

Is intrinsic asthma synonymous with infection?

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Summary

Rackemann described the 'intrinsic asthma' population over 50 years ago as a unique subgroup that was characterized by onset of progressive loss of lung function beginning later in life, possibly after a respiratory infection. It has also been associated with a female predominance, aspirin-sensitive bronchospasm, and nasal polyposis. While the aetiology is not understood, we propose that persistent respiratory infections play a central role in the development of intrinsic asthma.

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In 1947 Rackemann [1] described a population of patients who developed asthma in their adulthood; although no inciting cause was identified, there was speculation that a respiratory infection often preceded the onset of asthma symptoms. These patients also had the unique characteristic that they were not allergic to environmental factors. Based upon these characteristics, Rackemann defined these patients as having 'intrinsic asthma', largely due to a lack of an identifiable allergic component, thus contrasting with 'extrinsic asthma' where allergic sensitization existed. He found both forms of asthma to have similar clinical symptoms, airflow obstruction, and bronchial hyperresponsiveness. The intrinsic population, however, had the onset of their airway disease later in life as well as a disproportionate percentage of women and a greater incidence of sinusitis, nasal polyps, and aspirin sensitivity [2, 3]. Moreover, their disease was less responsive to treatment. Finally, patients with intrinsic asthma did not have a family history of asthma or allergic disease. While diagnostic criteria have not been established, it is those patients with late-onset, non-atopic asthma that have been considered to have 'intrinsic' asthma or non-allergic asthma.

Since Rackemann first began this early phenotypic classification of asthma into extrinsic (allergic) and intrinsic (non-allergic), there has been tremendous progress in our understanding the immune histopathology and pathogenesis of asthma. However, the majority of research, both in animal models and human asthma, has focused on allergic sensitization as a key factor or model for study. Respiratory infections can also have a significant influence on many aspects of asthma: inception, exacerbations, and possibly persistence (Fig. 1). In early life, viral respiratory infections provoke wheezing, which may become recurrent in some patients. Infants with frequent wheezing events in early life with respiratory infections appear to be at risk for asthma [4]. To study the importance of early life events in asthma, birth cohorts are often selected on the basis of a family history of 'allergies'. The focus on allergies in the pathogenesis of asthma has greatly limited the study of 'intrinsic' asthma to the point where the concept and investigation of intrinsic asthma has fallen by the wayside.

Physicians, however, still see patients who, apparently, have the onset of asthma as an adult and without apparent

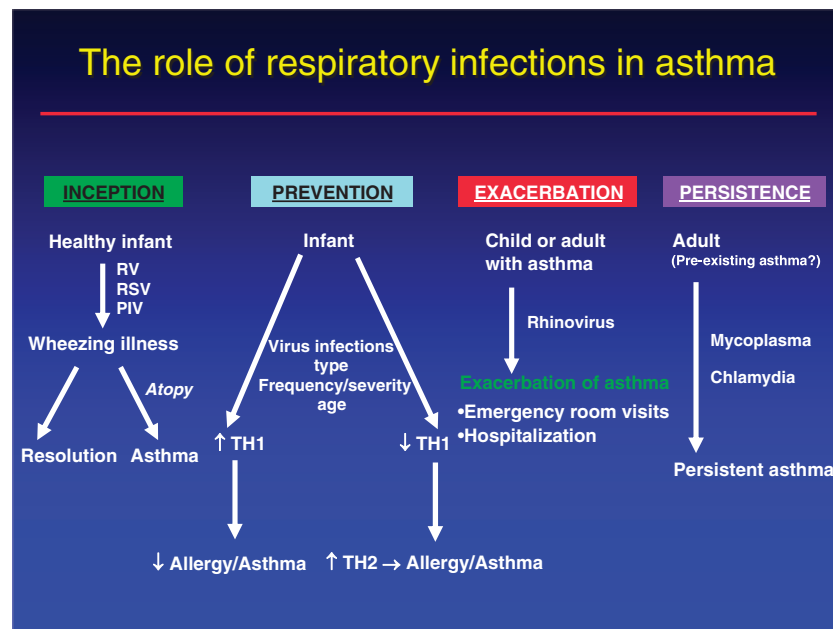


Fig. 1. Respiratory tract infections incite established asthma and likely participate in the initiation of chronic allergic pulmonary inflammation in both infancy and adulthood.

evidence of underlying allergic causes. Progress in the study of 'intrinsic' asthma has been greatly limited and new insights into the origin of this apparent phenotype of asthma appear at a stand still. Unfortunately, little histopathologic data are available that clearly delineates the differences between atopic and non-atopic asthma. Nonetheless, the possibility raised early on by Rackemann that a respiratory infection may be a provoking factor in this process of non-allergic asthma is still tenable and of interest. Respiratory tract infections may have multiple histopathologic and clinical consequences, of which reversible airflow obstruction and allergic sensitization are possibilities. The interplay between respiratory viral infections and allergic sensitization is not clearly established or potentially even linked. However, in allergic asthma, IgE plays a key role and allergen exposure can provoke airway inflammation and changes in pulmonary hyperresponsiveness. In intrinsic asthma, it is not known how the inflammatory processes that alter lung function are initiated and regulated. Contributing to this quandary is the observation that although patients with intrinsic asthma do not produce antigen-specific IgE, they may have an elevated total serum IgE level [5, 6]. Thus, a key question to consider is how airway inflammation can be initiated and sustained where there is no identifiable IgE-specific trigger or any familial predisposition to develop such a reaction? Furthermore, the role of an elevated total serum IgE and what it tells us of the pathophysiology of intrinsic asthma remains in question.

Rackemann's original description of intrinsic asthma speculated that intrinsic asthma occurs in presumably

'innocent non-atopic bystanders', who may have subtle immune deficiencies that may allow an innocuous respiratory infection to provoke injury to the airway, which then sets up a vicious cycle of an ongoing inflammatory process leading to clinical asthma. There are observations that under the 'right' conditions and with the 'right' infection chronic inflammation may occur and thus set up an asthmatic process.

A number of observations build on this premise. Rhinitis and sinusitis frequently occur in asthma, including non-allergic or intrinsic asthma. For example, *Staphylococcus aureus* colonization occurs in some asthma patients with aspirin hypersensitivity. Furthermore, these clinical features co-segregated with local Staphylococcal enterotoxin-specific IgE production and elevated markers of eosinophilic inflammation in nasal polyp samples [7]. In addition, serum Staphylococcal enterotoxin-specific IgE levels were positively associated with the severity of asthma [8], indirectly suggesting a role of this pathogen in the aetiology of airway disease and implying that pathogen-specific IgE production and allergic-type inflammation may occur with a chronic infectious inflammatory process.

Respiratory infections may also contribute to or initiate allergic inflammation. In a mouse model of an acute *Chlamydia pneumoniae* infection, there is a 5-day window post-inoculation during which allergic sensitization develops, without further adjuvant, if respiratory antigen exposure occurs [9]. A number of factors influenced this sensitization process. If higher titres of *C. pneumoniae* exist, sensitization is less likely, suggesting that mild

infections may provide a distinct immunologic context sufficient for T-helper type 2 inflammation to develop. Furthermore, sensitized mice have greater eosinophilic inflammation during antigen challenge if they are concurrently inoculated with rhinovirus [10]. These findings suggest that respiratory infections may enhance the underlying allergic inflammatory response.

For the past two decades there has been emerging evidence that both asthma and wheezing exacerbations may be linked to atypical bacterial infections [11]. *C. pneumonia* is a common and potentially subclinical intracellular respiratory pathogen known to cause chronic infections. *C. pneumonia*-specific secretory IgA levels, a possible indicator of an ongoing infection, have been linked to symptomatic asthma in children [12] and adults [13]. Cases of adult-onset asthma have also been found in association with recently documented *C. pneumonia* infections [11]. The diagnosis of *Chlamydia* infections is, however, often difficult to establish, but in one study, the pathogen was detected by PCR analysis in 23% of nasal aspirate samples from symptomatic and 28% of asymptomatic children with asthma [12]. Furthermore, the presence of one positive aspirate increased the likelihood of subsequent positive tests, suggesting either a chronic infection or a predisposition to become re-infected in those individuals with asthma. Moreover, and of interest to intrinsic asthma, 43% of these children were non-atopic.

More recently, in an adult-onset, non-atopic population of patients with severe asthma, a positive correlation was found between IgG seropositivity to *C. pneumonia* and the rate of post-bronchodilator forced expiratory volume in 1 s/forced vital capacity (FEV₁/FVC) decline [14]. The steep decline in lung function was proposed to be secondary to a persistent infection, which can occur with *Chlamydia*. Given the nature of a persistent contagion, it has been hypothesized that a periodic flare of the underlying infection would either exacerbate asthma or amplify the inflammatory process, thus leading to more severe disease, a greater loss of lung function, and a lessened response to usual treatment. Whether this loss in lung function occurs generally in the intrinsic asthma population or if it is restricted to specific aetiologies is not currently established.

Mycoplasma pneumoniae may not only exacerbate an acute asthmatic event, but may also lead to a chronic infection. There is evidence of new adult-onset chronic airway obstruction that developed 1 month after a *Mycoplasma* infection [15]. In a sentinel case, an individual with *Mycoplasma*-specific IgE was identified by RAST and skin prick testing. The clinical relevance of these findings was further supported by a positive inhalational challenge, thus suggesting that infectious agents may also act as an allergen and lead to airway responses similar to provocations with inhalant allergens.

Respiratory viruses can also cause chronic infections and influence underlying pathophysiology. Recently, rhinovirus infections have been linked to chronic infection in lung transplant recipients [16]. Also, rhinoviruses have been detected in patients with chronic asthma [17], where the presence of this respiratory virus was associated with more severe disease. In addition, rhinovirus has been found with recurrent respiratory symptoms in infants [18]. Finally, a study by Wos and colleagues examined adult patients with asthma where half were non-atopic and 73% (vs. 22% in the control group) were positive for lower respiratory tract rhinovirus infection by PCR. The patients evaluated were not experiencing respiratory infection thus raising the question as to whether these subjects had a chronic infection. In addition, those with detectable rhinovirus had lower FEV₁, FEV₁/FVC and forced expiratory volume between 25% and 75% of vital capacity values raising the possibility that a 'persistent' infection may contribute to the severity of their disease. Also of note, rhinovirus was detected in all of the aspirin-sensitive patients, further suggesting the importance of infection in the intrinsic asthmatic population [17].

The adenovirus infections have also been shown to persist in children (1–14 years old) where their presence related to chronic airflow obstruction [19]. In this population, treatment with inhaled corticosteroids improved peak expiratory flow rates, but full reversibility was not obtained, suggesting that the presence of the adenovirus infection may lead to corticosteroid insensitivity and ongoing inflammation. It has been subsequently shown in an animal model of allergic airway inflammation that the responsiveness of eosinophils to corticosteroids is reduced in animals with a latent adenoviral respiratory infection [20], suggesting that pathogen persistence in severe asthma with eosinophilia-predominant airway inflammation may alter the response to treatment and become the driving force of the disease process.

Pulmonary colonization with *Aspergillus* in asthma can lead to the clinical syndrome allergic bronchopulmonary aspergillosis (ABPA), which is frequently manifested by a progressive decline in lung function. ABPA may be one extreme on a spectrum of chronic infections that trigger respiratory inflammation. If this is the case, then other manifestations of similar pathologic processes may also respond to anti-microbial therapy. For example, Denning et al. [21] treated a cohort of patients with severe asthma who were sensitized to fungi, but did not meet criteria for ABPA, with oral itraconazole or placebo for 32 weeks. Those patients on active treatment experienced a significant improvement in quality of life and a decrease in the total serum IgE. While appropriate therapy for all of the potential infectious agents mentioned above does not exist, there may be other methods to minimize morbidity in affected individuals (Fig. 2).

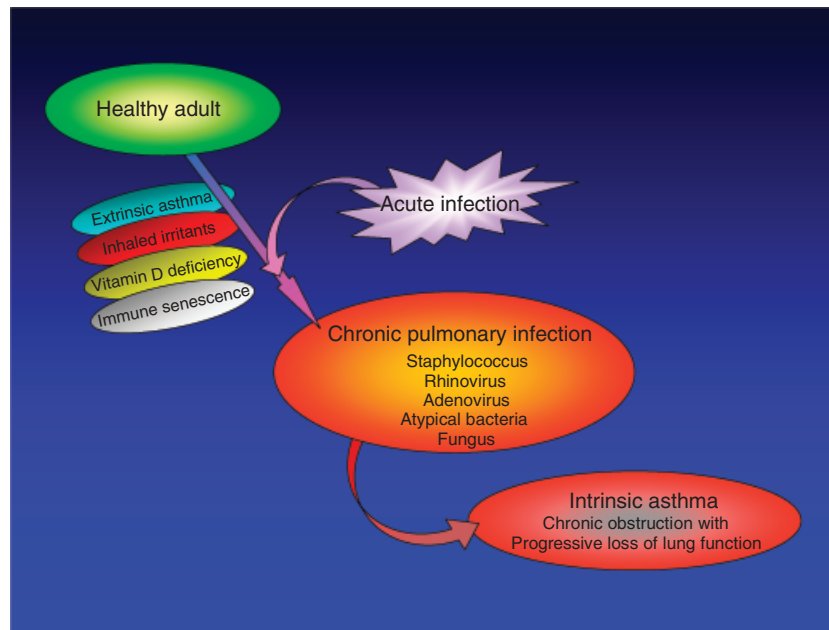


Fig. 2. Intrinsic asthma may develop in individuals who are unable to eliminate an acute respiratory infection due to previously acquired subtle immune impairments.

If chronic respiratory infections occur in some asthmatic patients, it is also likely that acquired immunological perturbations may be a predisposing factor. While in some cases the impairments that lead to chronic infections may be anticipated and the mechanisms well known, the majority of the immune impairments that exist are likely to be subtle or silent if not paired with other deficits. The most obvious of these would be epithelial injury, which can occur from a variety of exposures, like occupational materials, pollutants, or smoking. While denuded epithelium leads to impaired clearance and increases the susceptibility to super-infection from decreased barrier function, less obvious impairments may occur from exposure to certain byproducts of combustion which could paralyse respiratory cilia and limit pulmonary clearance [22].

Recently, the influence of vitamin D on the immune system has been of interest. Not only has it been demonstrated that impaired killing of respiratory pathogens phagocytosed by macrophages can be resolved *in vitro* with calcitriol administration [23], but oral supplementation in humans may also decrease symptomatic viral infections in a non-asthmatic population [24]. Interestingly, the bronchial epithelium can convert 25-hydroxy-vitamin D to its active form, 1, 25-dihydroxyvitamin D, which then up-regulates the expression of CD14 [25] and the anti-microbial protein, cathelicidin [25, 26]. These interactions help explain how this immunomodulatory hormone affords protection against pulmonary infection to adults with sufficient levels [27, 28]. As deficiency is highly prevalent in western societies, if infection is shown

to play a causal role, vitamin D levels may prove to be a modifiable factor in preventing this disease.

While serum vitamin D levels decline in aged populations, other factors are likely to contribute to the development of intrinsic asthma in adults. A decline in the responsiveness of the immune system may occur and is termed immunosenescence. While this process is complex and not fully understood, chronic respiratory infections could be a manifestation of the early stages of these age-related changes. Until a greater comprehension of these events exists, the specific deficits that would increase susceptibility to developing a sustained infection will remain obscure.

Pre-established atopic asthma may also predispose to the development of a 'mixed' extrinsic and intrinsic picture. In asthma, impaired cytokine responses [29, 30] reduce expression of co-stimulatory molecules and alter CD14 expression on peripheral blood mononuclear cells in response to *in vitro* rhinovirus infection [31]. Furthermore, two laboratories have shown primary bronchial epithelial cell cultures from asthmatic subjects have impaired innate responses to rhinovirus [32, 33]. These data suggest that extrinsic asthmatics may actually be at increased risk for developing chronic respiratory infections with a subsequent worsening of their symptoms. If this is indeed the case, the boundaries between intrinsic and extrinsic asthma may be more clouded than previously thought with populations of patients who harbour features of both phenotypes.

While Rackemann recognized the possible importance of respiratory infections to the aetiology of intrinsic

asthma over 60 years ago, only recently have pathogen--host interactions been demonstrated to lead to allergic-type inflammation. The likely presence of a persistent viral infection in non-atopic asthmatic subjects raises the possibility that a variety of agents can lead to this pathophysiology, however, the most thoroughly explored of these associations have been with atypical bacterial infections, and even here the answers are far from lucid. It remains to be defined if a persistent infection is truly necessary for the induction of intrinsic asthma. Whether acute infections have lasting effects on airway physiology and function, or if persistence of the infection is required, is not known. Furthermore, many of the studies to suggest correlations between intrinsic asthma and infection are limited; thus, we recognize that our hypothesis remains highly speculative. Nonetheless, there remains a significant proportion of asthmatic patients in whom allergen sensitization and a family history of allergic disease is lacking, and yet asthma exists. Therefore, the term 'intrinsic' asthma can be of clinical relevance and interest, and raise the possibility that respiratory infections may play an important role in this asthma phenotype.

References

- 1 Rackemann FM. A working classification of asthma. *Am J Med* 1947; 33:601-6.
- 2 Settipane GA, Chafee FH. Nasal polyps in asthma and rhinitis. A review of 6,037 patients. *J Allergy Clin Immunol* 1977; 59:17-21.
- 3 Charpin D, Ramadour M, Lanteaume A, Vervloet D. Triggers in intrinsic asthma in the EGEA study. *J Asthma* 2003; 40: 87-91.
- 4 Jackson DJ, Gangnon RE, Evans MD *et al.* Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med* 2008; 178:667-72.
- 5 Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE levels and skin-test reactivity to allergens. *N Engl J Med* 1989; 320:271-7.
- 6 Beeh KM, Ksoll M, Buhl R. Elevation of total serum immunoglobulin E is associated with asthma in nonallergic individuals. *Eur Respir J* 2000; 16:609-14.
- 7 Perez-Novo CA, Kowalski ML, Kuna P *et al.* Aspirin sensitivity and IgE antibodies to *Staphylococcus aureus* enterotoxins in nasal polyposis: studies on the relationship. *Int Arch Allergy Immunol* 2004; 133:255-60.
- 8 Bachert C, Gevaert P, Howarth P, Holtappels G, van Cauwenberge P, Johansson SG. IgE to *Staphylococcus aureus* enterotoxins in serum is related to severity of asthma. *J Allergy Clin Immunol* 2003; 111:1131-2.
- 9 Schroder NW, Crother TR, Naiki Y *et al.* Innate immune responses during respiratory tract infection with a bacterial pathogen induce allergic airway sensitization. *J Allergy Clin Immunol* 2008; 122:595-602, e5.
- 10 Bartlett NW, Walton RP, Edwards MR *et al.* Mouse models of rhinovirus-induced disease and exacerbation of allergic airway inflammation. *Nat Med* 2008; 14:199-204.
- 11 Hahn DL, Dodge RW, Golubjatnikov R. Association of *Chlamydia pneumoniae* (strain TWAR) infection with wheezing, asthmatic bronchitis, and adult-onset asthma. *JAMA* 1991; 266:225-30.
- 12 Cunningham AF, Johnston SL, Julious SA, Lampe FC, Ward ME. Chronic *Chlamydia pneumoniae* infection and asthma exacerbations in children. *Eur Respir J* 1998; 11:345-9.
- 13 Hahn DL, Anttila T, Saikku P. Association of *Chlamydia pneumoniae* IgA antibodies with recently symptomatic asthma. *Epidemiol Infect* 1996; 117:513-7.
- 14 ten Brinke A, van Dissel JT, Sterk PJ, Zwinderman AH, Rabe KF, Bel EH. Persistent airflow limitation in adult-onset nonatopic asthma is associated with serologic evidence of *Chlamydia pneumoniae* infection. *J Allergy Clin Immunol* 2001; 107: 449-54.
- 15 Yano T, Ichikawa Y, Komatsu S, Arai S, Oizumi K. Association of *Mycoplasma pneumoniae* antigen with initial onset of bronchial asthma. *Am J Respir Crit Care Med* 1994; 149:1348-53.
- 16 Kaiser L, Aubert JD, Pache JC *et al.* Chronic rhinoviral infection in lung transplant recipients. *Am J Respir Crit Care Med* 2006; 174:1392-9.
- 17 Wos M, Sanak M, Soja J, Olechnowicz H, Busse WW, Szczeklik A. The presence of rhinovirus in lower airways of patients with bronchial asthma. *Am J Respir Crit Care Med* 2008; 177:1082-9.
- 18 Malmstrom K, Pitkaranta A, Carpen O *et al.* Human rhinovirus in bronchial epithelium of infants with recurrent respiratory symptoms. *J Allergy Clin Immunol* 2006; 118:591-6.
- 19 Macek V, Sorli J, Kopriva S, Marin J. Persistent adenoviral infection and chronic airway obstruction in children. *Am J Respir Crit Care Med* 1994; 150:7-10.
- 20 Yamada K, Elliott WM, Hayashi S *et al.* Latent adenoviral infection modifies the steroid response in allergic lung inflammation. *J Allergy Clin Immunol* 2000; 106:844-51.
- 21 Denning DW, O'Driscoll BR, Powell G *et al.* Randomized controlled trial of oral antifungal treatment for severe asthma with fungal sensitization: The Fungal Asthma Sensitization Trial (FAST) study. *Am J Respir Crit Care Med* 2009; 179:11-8.
- 22 Pedersen M. Ciliary activity and pollution. *Lung* 1990; 168 (Suppl.):368-76.
- 23 Liu PT, Stenger S, Tang DH, Modlin RL. Cutting edge: vitamin D-mediated human antimicrobial activity against *Mycobacterium tuberculosis* is dependent on the induction of cathelicidin. *J Immunol* 2007; 179:2060-3.
- 24 Aloia JF, Li-Ng M. Re: epidemic influenza and vitamin D. *Epidemiol Infect* 2007; 135:1095-6, author reply 1097-8.
- 25 Hansdottir S, Monick MM, Hinde SL, Lovan N, Look DC, Hunninghake GW. Respiratory epithelial cells convert inactive vitamin D to its active form: potential effects on host defense. *J Immunol* 2008; 181:7090-9.
- 26 Yim S, Dhawan P, Ragunath C, Christakos S, Diamond G. Induction of cathelicidin in normal and CF bronchial epithelial cells by 1,25-dihydroxyvitamin D(3). *J Cyst Fibros* 2007; 6: 403-10.
- 27 Laaksi I, Ruohola JP, Tuohimaa P *et al.* An association of serum vitamin D concentrations <40 nmol/L with acute respiratory tract infection in young Finnish men. *Am J Clin Nutr* 2007; 86:714-7.
- 28 Ginde AA, Mansbach JM, Camargo Jr CA. Association between serum 25-hydroxyvitamin d level and upper respiratory tract

- infection in the third national health and nutrition examination survey. *Arch Intern Med* 2009; **169**:384–90.
- 29 Brooks GD, Buchta KA, Swenson CA, Gern JE, Busse WW. Rhinovirus-induced interferon-gamma and airway responsiveness in asthma. *Am J Respir Crit Care Med* 2003; **168**:1091–4.
- 30 Papadopoulos NG, Stanciu LA, Papi A, Holgate ST, Johnston SL. A defective type 1 response to rhinovirus in atopic asthma. *Thorax* 2002; **57**:328–32.
- 31 Papadopoulos NG, Stanciu LA, Papi A, Holgate ST, Johnston SL. Rhinovirus-induced alterations on peripheral blood mononuclear cell phenotype and costimulatory molecule expression in normal and atopic asthmatic subjects. *Clin Exp Allergy* 2002; **32**:537–42.
- 32 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.
- 33 Contoli M, Message SD, Laza-Stanca V *et al.* Role of deficient type III interferon-lambda production in asthma exacerbations. *Nat Med* 2006; **12**:1023–6.