


Asthma management: A new phenotype-based approach using presence of eosinophilia and allergy

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Abstract

Asthma is a heterogeneous disease. The Czech Pneumology and Allergology Societies commissioned 10 experts to review the literature and create joint national guidelines for managing asthma, reflecting this heterogeneity. The aim was to develop an easy-to-use diagnostic strategy as a rational approach to the widening opportunities for the use of phenotype-targeted therapy. The guidelines were presented on websites for public comments by members of both the societies. The reviewers' comments contributed to creating the final version of the guidelines. The key hallmark of the diagnostic approach is the pragmatic concept, which assesses the presence of allergy and eosinophilia in each asthmatic patient. The guidelines define three clinically relevant asthma phenotypes: eosinophilic allergic asthma, eosinophilic nonallergic asthma and noneosinophilic nonallergic asthma. The resulting multifunctional classification describing the severity, level of control and phenotype is the starting point for a comprehensive treatment strategy. The level of control is constantly confronted with the intensity of the common stepwise pharmacotherapy, and the concurrently included phenotyping is essential for phenotype-specific therapy. The concept of the asthma approach with assessing the presence of eosinophilia and allergy provides a way for more precise diagnosis, which is a prerequisite for using widening options of personalized therapy.

KEYWORDS

allergy, asthma heterogeneity, eosinophilia, phenotype-specific therapy

1 | INTRODUCTION

With the increasing level of knowledge, asthma is now being considered as a markedly heterogeneous disease.¹⁻³ Besides the general preventive approaches and the “blanket” stepwise pharmacologic treatment strategy described in the Global Initiative for Asthma (GINA) guidelines, a number of new specific therapeutic options have emerged in recent years, although these options may not be applicable to all patients.²⁻¹¹ Therefore, two decisive medical societies, the Czech Pneumology and Phthisiology Society (CPFS) and the Czech Society of Allergology and Clinical Immunology (CSAKI), whose members care for most patients with asthma in the Czech

Republic, collaborated to review recent developments and create an easy-to-use diagnostic strategy as a basis for national guidelines, thus offering a rational approach to both blanket and personalized phenotypically targeted therapies in routine clinical practice.

These guidelines are focussed on the management of new asthma cases in adults and children aged 12 years. They do not include management of asthma exacerbations, detailed management of difficult-to-treat asthma or patients re-evaluated because of poor control of the disease; for these situations, other national guidelines are in place.¹²

The main highlight of the aforementioned guidelines is a pragmatic concept, which takes into account the presence of eosinophilia

and allergies in each asthmatic patient considering that “the path to correct diagnosis is also the path to choosing the best treatment options” (Figure 1). The recommendations are related to the actual healthcare system and clinical practice in the Czech Republic, where (i) the majority of asthma patients are under the care of pulmonologists and allergologists with unlimited access to lung function testing, tests for fractional exhaled nitric oxide (FeNO) measurement and allergology investigations, (ii) all treatment options are available and (iii) the patient’s health insurance covers most of the treatment costs.

The aim of this article is to primarily update the recent developments and concurrently present the distinctive, specific points of the asthma management strategy included in the Czech national guidelines.

2 | DEFINITION

Bronchial asthma is a heterogeneous disease characterized by chronic bronchial inflammation and remodelling, associated with hyperresponsiveness and variable, often reversible, obstruction. It is manifested with recurrent episodes of wheezing, cough, shortness of breath and chest tightness.

3 | EPIDEMIOLOGY

Worldwide, the prevalence of asthma varies between regions and countries, ranging from 1% to 16% globally, and from 5% to 16% in the European Union (EU). The global burden of asthma is gradually increasing, while the differences between regions and countries are shrinking.² The exact prevalence in the Czech Republic, with a population of 10 million, remains unknown, and qualified estimates suggest a prevalence of 7%-8% (ie 700 000-800 000 people). In 2014, approximately 360 000 people, half of the patient population, were managed by allergy and respiratory specialists.¹³

4 | DIAGNOSIS

Efforts to reflect the basic characteristics of asthma—bronchial inflammation, bronchial hyperresponsiveness (BHR) and remodelling—are essential for both diagnosis and treatment.¹⁴⁻¹⁹ Many of the investigative methods used to diagnose and monitor asthma in routine clinical practice do not evaluate these attributes directly but use more easily detectable clinical outcomes such as dyspnoea, presence of wheezing and variability and reversibility of the bronchial obstruction.^{2,20} Therefore, it is important to be aware of the limits of most diagnostic and therapeutic processes, and in case of doubt, use more exact methods (direct investigation of bronchial inflammation and BHR).^{14,21-25}

The use and interpretation of several diagnostic methods differs when used in new (recent) patients without established, preventive anti-inflammatory treatment or in newly diagnosed patients for whom anti-inflammatory treatment (usually in a different health facility) has been already started.

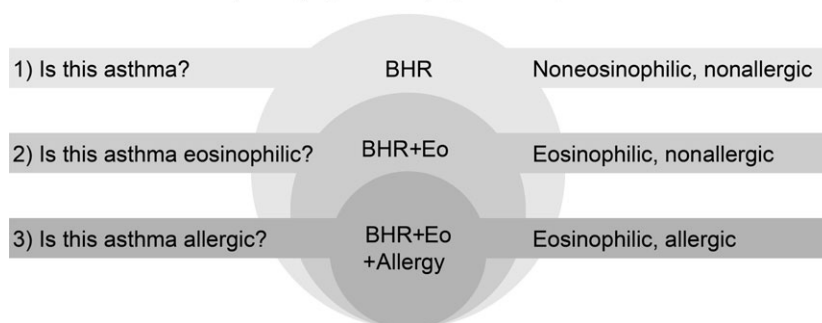
Following initiation of an effective anti-inflammatory treatment in eosinophilic asthma, FeNO and sputum eosinophilia recede most rapidly (within days to 2 weeks), followed by improvements in the main symptoms and normalization of lung function within weeks or months. The residual signs of inflammation recede significantly later (within months), with BHR subsiding after even longer.²⁶ Evidence on the effects of inhaled corticosteroids (ICS) on eosinophils and eosinophil cationic protein (ECP) in blood is limited; such effects, if any, can be expected after 2 weeks of treatment.

The aims of the diagnostic processes are as follows:

- *Basic evidence of the disease* by confirming variable bronchial obstruction and/or bronchial hyperreactivity. The presence of eosinophilic inflammation of the bronchial wall may contribute to the diagnosis, even though cases of noneosinophilic asthma exist.^{3,10,24,27,28}
- *Closer determination of other characteristics of the disease* (classification) such as severity, level of control, phenotyping (or rather endotyping) and presence of comorbidities that may complicate

Simplified three-step diagnostic approach

Patient with (recent) signs and symptoms suspected for asthma



In all new asthma patients, an effort to answer all three questions should be made. The proof of (bronchial) eosinophilia increases the probability of asthma diagnosis. The proof of clinically significant respiratory allergy is an indirect marker of bronchial eosinophilia presence. See text and tables for further details.

FIGURE 1 Schema for a simplified three-step diagnostic approach

the treatment and course of the disease.^{2,24,29-32} For asthma phenotyping, along with evaluation of eosinophilia, allerge-immunology examination is also necessary.

4.1 | Evidence of asthma

Bronchial obstruction has three components: a constrictive component that responds to bronchodilators; an inflammatory component, responsive to anti-inflammatory treatment; and a remodelling component that persists even after the bronchodilator and anti-inflammatory treatment. As the severity of the asthma increases, the proportion and significance of the latter two components mostly increases.^{1,17,18,24} The fundamental for diagnosing asthma is to equate the obstructive ventilatory disorder, its severity, reversibility and variability (ie the proof of BHR). These findings should be properly documented for each patient. An increase in forced expiratory volume in 1 second (FEV₁) of $\geq 12\%$ and ≥ 200 mL compared to the prebronchodilator values is generally used to confirm the diagnosis of asthma. An FEV₁ increase of 400 mL or 15% is considered highly significant.^{33,34}

However, many asthmatic patients do not meet these criteria during a single examination. Multiple measurements on different days, usage of higher doses or other bronchodilators (eg standard 400 μg salbutamol by spacer) and evaluation of the shape of the flow/volume curve are recommended in these situations.^{19,33,35} If an obstructive ventilatory disorder cannot be proved, a bronchoconstriction test is recommended—ideally, the indirect test with mannitol or the direct test with methacholine, which is less specific.^{14,25} If the reversibility of the bronchial obstruction cannot be demonstrated, a corticosteroid hit is recommended.³⁴ The diagnosis of asthma is lifelong, and consistency in diagnosis is therefore necessary.

Proving eosinophilic airway inflammation significantly contributes to the diagnosis of asthma, especially when it is performed before starting preventive anti-inflammatory treatment. The presence of eosinophilia predicts Th-2-driven type of inflammation and a good response to corticosteroids.^{3,24,34,36-39} If the inflammation is noneosinophilic in nature (neutrophilic, paucigranular, etc.), the asthma diagnosis and response to corticosteroid treatment are less probable.^{3,6,24} The “basic” attempt to demonstrate the presence of airway eosinophilia should be made during the diagnostic process in every asthma patient (see Table 1). Wherever possible, we recommend using all three eosinophilia markers, or at least two of them listed in Table 1—preferably FeNO and one from blood.⁴⁰ In less severe forms of asthma, the systemic signs of eosinophilia may not be present (differential blood count and ECP). In clinical practice, we rely on FeNO testing or indirect signs of eosinophilic inflammation (Table 1).^{24,39,41-46}

Even if the relevance and interpretation of FeNO and bronchoconstriction tests cannot be considered equal, measuring FeNO may help in diagnosing asthma.^{47,48} In certain situations where the signs of asthma are typical and the steroid-naïve patient shows high values of FeNO (>80 ppb), the bronchoconstriction test can be left

TABLE 1 Basic options for proof of the presence of eosinophilic inflammation in asthma

Parameter	Positive values
FeNO ^a	≥ 50 ppb
Eosinophils in the blood differential count ^b	$\geq 4\%$ or $\geq 400/\text{mm}^3$
ECP in serum ^b	≥ 20 $\mu\text{g}/\text{L}$
Eosinophilia is indirectly supported by	

- Evidence of clinically relevant allergies (in milder forms of allergic asthma, eosinophilia, especially in the blood, may not be detectable)
- Evidence of significant bronchial hyperreactivity, that is reversibility of BO^c
- Good response to (I)CS
- Presence of nasal polyps and aspirin sensitivity (ASA)

ECP, eosinophilic cationic protein; FeNO, fractional exhaled nitric oxide; (I)CS, (inhaled) corticosteroid; BO, bronchial obstruction; ASA, aspirin-sensitive asthma.

^aFeNO: May be positive in allergic rhinitis without asthma. The close relationship of eosinophilia and asthma is not valid in smokers.

^bEosinophils, ECP: Limited significance, positive values may be caused by other diseases (atopic eczema, helminthiasis, etc.)

^cSignificant long-term eosinophilic inflammation may concurrently lead to irreversible remodelling.

out, even though the results of the lung function tests do not reach the arbitrary values for obstructive ventilatory disorder and its reversibility.^{34,49} FeNO is also significant because of its negative predictive value; a low FeNO value (<25 ppb) in an untreated patient with a negative bronchoconstriction test almost always excludes asthma.^{29,43}

In recent patients, who are already on anti-inflammatory treatment, efforts should be made to obtain FeNO and peripheral blood eosinophilia values before treatment initiation. If no results are available, it is recommended to rely on the indirect signs of eosinophilic inflammation: clinically relevant allergy presence, nasal polyposis, aspirin sensitivity etc. (see Table 1). If in addition to eosinophilia, the reversibility of bronchial obstruction/BHR cannot be proved, the diagnosis of asthma is questionable. In such patients, reduction or withdrawal of the anti-inflammatory treatment is desirable, with eosinophilia re-examinations (FeNO, blood) being repeated with a washout interval of at least 2-5 weeks.^{43,50}

Only in case of difficult-to-treat asthma or re-evaluation of asthma because of a poor control of the disease, we recommend using more airway-specific and direct tests: sputum eosinophils, bronchial biopsy and bronchoalveolar lavage.^{14,21,22,24,51,52} In the Czech healthcare system, these tests are mainly performed by specialized clinics of The National Centres for Severe Asthma (NCTA; www.tezke-astma.cz),¹² where phenotype therapy is also available.

4.2 | More detailed characteristics (classification) of asthma

A major part of the diagnostic process is the further classification of asthma, which is the basis of appropriate treatment to achieve complete control.^{2,24,29-31,34,47,53-56}

A specific feature of the Czech National guidelines is the multi-functional classification of asthma. The achieved level of control is constantly compared with the disease severity assessment and its phenotyping/endotyping, the core of which is a pragmatic view of asthma based on the assessment of the presence of eosinophilia and allergy (Tables 1 and 2; Figure 2).

This approach allows a comprehensive treatment strategy to be used, applying a general stepwise approach as well as widening options of individual phenotype-targeted therapy. If the asthma is under full control, it is appropriate to strive for pharmacotherapy reduction/step down.⁵⁷ Furthermore, there is no need to consider phenotype-specific treatment, except for allergen immunotherapy (AIT), mainly in milder forms of the disease.⁵⁸ Conversely, with increasing asthma severity and problems with achieving control, phenotypically oriented treatment options are of greater importance (Figure 2).

Asthma control must be causal, targeted at the root of the disease and aimed at bronchial inflammation, remodelling and hyperresponsiveness versus merely a perceived control of the current symptoms.^{2,6,29,30,55,56} The primary expectation of the patients is symptom control. It is the responsibility of the physicians to prevent unfavourable asthma outcomes associated with residual disease activity. In clinical practice, well-controlled asthma is characterized by the following: no symptoms or only minimal daytime symptoms and need for relief medication (both maximally 2 times a week), unlimited physical activity and permanent absence of nocturnal problems in the last month, and in the long term, lasting normal lung function and absence of exacerbations and adverse effects due to the treatment.²

The designations “well-controlled asthma,” “partly controlled asthma” or “uncontrolled asthma” provide very little understanding regarding the severity of the disease. Well-controlled asthma may be a mild form of asthma where only low doses of ICS are needed, or a severe form of asthma requiring a combination therapy of long-acting β_2 -agonist (LABA)/high doses of ICS+leukotriene receptor

TABLE 2 Asthma phenotyping based on the presence of eosinophilia and allergy

Phenotype ^a	Feature ^b
I. Eosinophilic, allergic	The dominant feature is the presence of a clinically significant allergy
II. Eosinophilic, nonallergic	The dominant feature is the presence of a marked eosinophilia (see Table 1)
III. Noneosinophilic, nonallergic	Absence of eosinophilia and clinically significant allergies

^aAnalogies of the suggested types of asthma are reported in the works of Wenzel, Bousquet, Hashimoto, Custovic and Chung.^{1,3,5,6,10,11,24,74} The first type is called “early onset atopic asthma, atopic form”; the second (“severe), less atopic group or later onset inflammation predominant asthma or (severe) ‘intrinsic’ asthma”; the third “the more severe, late onset obese group or obese noneosinophilic asthma, or (severe) asthma with obesity.” Both eosinophilic types of asthma (allergic and nonallergic) are characterized by the Th2 type of inflammatory process; noneosinophilic asthma is conversely characterized by the non-Th2 type of inflammation.^{3,75}

^bDeeper/closer characterization; see text section 4.2 More detailed characteristics (classification) of asthma

antagonist (LTRA), etc. Therefore, we recommend maintaining assessment of asthma severity, which can be inferred from the minimal level of pharmacotherapy needed to obtain full control of the asthma. In accordance with the five steps of asthma pharmacotherapy, we recommend retaining five degrees of asthma severity: (i) intermittent asthma, (ii) mild asthma, (iii) moderate asthma, (iv) severe asthma and (v) severe refractory asthma.

Even though the above-mentioned asthma severity assessment in clinical practice is not exact—reality is often encumbered by overtreatment and undertreatment—maintaining the asthma severity classification can be considered rational (epidemiological data used for regulatory authorities etc.).

Given the increased possibilities of specific uncommon treatment options, we recommend an easy phenotypic classification, reflecting the presence of clinically significant eosinophilia and allergy (which seems to be in close relationship to endotypes)¹⁰ (Table 2).

An allerge-immunology examination is recommended for every patient with asthma in two basic situations: (i) always when first determining the diagnosis and (ii) when control is lost for unknown reasons. The starting point for allergy diagnosis is the medical history comprising both current potential allergy signs and causes and also past medical history focused on extrapulmonary signs of allergy (respectively, the existence of atopic march: food allergy, atopic eczema, hay fever, extrapulmonary symptoms of pet allergy etc.). The total immunoglobulin E (IgE) level test has limited information value as well as the sensitization proof (positive prick tests, specific IgE) that does not necessarily confirm the clinically important allergy. In severe asthma cases, mould allergy testing (especially for *Alternaria* and *Aspergillus*) should be performed as part of the allergy examination.

The principle of assessing the presence of eosinophilia and allergy and related clinical indicators is also included in the Czech National guidelines for chronic obstructive pulmonary disease (COPD), as part of the major and minor criteria used to diagnose COPD/asthma overlap syndrome (ACOS).^{59,60} The presence of ACOS is probable in asthma patients with dominant exertional dyspnoea, chronic expectoration, a history of smoking, persistent obstruction after steroid tests and a reduced carbon monoxide transfer factor (TLCO).^{59,61} For patients with ACOS, it is convenient to include lung high-resolution computed tomography (HRCT) examination.^{59,61,62}

4.2.1 | Eosinophilic allergic asthma

The dominant feature of eosinophilic allergic asthma is the presence of a clinically significant allergy/atopy. The onset is usually in childhood; atopic eczema and other allergic/atopic diseases are frequently present and often precede the asthma (atopic march). Eosinophilia in the bronchial wall is generally difficult to detect, especially after commencing ICS preventive treatment. In case of a clear diagnosis of asthma together with a clinically significant allergy, there is no strict need to prove bronchial eosinophilia; however, such efforts are still desirable (FeNO). Eosinophilic allergic asthma is the most common, most classic and usually the best treatable type of

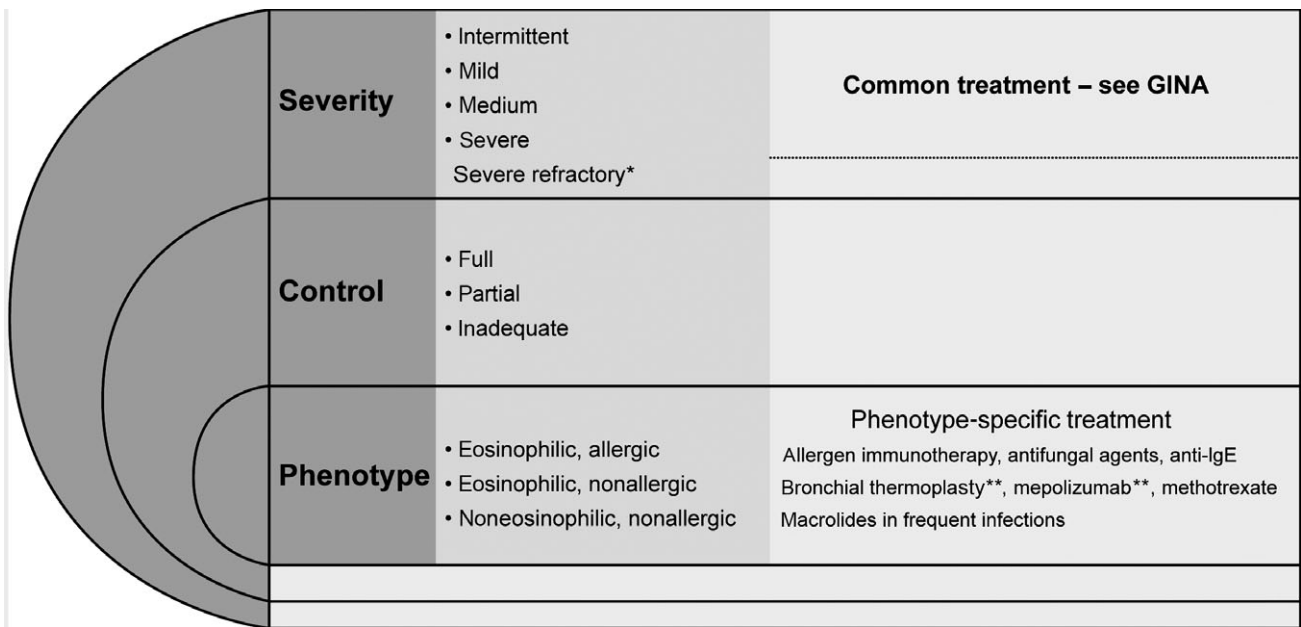


FIGURE 2 Multifunctional classification of asthma with phenotype-specific treatment. There is no clear connection between the asthma control, asthma severity and phenotypes in a particular patient. *Severe asthma with fungal sensitization/allergic bronchopulmonary aspergillosis (SAFS/ABPA), asthma as part of Samter's-triad, asthma as part of Churg-Strauss syndrome, asthma with dominant small airways disease (SAD), asthma as part of asthma/COPD overlap syndrome (ACOS), asthma with rapid decline in lung functions etc. **Can also be used in eosinophilic, allergic phenotype

asthma. The most serious cases are those with mould sensitization (ie severe asthma with fungal sensitization [SAFS] or allergic bronchopulmonary aspergillosis [ABPA]).^{8,9,63,64}

4.2.2 | Eosinophilic nonallergic asthma

The dominant feature of eosinophilic nonallergic asthma is the presence of a marked eosinophilia (Table 1). The onset is usually in middle age, and allergy testing is usually negative (if positive, it does not have a substantial clinical significance).^{1,6,24,31,32} Eosinophilia of the bronchial wall is accompanied by considerable BHR, along with a risk of irreversible remodelling.^{6,24} The most severe forms of eosinophilic nonallergic asthma are frequently associated with nasal polyps and nonsteroidal anti-inflammatory drug (NSAID) intolerance or autoimmune eosinophilic vasculitis (Samter's triad and Churg-Strauss syndrome).^{5,24,65}

4.2.3 | Noneosinophilic nonallergic asthma

In noneosinophilic nonallergic asthma, eosinophilia and a clinically relevant allergy are absent, but BHR, variable bronchial obstruction and the typical symptoms of asthma are present. The onset is usually in adulthood, and the severity tends to correspond to obesity, other comorbidities and female gender.^{5,24,31,32,66}

5 | THERAPY

The aim of asthma therapy is not only to eliminate the current symptoms but also to minimize inflammation, bronchial

hyperreactivity and prevent exacerbations and irreversible remodelling. At the same time, it is desirable to continuously strive to minimize the necessary pharmacotherapy, considering that long-term high-dose medications, especially corticosteroids, are associated with a significant risk of systemic adverse effects.^{2,5,6,67} A comprehensive treatment strategy, taking into account both these factors, in some views contradictory, is based on the proposed multifunctional classification, wherein the level of achieved control is constantly compared with the determination of asthma severity and phenotyping.

5.1 | Common stepwise asthma treatment

The common stepwise treatment strategy is analogous to the worldwide accepted guidelines and includes five levels based on the GINA guidelines, corresponding to the recommended five degrees of asthma severity in our guidelines. The dominant clue is achieving full asthma control. If achieving asthma control with low and medium doses of ICS is difficult, it is recommended that a combination of other controlling anti-asthma medication is used instead of increasing the ICS dose (because of the low benefit and higher risk of adverse effects).^{5,67} Step 4 of the treatment already includes the option of tiotropium administered using a soft mist inhaler.^{1,4,68} According to step 3, a fixed combination of low doses of ICS with formoterol (rapid onset LABA) can be used as relief medication instead of short-acting β_2 -agonist/rapid-acting β_2 -agonist (SABA/RABA) or short-acting muscarinic antagonist (SAMA) or a combination of both as a new modification of the SMART system.²

The intensity of the minimum treatment needed to gain full control determines the current severity of the disease. Usually, low doses of ICS are needed to commence the treatment for patients

who have not yet received controller medication; in practice, starting therapy with moderate to high doses or a combination therapy, including fixed combinations of ICS+LABA, may be acceptable, especially in patients with worse symptoms.⁵³ If full control is achieved and maintained for at least 3 months, an effort should be made to gradually reduce the number and doses of medications. After this reduction, careful monitoring, including residual activity of the disease, is recommended.⁵⁷ For seasonal allergic asthma, only seasonal preventive treatment may be acceptable.² If control cannot be achieved, the following steps are recommended before stepping-up the therapy^{2,35,56,57}:

- Check the adherence and inhalation technique
- Check the living and working environment and precautionary regime measures (especially professional exposure to allergens and noxious substances)
- Manage other comorbidities (rhinosinusitis, gastroesophageal reflux disease, vocal cord dysfunction and obstructive sleep apnoea)

The last two measures coincide closely with the approach to asthma management using eosinophilia and allergy evaluation and phenotype-oriented treatment. If full control cannot be achieved with step 4 treatment, it is recommended that the patient is referred to one of the specialized sites of the NCTA to review the diagnosis, especially when long-term systemic corticosteroid therapy is being considered.¹²

5.2 | Phenotype-specific therapy

Demonstrating eosinophilic allergic asthma offers the greatest options for phenotypic treatment. AIT should be considered in every asthmatic patient with verified and clinically significant allergies (pollen, dust mites, cat and dog allergens, certain moulds and rarely other allergens), preferably in milder forms of asthma. AIT is not an alternative or competitor for asthma pharmacotherapy; it is a treatment for allergic hypersensitivity. It is associated with specific risks; the asthma must be fully controlled and AIT must be administered by an allergy specialist.^{35,58,69-71} Patients with eosinophilic asthma who cannot achieve full control even with step 4 treatment and with proof or suspicion of a significant perennial allergy (ie severe refractory, eosinophilic allergic asthma) should be referred to one of the specialized sites of the NCTA.¹² These sites indicate and administer biological treatment using anti-IgE antibody (omalizumab) and possibly antifungal therapy (for SAFS or especially ABPA).^{8,9,11,64,71,72}

NCTA workplaces in the Czech Republic also indicate treatment using bronchial thermoplasty (BT). The inclusion criteria for BT include inadequate control of asthma with step 4 treatment, along with proof of considerable bronchial hyperreactivity in the last 12 months (positive bronchodilator test of >15% and/or >400 mL or positive bronchial provocation test with methacholine on preventive treatment) as indirect signs of significant bronchial smooth muscle hypertrophy/hyperplasia. Previous experience with this treatment in the Czech Republic suggests that patients with eosinophilic

nonallergic asthma meet these criteria most frequently.⁴⁶ At NCTA sites, a decision is made for a patient who requires high doses of daily oral corticosteroids to use methotrexate, and innovative treatment products are tested in pharmacological studies, from which mepolizumab is currently approved for clinical use in the Czech Republic, from 1 April, 2016.^{1,4,6,32}

In noneosinophilic nonallergic asthma, thorough treatment of comorbidities is of great importance (obesity, sleep apnoea syndrome, gastroesophageal reflux disease, etc.)^{1,2,56}; in the case of infectious exacerbations, a therapeutic trial with long-term treatment using intermittently administered macrolides should be considered in specific cases.⁷³ For patients with ACOS, therapeutic modalities reserved for COPD can be offered.^{59,61,62}

6 | CONCLUSION

With the increasing level of knowledge, asthma is being considered as a disease of a widely heterogeneous nature. The Czech National guidelines, based on diagnosing the actual clinical significance of eosinophilia and allergy, are a rational way of using both the options of common pharmacotherapy and individualized phenotype-targeted therapy.

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CONFLICT OF INTEREST

M. Terl has board memberships with AstraZeneca, GSK, Novartis, TEVA; serves as a consultant for Boehringer Ingelheim, Stallergen; and has received meeting expenses from Boehringer Ingelheim, Berlin-Chemie, GSK and Novartis. V. Sedlák has board memberships and serves as a consultant for Boehringer Ingelheim, AstraZeneca, GSK and Novartis, and has received meeting expenses from Boehringer Ingelheim and AstraZeneca. P. Cap has no conflict of interests to declare. R. Dvořáková has received meeting expenses from Boehringer Ingelheim, Thorex Chiesi and Mundipharma. V. Kašák has board memberships with AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Teva and serves as a consultant for AstraZeneca, Boehringer Ingelheim and Novartis. T. Kočí has board membership with ALK, Allergy Therapeutics, AstraZeneca, MSD, Stallergenes and received travel support and meeting expenses from ALK, AstraZeneca, GSK, Menarini, MSD and Stallergenes. B. Novotna has received travel support and meeting expenses from Novartis, TEVA. E. Seberova has board membership with ALK, Stallergenes and has received

meeting expenses from Berlin-Chemie and GSK. P. Panzner has board membership with AstraZeneca, Novartis, GSK, ALK, Stallergenes and MSD. V. Zindr has board membership with, is a consultant for, and has received meeting expenses from Boehringer Ingelheim.

AUTHOR CONTRIBUTIONS

M. Terl, V. Sedlák and T. Kočí substantially contributed to the conception, design and planning of the study. M. Terl, V. Sedlák and P. Cap substantially contributed to data acquisition and analysis, interpretation of the results and drafting of the manuscript. R. Dvořáková, V. Kašák and T. Kočí substantially contributed to interpretation of the results. V. Kašák substantially contributed to data acquisition and analysis. B. Novotna substantially contributed to data acquisition and interpretation of results. E. Seberova substantially contributed to data acquisition and analysis and interpretation of the results. P. Panzner and V. Zindr substantially contributed to data analysis and interpretation of the results. All authors substantially contributed to critically revising the manuscript for important intellectual content. All the authors have reviewed the version of the manuscript to be submitted and are in agreement with its content and submission. All authors agree to be accountable for all aspects of the work and will ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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