



A century of “intrinsic asthma”

A view on the development of phenotyping in asthma in the last 100 years

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Abstract

Background One hundred years ago Rackemann published the first description of Intrinsic Asthma. This was the beginning of a process of phenotyping the disease.

Materials and methods The literature regarding asthma phenotypes of the last 100 years has been checked. Lately, there have been many new publications dealing with this specific asthma phenotype.

Conclusion Today, the term asthma is looked at as an umbrella covering different phenotypes of the disease. According to a recent publication, Intrinsic Asthma is most often cited now as eosinophilic adult-onset asthma. New treatment strategies for this phenotypes have evolved in recent years.

Keywords Asthma · Allergy · Intrinsic asthma · Eosinophilic asthma · Asthma phenotypes

Asthma—an umbrella of different phenotypes

A hundred years ago, based on the observation of 150 patients with asthma, Rackemann [1] defined in the US a new phenotype of asthma, which differed from the previously known form of allergic asthma. In the German language, a comprehensive review on this subject was published in 1973 [2]. This new term *Intrinsic Asthma* was not intended to refer to all patients where symptoms are not caused by an allergic reaction, but to refer to a newly defined distinct disease entity. It describes subjects who manifest asthma in adulthood, with perennial symptoms that are not driven by allergen exposure, and

a pronounced eosinophilic inflammation including the upper respiratory tract too.

Dame Turner-Warwick [3], who came up with the term *morning dipping* of the peak flow as an expression of bronchial hyperresponsiveness, identified a group of patients in whom bronchial obstruction develops slowly over the course of time and is not reversible with beta agonists, but with systemic corticosteroids. Due to its behaviour in the peak flow curve, she called this the *Drifter Type* of asthma. It corresponded very well to the Intrinsic Asthma described by Rackemann. In contrast to the primary allergic, usually *early onset asthma*, bronchial hyperresponsiveness is often much less pronounced in this phenotype.

This was also confirmed in the study of Ian Pavord's working group in England [4]. They conducted a cluster analysis with the aim of identifying phenotypes of asthma according to scientific criteria rather than based on empirical data. In this analysis a large group of patients with allergic early onset asthma showed a concordance of intensity of eosinophilic inflammation and the extent of typical asthma symptoms (Fig. 1). These symptoms include nocturnal coughing, nighttime awakenings with breathlessness and exercise-induced asthma. However, they also discovered a cluster of patients with massive eosinophilic inflammation but few typical asthma symptoms, i.e. partial lack of bronchial hyperresponsiveness. The authors highlighted here the discordance between asthma symptoms and the extent of eosinophilic inflammation in the airways or in the blood.

Eosinophilic adult-onset asthma

This phenotype, which Haldar et al. [4] called *eosinophilic adult-onset asthma*, is predominantly non-allergic and corresponds clinically to Intrinsic

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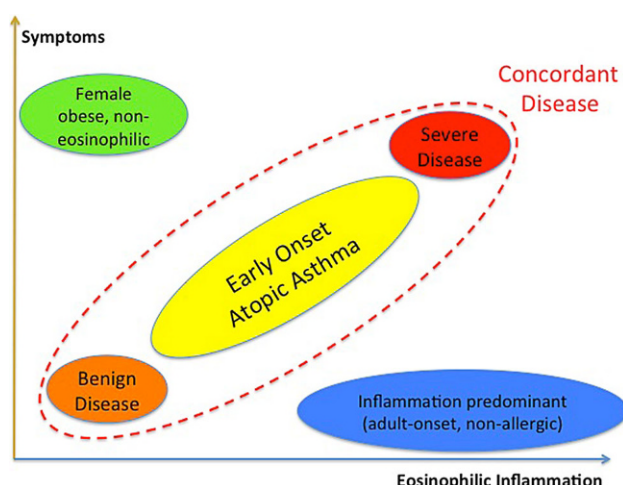


Fig. 1 Asthma phenotypes. (Adapted from [4])

Asthma and the Drifter Type of asthma. Acute bronchospasm plays only a marginal role here. Instead, the swelling of the mucosa in the upper and lower respiratory tract may increase spontaneously, without exogenous trigger factors. This results in exertional dyspnoea, which improves when standing still again. It therefore differs from exercise-induced asthma with acute bronchospasm caused by intense physical activity that persists after the end of the physical effort.

Inflammatory swelling of the upper respiratory tract frequently occurs, partly due to the formation of eosinophilic nasal polyps. As the thickness of the mucous membrane increases, the sense of smelling decreases. With a systemic steroid burst, the bronchial obstruction disappears, the sense of smelling improves again and the nasal polyps shrink. Due to the intrinsically present eosinophilic inflammation, exacerbations are not triggered by allergen contact and only partly by viral infections. In perennial eosinophilic adult-onset asthma, the reduction of therapeutic corticosteroids below an individual threshold may already trigger a spontaneous exacerbation. However, this can be confused with a viral infection, as an increase in eosinophilic inflammation in the upper and lower respiratory tracts leads to rhinorrhoea and productive cough, similar to a virus.

In eosinophilic adult-onset asthma an intolerance reaction to acetylsalicylic acid (ASA) and non steroidal anti-inflammatory drugs (NSAIDs) (Samter Triad = Aspirin Exacerbated Respiratory Disease) is much more likely than in allergic asthma [5].

In recent years, the pathophysiology of this asthma phenotype has been studied more intensely. Fig. 2, adapted from the paper of Brusselle et al. [6], shows the current state of knowledge regarding the immune reaction in eosinophilic asthma. At the beginning of the inflammatory cascade leading to non-allergic eosinophilic adult-onset asthma, a cigarette is drawn. It seems plausible that one of the factors leading to the manifestation of asthma in the second half of life

is smoking or intensive exposure to air pollution, as is true for COPD and lung cancer. It has clearly been shown that smoking significantly increases the likelihood of asthma in adolescence and adulthood [7, 8]. The higher the exposure with fine particles in the air, the more severe this type of asthma becomes [9].

Asthma–COPD overlap

Patients can meet the criteria of both asthma and COPD. GINA [10] and the GOLD [11] guidelines of COPD therefore defined the *asthma–COPD overlap syndrome* (ACOS) a few years ago. However, this is not a syndrome, since the overlap can occur in different ways.

On the one hand, there are patients who suffered from asthma in childhood, which they often “grew out” of in puberty and then started smoking later on. Especially in these cases, the risk of COPD manifestation is significantly higher than in smokers without pre-existing asthma [12]. Bronchial hyperresponsiveness with partial reversibility of the obstruction may persist even when COPD dominates the clinical picture [13].

Conversely, patients without the history of early childhood asthma, with COPD objectified, e.g. by a relevant portion of fixed airway obstruction or the detection of pulmonary emphysema in a high-resolution CT scan of the lung, may develop the onset of eosinophilic airway inflammation in the course of their disease. Frequent exacerbations may occur. If blood eosinophilia of >2% is found, this is referred to *eosinophilic COPD* and in exacerbation, an oral steroid burst is very effective [14, 15]. These patients benefit from treatment with inhaled steroids, in some cases even with daily oral corticosteroids or treatment with mepolizumab [16], analogous to asthma. Presumably, eosinophilic adult-onset asthma has manifested here on top of pre-existing COPD. Why should an existing COPD provide protection against the manifestation of eosinophilic adult-onset asthma?

Allergic asthma

There is still no uniform definition of allergic asthma today. In studies, asthma is often classified as allergic when sensitisation to at least one of the most important local aeroallergens is present. This definition is inadequate for clinical practice [17], since anti-allergic treatment strategies such as allergen avoidance measures, allergen immunotherapy (AIT) and the use of omalizumab are only justified if the eosinophilic inflammation is predominantly maintained by an IgE-mediated allergic reaction.

More than 20 years ago, a good empirical overview [18] defined 3 subtypes of early onset allergic asthma that is still useful in everyday clinical practice:

Fig. 2 Pathophysiology of eosinophilic “type 2” asthma. (Adapted from [6])

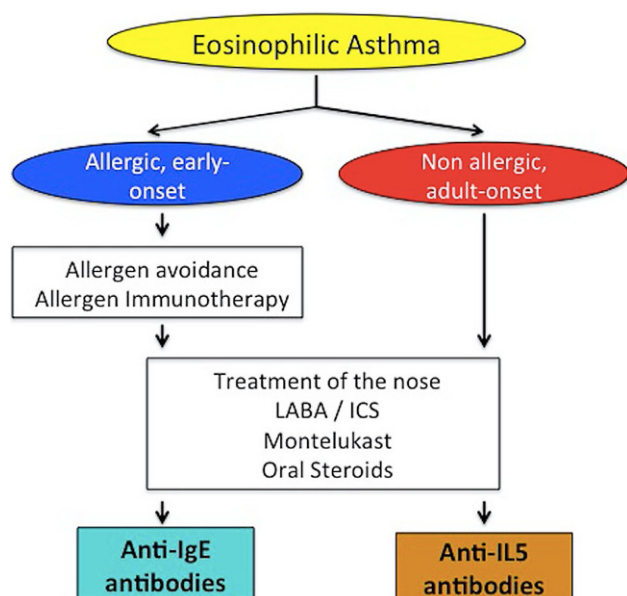
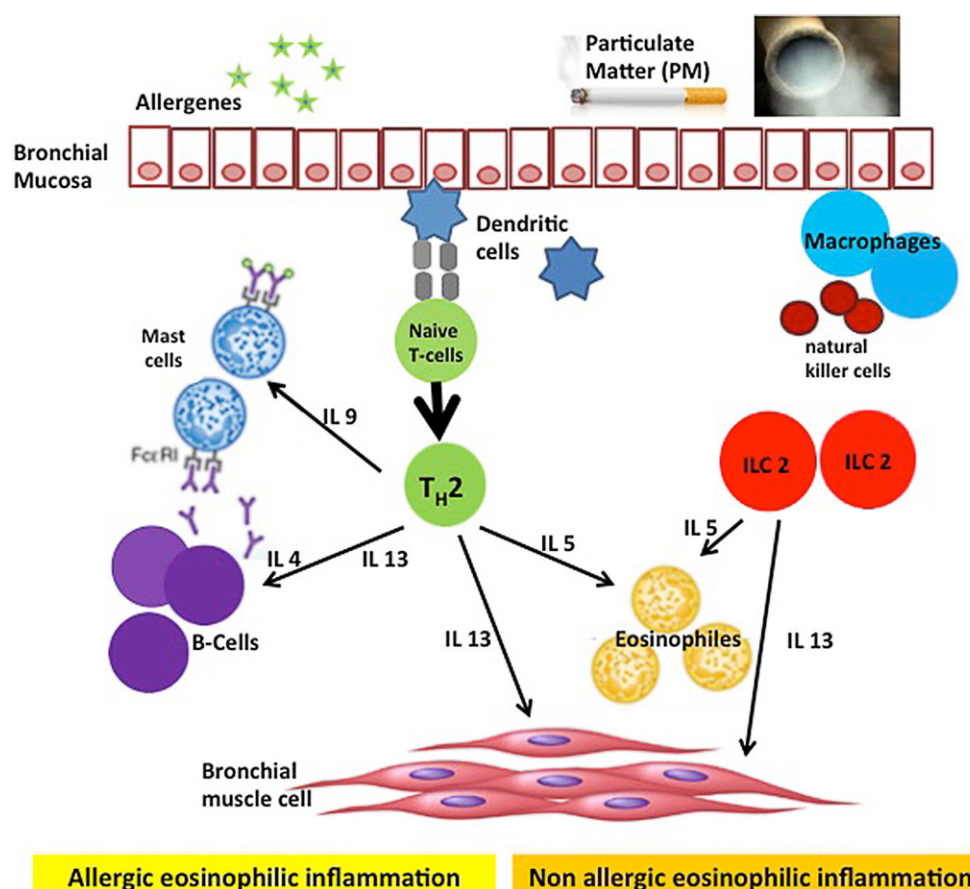


Fig. 3 Treatment of eosinophilic asthma

- Seasonal asthma associated with mono-sensitisation to pollen, lack of bronchial hyperresponsiveness in winter and only marginally elevated total IgE. Here the prognosis is relatively good, spontaneously, or even to a higher extent with the help of AIT.

- If polyvalent sensitisations against perennial allergens are present with a significantly increased total IgE, the chance of out-growing the disease decreases.
- Early onset asthma persists into adulthood. Over the years, the risk of decoupling of allergy and asthma increases. Patients may show symptoms despite absence of allergen exposure. In the long term, the sensitisations may even lose clinical relevance.

Diagnosis and therapy of asthma

At the time of the initial manifestation of eosinophilic adult-onset asthma, there is often a risk that the diagnosis of COPD is mistakenly made. Patients are usually already in the second half of their life, have often smoked prior to the asthma onset, or still smoke, and they show bronchial obstruction not reversing when salbutamol (albuterol) is given. Consecutively, exertional dyspnoea is a major symptom and typical asthma symptoms may be absent. Then, the eosinophilic nature of the bronchial inflammation can only be detected if blood eosinophilia is actively searched for and an oral *steroid trial* of about 40 mg prednisolone equivalent is performed over a period of 7–10 days. Spirometry must be performed prior to

and right after the steroid burst. A relevant or even complete reversibility of the bronchial obstruction due to the steroid burst allows COPD to be ruled out and eosinophilic adult-onset asthma to be diagnosed.

Eosinophils in the differential blood cell count are a good surrogate marker of sputum eosinophilia, but are much easier to access in daily practice [19]. Parallel to blood eosinophilia, often an elevated value of nitric oxide in fractional exhaled air (FeNO) can be detected.

Since eosinophilic adult-onset asthma and allergic asthma share the eosinophilic nature of inflammation, allergy testing must be part of every asthma assessment. However, the proof of sensitisation does not necessarily prove that the asthma is IgE driven. The SAPALDIA I study carried out in Switzerland in 1991 showed that about 30% of all Swiss citizens are sensitised to at least one of the local major aeroallergens [20]. Interestingly, only half of the sensitised subjects showed typical allergic symptoms when being exposed naturally to the allergen, i.e. in 50% of the cases the sensitisations were clinically *latent*.

If, for example, an adult person is diagnosed with a new manifestation of perennial eosinophilic asthma and extensive allergy testing is only positive for pollen antigens, the disease should not be identified as *pollen asthma* when a seasonal symptom peak is clearly lacking. The sensitisation may be an expression of allergic seasonal rhinoconjunctivitis, which may be totally independent of the asthma, or it is latent. In the case the proven sensitisation is not to pollen but to a perennial allergen it may be more difficult to judge its clinical relevance. Here, *diagnostic allergen avoidance* may help as a diagnostic tool [21].

Overlapping of both eosinophilic phenotypes may sometimes occur in one patient, i.e. contact with a specific allergen leads to increased asthma symptoms, but even in the total absence of allergen exposure there is on-going eosinophilic inflammation and presence of clinical symptoms, which can only be suppressed by intense medication with corticosteroids or mepolizumab [22].

Fig. 3 shows the treatment options for eosinophilic asthma depending on phenotype and severity of symptoms. In severe asthma [23], where GINA level 4 and 5 treatment is required to achieve symptom control, antibody therapies exist as an alternative to oral steroids. In allergic asthma, this has been omalizumab (Xolair®) for over 10 years. The anti-IL 5 antibodies mepolizumab (Nucala®) and reslizumab ([24]; Cinquero®) have been on the market for eosinophilic adult-onset asthma for 2 and 1 year, respectively. An anti-IL-5 receptor antibody (benralizumab [25]) will be approved in 2018. Mepolizumab also has proven to be effective in the treatment of nasal polyposis in chronic hyperplastic eosinophilic sinusitis [26].

This implies that in many patients with asthma being highly dependent on systemic corticosteroids and suffering from associated steroid side effects, a mas-

sive reduction in symptoms and a large potential to reduce systemic corticosteroids is achievable.

However, these treatment options are very expensive, so that the reimbursement of costs by the health insurance is linked to a strict limitation. In addition to other criteria, the medication can only be prescribed by a pneumologist or allergist and only after written request to the health insurance company.

Conclusion

The different asthma phenotypes can overlap in rare cases. A patient with early onset asthma may also manifest in the second half of life a non-allergic, highly eosinophilic adult-onset asthma. Allergic and non-allergic asthma can also overlap with COPD.

At the stage of the first work-up of newly diagnosed asthma or when re-evaluating an uncontrolled asthma, precise phenotyping is required in addition to the control of inhalation technique and therapeutic adherence. This includes a detailed patient history, allergy testing, lung function tests, differential blood count (eosinophilia?), possibly also a methacholine challenge and the measurement of fractional exhaled nitric oxide (FeNO). Only in this way is it possible to proceed to a phenotype-specific treatment. In allergic asthma, this may consist of allergen avoidance measures, AIT and treatment with omalizumab. In eosinophilic adult-onset asthma, at least if severe, there is the option to reduce or even stop oral corticosteroids by new anti-IL-5 antibodies in order to protect the patients from severe side effects of a systemic steroid therapy.

In the case of an exacerbation in a patient with an obstructive pattern in spirometry, a differential blood cell count should be performed. If an eosinophilia of >2% is evident, a steroid burst is indicated. Subsequently, spirometry must be repeated in order to detect a possible improvement of FEV₁ to diagnose asthma or asthma-COPD overlap, and rule out pure COPD.

Less common asthma phenotypes, such as non-eosinophilic female obese asthma, asthma in athletes, and neutrophilic asthma are deliberately not discussed in this article. The proof of neutrophilic inflammation in asthma is often not consistent over time [27].

Conflict of interest T. Rothe gave advice and has given lectures for: AstraZeneca, GSK, TEVA, and Novartis Pharma Schweiz.

References

1. Rackemann FM. A clinical study of one hundred and fifty cases of bronchial asthma. *Arch Intern Med*. 2018;2:517–22.
2. Virchow C. Intrinsic Asthma: Symptome, Gesamt-IgE Spiegel, Pathophysiologie. *Prax Pneumol*. 1973;10:578–572.

3. Turner-Warwick M. On observing patterns of airway obstruction in chronic asthma. *Br J Dis Chest*. 1977;71:73–86.
4. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med*. 2008;178:218–24.
5. Amelink M, de Groot JC, de Nijs SB, Lutter R, Zwinderman AH, Sterk PJ, et al. Severe adult-onset asthma: a distinct phenotype. *J Allergy Clin Immunol*. 2013;132:336–41.
6. Brusselle G, Maes T, Bracke K. Eosinophils in the spotlight: eosinophilic airway inflammation in nonallergic asthma. *Nat Med*. 2013;19(8):977. <https://doi.org/10.1038/nm.3300>. <http://www.nature.com/nm/journal/v19/n8/full/nm.3300.html>.
7. Künzli N, Bridevaux PO, Liu LJ, Garcia-Esteban R, Schindler C, Gerbase MW et al. Traffic-related air pollution correlates with adult-onset asthma among never-smokers. *Thorax*. 2009;64:664–70.
8. Coogan PE, Castro-Webb N, Yu J, O'Connor GT, Palmer JR, Rosenberg L. Active and passive smoking and the incidence of asthma in the black women's health study. *Am J Respir Crit Care Med*. 2015;191:168–76.
9. Westerhof GA, Vollema EM, Weersink EJ, Reinartz SM, de Nijs SB, Bel EH. Predictors for the development of progressive severity in new-onset adult asthma. *J Allergy Clin Immunol*. 2014;134:1051–6.
10. www.ginasthma.org. Accessed January 15, 2018
11. www.goldcopd.org. Accessed January 15, 2018
12. Brutsche MH, Downs SH, Schindler C, Gerbase MW, Schwartz J, Frey M, et al. Bronchial hyperresponsiveness and the development of asthma and COPD in asymptomatic individuals: SAPALDIA cohort study. *Thorax*. 2006;61:671–7.
13. Sin DD, Miravittles M, Mannino DM, Soriano JB, Price D, Celli BR, et al. What is asthma—COPD overlap syndrome? Towards a consensus definition from a round table discussion. *Eur Respir J*. 2016;48:664–73.
14. Bafadhel M, Greening NJ, Harvey-Dunstan TC, Williams JE, Morgan MD, Brightling CE, et al. Blood eosinophils and outcomes in severe hospitalized exacerbations of COPD. *Chest*. 2016;150:320–8.
15. Watz H, Tetzlaff K, Wouters EF, Kirsten A, Magnussen H, Rodriguez-Roisin R, et al. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. *Lancet Respir Med*. 2016;4:390–8.
16. Pavord ID, Chanez P, Criner GJ, Kerstjens HAM, Korn S, Lugogo N, et al. Mepolizumab for eosinophilic chronic obstructive pulmonary disease. *N Engl J Med*. 2017;377:1613–29.
17. Wenzel S. Defining of the persistent adult phenotypes. *Lancet*. 2006;368:804–13.
18. Ruffilli A, Bonini S. Susceptibility genes for allergy and asthma. *Allergy*. 1997;52:256–73.
19. Wagener AH, Nijs SB, Lutter R, Sousa AR, Weersink EJ, Bel EH, et al. External validation of blood eosinophils, FeNO and serum periostin as surrogates for sputum eosinophils in asthma. *Thorax*. 2015;70:115–20.
20. Wüthrich B, Schindler C, Leuenberger P, Ackermann-Lieblich U. Prevalence of atopy and pollinosis in the adult population of Switzerland (SAPALDIA study). *Int Arch Allergy Immunol*. 1995;106:149–56.
21. Rothe T. High-altitude sojourn: a treatment option in allergic asthma. *Swiss Med Wkly*. 2013;143:w13833.
22. Bel EH, Wenzel SE, Thompson PE, et al. Oral glucocorticoid sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371:1189–97.
23. Chung KF, Wenzel SE, Brozek L, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43:343–73.
24. Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germano M. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study. *Chest*. 2016;150:789–98.
25. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al. Oral glucocorticoid-sparing effect of Benralizumab in severe asthma. *N Engl J Med*. 2017;376:2448–58.
26. Bachert C, Sousa AR, Lund VJ, Scadding GK, Gevaert P, Nasser S, et al. Reduced need for surgery in severe nasal polyposis with mepolizumab: randomized trial. *J Allergy Clin Immunol*. 2017;140:1024–31.
27. Al Samri MR, Benedetti A, Préfontaine D, Olivenstein R, Lemière C, Nair P, et al. Variability of sputum inflammatory cells in asthmatic patients receiving corticosteroid therapy: a prospective study using multiple samples. *J Allergy Clin Immunol*. 2010;125:1161–3.