, QUAGLIA A, BRUSASCO V. Comparison of early and late asthmatic response between patients with allergic rhinitis and mild asthma. *Eur Respir J* 1996;**9**:905–909.
29. CORREN J, ADINOFF AD, BUCKMEIER AD, IRWIN CG. Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. *J Allergy Clin Immunol* 1992;**90**:250–256.
30. FORESI A, PELUCCHI A, GHERSON G et al. Once daily intranasal fluticasone propionate (200 micrograms) reduces nasal symptoms and inflammation but also attenuates the increase in bronchial responsiveness during the pollen season in allergic rhinitis. *J Allergy Clin Immunol* 1996;**98**:274–282.
31. WATSON WT, BECKER AB, SIMONS FER. Treatment of allergic rhinitis with intranasal corticosteroids in patients with mild asthma: effect on lower airway responsiveness. *J Allergy Clin Immunol* 1993;**91**: 97–101.
32. AUBIER M, LEVY J, CLERICI C et al. Different effects of nasal and bronchial glucocorticosteroid administration on bronchial responsiveness in patients with rhinitis. *Am Rev Respir Dis* 1992;**146**:122–126.
33. GRANT JA, NICODEMUS CF, FINDLAY SR et al. Cetirizine in patients with seasonal rhinitis and concomitant asthma: prospective, randomized controlled trial. *J Allergy Clin Immunol* 1995;**95**:923–932.
34. CORREN J, HARRIS AG, AARONSON D et al. Efficacy and safety of loratadine plus pseudoephedrine in patients with seasonal allergic rhinitis and asthma. *J Allergy Clin Immunol* 1997;**100**:781–788.
35. ROQUET A, DAHLEN B, KUMLIN M et al. Combined antagonism of leukotriene and histamine produces a predominant inhibition of allergen-induced early and late phase airway obstruction in asthmatics. *Am J Respir Crit Care Med* 1997;**155**: 1856–1863.
36. MELTZER EO, MALMSTROM K, LU S et al. Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: a randomized, placebo controlled clinical trial. *J Allergy Clin Immunol* 2000;**105**: 917–922.
37. ETAC STUDY GROUP. Allergic factors associated with the development of asthma and the influence of cetirizine in a double-blind randomized placebo controlled trial. *Allergy* 1998;**3**:116–124.
38. WORLD ALLERGY ORGANIZATION. Combined allergic rhinitis and asthma syndrome. http://www.worldallergy.org/professional/allergy_update/caras/airwayssynopsis.shtml. Accessed 18 November 2002.
39. STRACHAN D, SIBBALD B, WEILAND S et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). *Pediatr Allergy Immunol* 1997;**8**:161–176.
40. PASSALACQUA G, CANONICA GW. Impact of rhinitis on airway inflammation: biological and therapeutic implications. *Respir Res* 2001;**2**:320–323.