Severe asthma
Diagnostic criteria and diagnostic problems

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Key words:
- refractory asthma,
- bronchial hyperresponsiveness,
- asthma phenotypes,
- asthma in the elderly,
- clusters,
- airway inflammation,
- COPD

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SUMMARY. **The correct diagnosis of asthma is usually made easily and most patients respond to treatment. Approximately 5 to 10% of patients, however, have severe refractory asthma that continues to be poorly controlled despite maximal inhaled therapy. Severe asthma is not a single disease, but a collection of different phenotypes, the identification of which is crucial since this can lead to better disease management and optimal response to appropriate treatment. Additionally, specific diagnostic problems characterize asthma in the elderly and obscure the differentiation of asthma from chronic obstructive pulmonary disease (COPD). In elderly patients with long-term asthma, reversibility of airway obstruction is diminished, and a disease pattern similar to that of COPD may develop. In addition, smoking and ageing both increase bronchial hyperresponsiveness (BHR) and neutrophil numbers, resulting in asthma with a COPD phenotype. On the other hand, a subgroup of patients with COPD shows reversibility of airway obstruction associated with increased exhaled nitric oxide (NO) and sputum eosinophilia. COPD is often accompanied by BHR, and both smoking and ageing appear to be risk factors for increasing BHR, while smoking cessation improves BHR, both in patients with asthma and those with COPD. Rigid diagnostic criteria, using a combination of tests of lung function, BHR and atopy status, high resolution computed tomography (HRCT) chest scan and the newly developed biological techniques for the assessment of biomarker profiles, can facilitate the correct diagnosis and the distinction between the severe asthma phenotypes.** ***Pneumon 2011, 24(4):453-459.***

INTRODUCTION

International guidelines recommend that asthma diagnosis be based on the presence of symptoms and objective measurements of variable airflow obstruction[1]. Reversible airflow obstruction on spirometry and/or bronchial hyperresponsiveness (BHR) in the bronchial challenge test, are highly valuable diagnostic tools for patients with a clinical history indica-

tive of asthma[1]. Most patients with asthma have mild to moderate disease that can be controlled by inhaled corticosteroids (ICS) combined with bronchodilators for relief of symptoms.

Unfortunately, a in a subset of patients with asthma adequate control of their symptoms cannot be achieved, despite appropriate treatment, including high-dose ICS[2,3]. The recently published international consensus statement of the Innovative Medicine Initiative of the European Union, recommends that the subgroup with true "severe refractory asthma" should be distinguished from patients with 'problematic' or 'difficult' asthma[2]. The term 'severe refractory asthma' should be used only for patients with asthma in whom alternative diagnoses have been excluded, comorbidities have been treated, trigger factors have been removed (if possible), and treatment compliance has been checked, but who still have poor asthma control or frequent (i.e., ≥2) severe exacerbations per year despite the prescription of high-intensity treatment, or who can only maintain adequate control by taking systemic corticosteroids, and are thereby at risk of serious adverse effects of treatment[2]. This heterogeneous group of patients presents a distinct challenge to clinicians to provide the best management of the disease, while limiting side effects. The mechanisms that make these patients so hard to manage are complex, multifactorial, and incompletely understood[4].

In addition, in daily practice, there are significant barriers to performing lung function tests, especially in the primary and secondary care settings[5,6]. Studies indicate that in many cases the diagnosis of asthma in primary care relies solely on clinical evaluation and/or response to treatment[5,6]. Recently, Aaron and colleagues[7] found that about one-third of individuals with physician-diagnosed asthma did not have asthma according to objective assessment. Conversely, in the elderly asthma is frequently underdiagnosed or misdiagnosed due to its atypical presentation, the age-related reduction of dyspnoea perception and associated comorbidities[8,9]. The coexistence of comorbidities such as chronic rhinitis, nasal polyposis and sinusitis, gastro-oesophageal reflux, obesity and sleep apnoea syndrome may, in turn, contribute to the severity of asthma. Obvious consequences of this confusion are inappropriate, and most probably unsuccessful, treatment, with increased costs and risk of adverse events.

THE DEFINITION OF SEVERE ASTHMA: DIAGNOSTIC CRITERIA

In 2000 an American Thoracic Society (ATS) Workshop[10] adopted the term 'refractory asthma' and developed a definition by consensus. The definition included one or two major diagnostic criteria, with two or more of 7 additional minor criteria. Figure 1 shows the major and minor criteria used for the diagnosis of severe refractory asthma.

The Global Initiative for Asthma (GINA) guidelines classified patients as having severe refractory asthma those who experience daily symptoms, frequent exacerbations, frequent nocturnal asthma symptoms, limitation of physical activities, forced expiratory volume in 1 second (FEV_1) or peak expiratory flow (PEF) ≤60% predicted and PEF or FEV_1 variability ≥30% before initiation of treatment[1,2].

According to the most recent definitions, "severe refractory asthma" or "severe asthma" is diagnosed in patients whose asthma remains difficult to control despite a thorough re-evaluation of the diagnosis and after 6 months of close follow-up by a physician specializing in asthma[1,2,11]. Poor asthma control is defined according to the Juniper Questionnaire as a score of ≥1.5 by the 7-item Asthma Control Questionnaire, or an equivalent

DIAGNOSTIC CRITERIA FOR SEVERE ASTHMA: ≥1 major & ≥2 minor.

MAJOR CRITERIA
- Use of oral CS ≥50% of the time
- Continuous use of high-dose Inhaled CS (≥1.200 g/day beclomethasone or equivalent)

MINOR CRITERIA
- Daily treatment with LABA, theophylline or leukotriene antagonists.
- Daily asthma symptoms requiring rescue medication.
- Irreversible airway obstruction (FEV1 <80% predicted); diurnal PEF variability 20%
- ≥1 urgent care visits for asthma in the last year
- ≥3 courses of oral steroid bursts in the last year
- Rapid deterioration with ≤25% reduction in oral or inhaled CS dose
- Near fatal asthma episode in the past

FIGURE 1. Major and Minor Diagnostic Criteria for Severe Asthma *(adapted from reference 10)*. CS=corticosteroids, LABA= long-acting β2 agonists, FEV_1= forced expiratory volume in 1 second.

score by any other standardized asthma control questionnaire. High-intensity treatment in adults is defined as >1000 mg/day fluticasone equivalent and/or daily oral corticosteroids combined with long-acting b2 agonists (LABAs) or any other controller medication[2].

The response to treatment is also important and this is measured by the level of control; thus, the diagnosis of "severe refractory asthma" is based on both the clinical features of the disease and the daily medication regime that the patient is receiving[1,2,10]. Specific features such as a lesser degree of atopy, lower performance on lung function testing, female sex and a history of pneumonia might be observed in severe asthma but not milder asthma. Many genetic and lung-specific biomarkers have also been proposed to distinguish mild asthma from severe asthma, but few have been proven diagnostic by multiple studies. A relatively long period of monitoring and treatment is necessary before labelling any patient as having severe/refractory asthma.

THE DIAGNOSIS OF SEVERE ASTHMA

For a correct diagnosis of severe refractory asthma, it is mandatory that patients who present severe asthma symptoms or recurrent exacerbations be evaluated in a stepwise manner[2]. Figure 2 illustrates an algorithm for the diagnosis of severe refractory asthma[2].

Diagnostic key features in the evaluation of patients with severe asthma are highlighted in Table 1. Factors that influence asthma control should be recognized and adequately addressed prior to confirming the diagnosis of severe asthma[11]. Spirometry, reversibility testing and airway challenge tests (unless contraindicated) are mandatory in the re-evaluation of the diagnosis of asthma[1,2]. Demonstration of reversible airways obstruction by short acting bronchodilators is valuable, but bronchial provocation testing is more sensitive and specific and should be performed when necessary to confirm the diagnosis of asthma. When airflow is very low, however, bronchial provocation may not be helpful and/or feasible from the safety and regulatory perspective[11]. In addition to basic spirometric measures, assessment of small airway function, including dynamic hyperinflation, and inflammation may be valuable[3,4,10,11]. Non-invasive measurements of airway inflammation include assessment of sputum cell counts, bronchoalveolar lavage (BAL) supernatants, exhaled nitric oxide (NO), and breathe condensates[11].

Environmental exposures (e.g., cigarette smoking, occupational exposures), co-morbid conditions, treatment adherence and, especially, inhalation technique, must be examined thoroughly[3,10,11]. Cigarette smoking in asthma is a risk factor for poor asthma control and reduced sensitivity to corticosteroids[12]. The frequency of exacerbations and healthcare system use (planned and emergency visits) should also be recorded[13]. The diagnosis and identification of additional factors influencing the severity of asthma should be approached systematically.

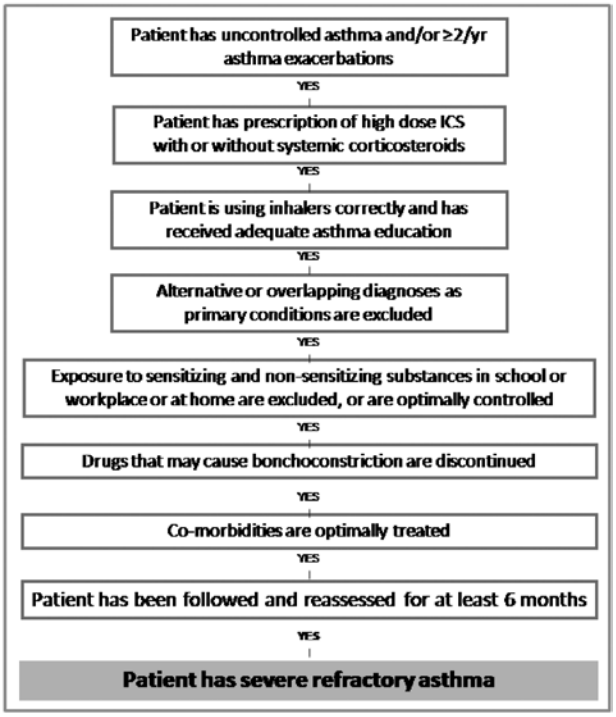

FIGURE 2. Severe Refractory Asthma Diagnosis Algorithm.

DIFFERENTIAL DIAGNOSIS

Severe refractory asthma can be mimicked by many conditions, which, as they do not respond to high-intensity asthma treatment, may easily be mistaken for severe asthma. A list of common alternative diagnoses and they ways in which they should be diagnosed is presented in Table 2.

DIAGNOSTIC CHALLENGES: THE PHENOTYPES OF SEVERE ASTHMA

Severe asthma is a heterogeneous condition that includes several phenotypes. The identification of a specific asthma phenotype can assist in its management. Phenotype investigation can lead to increased understanding of

TABLE 1. Key features in the (re)evaluation of severe asthma *(adapted from reference 11).*

Medical history	- Age of onset - Family history of asthma - Management of disease and response to treatment
Environmental exposures	- Allergens, occupational agents, and chemicals/pollutants - Smoking history
Physical examination (specific points)	- Body mass index - Evidence of nasal polyps - Evidence of alternative diagnoses, such as cardiac failure - Evidence of adverse effects of treatment
Diagnostic tests	- Spirometry (reversibility tests) - Airway challenge tests - Lung volume, Diffusing Capacity - Health status and asthma control questionnaires - Serum IgE and peripheral blood eosinophil count - Allergy skin tests - Non-invasive assessment of airway inflammation (sputum, exhaled breath condensate, etc) - Additional tests (blood gases, chest imaging, etc)
Exacerbations	Frequency and type of exacerbations (hospitalizations and/or intensive care unit admissions)
Co-morbidities and co-factors	- Rhinosinusitis or nasal polyps - Gastro-oesophageal reflux disease - Obstructive sleep apnoea - Influence of menstruation - History of psychiatric disease - Use of aspirin, NSAIDs, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, oestrogens.

the underlying pathobiology and help to direct current and future forms of treatment of asthma.

SEVERE ASTHMA PHENOTYPES

Phenotypes of severe asthma may be characterized by the presence of continuous symptoms[14], frequent exacerbations or fixed airway obstruction[15], the presence of severe inflammation and whether it is eosinophilic or neutrophilic, or treatment resistance. Many categories have been used to define asthma phenotypes, mostly according to general or clinical criteria[16-20]:

Exacerbation-prone asthma

Patients with this phenotype appear to be predisposed to frequent exacerbations, which can be very severe. They may have relatively normal lung function, or low lung function, or wide fluctuation of lung function between exacerbations[16,17]. Acute severe exacerbations activate pathways of inflammation and remodelling, resulting in deterioration of lung function. Accelerated loss of lung function in turn puts these patients at increased risk of recurrent exacerbation, resulting in a vicious cycle that may promote the exacerbation-prone phenotype. Predisposing factors for this particular phenotype include: low FEV_1, smoking, black ethnicity, obesity, gastro-oesophageal reflux, chronic rhinitis, sinusitis, aspirin sensitivity, premenstrual asthma, psychiatric disorders, decreased/absent anti-viral type I IFNs, and frequent viral infections[16,17]. Since exacerbation-prone asthma is a hallmark of severe disease and poor outcome, determination of the immunopathological factors that distinguish this phenotype is important.

Asthma defined by chronic airflow restriction.

Some patients with asthma present marked airflow restriction but have only moderately symptomatic or exacerbation-prone disease. Studies suggest that the allergic features of asthma are more likely to be associated with exacerbation-prone or difficult to control asthma than with the phenotype associated with persistent severe airflow restriction[16-21]. Risk factors associated with chronic airflow restriction in asthma are: late onset of asthma, female sex, older age, black ethnicity, current or past smoking history, aspirin sensitivity, occupational exposure and longer asthma duration[10,17,21].

Treatment-resistant asthma

This phenotype of asthma was believed to be due to a defect in the response of the patient to corticosteroids that restricts the anti-inflammatory effects of this class of drugs[17-20]. Later studies have shown that there are many different reasons for steroid resistance, such as abnormalities in histone deacetylation pathways, overexpression of the alternative, non-functional glucocorticoid receptor β, or transcription-factor interference with corticosteroid binding to the functional glucocorticoid receptor α[17-20].

TABLE 2: Differential or additional diagnoses to severe asthma, and relevant diagnostic tests *(adapted from reference 2)*.

Differential or additional diagnoses	Diagnostic tests
Bronchiolitis obliterans	Air trapping measured by body plethysmography
Emphysema or parenchymal lung disease	Carbon monoxide diffusion capacity
Parenchymal lung disease Bronchiolitis obliterans Bronchiectasis Congestive heart failure	Chest high resolution computed tomography (HRCT) scan
Recurrent pulmonary embolism	D-dimer
Intrabronchial obstruction	Bronchoscopy
Vocal cord dysfunction	Laryngoscopy during attack
Dysfunctional breathing/panic attacks	Blood gases during attack Hyperventilation provocation test
Recurrent microaspiration	Proximal oesophageal pH measurement Bile salts in bronchoalveolar lavage (BAL) fluid
Cystic fibrosis (CF)	Sweat test
Allergic bronchopulmonary aspergillosis	Aspergillus IgE/precipitins/sputum culture
Emphysema Hypersensitivity pneumonitis Bronchiectasis	Chest high resolutioncomputed tomography (HRCT) scan
Recurrent pulmonary embolism Pulmonary arterial hypertension	CT pulmonary angiography
Bronchiolitis Sarcoidosis	Transbronchial or thoracoscopic lung biopsy
Churg Strauss syndrome	Biopsy of affected organ(s) Antineutrophilic cytoplasmic antibodies

Some patients probably do not respond either because they have no inflammation, or they have a different type of inflammation (e.g., neutrophil)[16,17].

Asthma defined by age at onset

The age at which a patient develops asthma also differentiates phenotypes[16-19]. Generally, early-onset asthma appears to be a more homogeneous disease than late-onset asthma, which is aggravated to by a mix of allergic, infectious, and other factors[21]. For example, in a recent study by Moore and colleagues[22] patients with early onset atopic disease had normal lung function and little difficulty attaining asthma control, while patients with an older age of onset had poorly reversible, severe airflow obstruction, obesity, and a tendency to systemic hypertension.

Aspirin-induced Asthma

Aspirin-induced asthma is characterized by a combination of chronic rhinosinusitis progressing to chronic hyperplastic eosinophilic sinusitis, moderate-to-severe asthma, and nasal polyposis. It has high morbidity and the symptoms are life-long once developed. It is rare in childhood, with a peak age of onset between 29 and 34 years. Previous exposure to aspirin is not a risk factor for its development, but once established, ingestion of aspirin or other NSAIDS induces an acute worsening of rhinosinusitis and asthma. It responds poorly to steroids and is characterized by persistent inflammation of the upper and lower respiratory tracts. Aspirin intake has also been associated with severe asthma attacks and remodelling changes[16,17].

Cluster analysis: a new approach to the phenotyping of asthma

Cluster analysis organizes information about variables so that heterogeneous groups of subjects can be classified into relatively homogeneous "clusters"[22]. Early studies using cluster analysis identified 4 distinct severe asthma phenotypes:

1) Patients with well-controlled symptoms and minimal airway inflammation;
2) Patients with early-onset atopic asthma with severe symptoms, persistent airway inflammation, and markedly variable airflow obstruction;
3) Patients, mainly female, who have late-onset asthma with symptoms but minimal eosinophilic inflammation, many of whom are obese;
4) Patients, mainly male, who have late-onset asthma characterized by persistent eosinophilic inflammation in the absence of symptoms.

More recently Haldar and colleagues[23] identified two clusters specific to refractory asthma, the "early-onset, symptom predominant" and the "late-onset, inflammation predominant". Both clusters had marked discordance between symptom expression and eosinophilic inflammation. Inflammation-guided management led to a reduction in exacerbation frequency in the inflammation predominant cluster and a dose reduction of ICS in the symptom-predominant cluster.

SPECIFIC DIAGNOSTIC PROBLEMS

1. Asthma in the elderly

In clinical practice, asthma in the elderly is often either underdiagnosed and undertreated or overdiagnosed and mistreated. The age-related reduction in perception of shortness of breath and the high incidence of co-morbidities in the elderly makes the diagnosis and management more difficult and challenging for clinicians. The differentiation between symptoms is not always as straightforward as in younger age-groups. Wheezing, the most common symptom of asthma in the elderly[24,25] can also be attributed to other pathological conditions, such as COPD, cardiac failure, acute bronchitis, bronchiectasis, gastro-oesophageal reflux, aspiration or inhalation of a foreign body, and tracheobronchial tumours[26,27]. Breathlessness is usually perceived as part of the normal process of ageing. Clinicians must rule out other diseases, such as COPD, congestive heart failure, pulmonary embolism, hyperventilation/panic disorder, Churg-Strauss syndrome and other forms of vasculitis[26,27]. The investigation may present problems; for example, spirometry before and after bronchodilation may entail additional difficulties in the elderly. Several studies have reported that spirometry can be adequately performed in the majority of older patients when the staff is properly trained, and with the appropriate application of reference values for this age group[28]. The ATS/European Respiratory Society (ERS) pulmonary function test interpretation guidelines recommend that the lower limit of the normal range for FEV_1/FVC ratio, based on the fifth percentile corrected for age, sex, height, and race, be used to detect airflow obstruction[28].

BHR has long been considered a differentiating feature of asthma[1,2], but its role in the elderly is a matter of debate. Scichilone and colleagues[29], in a review of 18 studies, showed a positive association between age and BHR, the prevalence of which appears to increase in the elderly[29]. The most important determinants were reduced lung function, probably due to geometric factors, and a history of smoking. Atopy, female sex, inflammatory and neuronal mechanisms should also be considered as determinants of BHR in the elderly[29]. Elderly individuals experience less awareness of bronchoconstriction during methacholine bronchoprovocation, despite degrees of bronchoconstriction similar to those of younger subjects. The presence of one or more comorbid conditions, which are common in the elderly, significantly impairs perception of bronchoconstriction, which could lead to the occurrence of unnoticed severe airway narrowing[25-27].

2. Differential diagnosis between severe asthma and chronic obstructive pulmonary disease (COPD)

COPD is usually easy to distinguish from asthma but sometimes its differentiation from late-onset asthma in older patients, particularly cigarette smokers, is difficult, and may be impossible. Both diseases are characterized by the presence of airflow obstruction but each has a distinct pathogenesis, inflammatory pattern, and prognosis[1,2,30].

The distinction between asthma and COPD based simply on spirometric parameters is difficult, particularly in severe asthma, and especially in the elderly. A negative bronchodilator response may indicate COPD, or rarely refractory asthma (corticosteroid resistant)[31,32]. Population studies have shown that as many as 30% of patients with fixed airflow obstruction have a past history of asthma[33]. Often there is a need for further tests, such as lung volume measurements [e.g., total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV), RV/TLC %, or diffusing capacity of carbon monoxide of the lung (DLCO)].

Lung volumes are elevated in COPD[30]. The presence of a normal DLCO can be useful to differentiate patients with asthma from those with COPD, although patients with asthma who have a history of smoking may also present reduced DLCO[33,34].

Recently, chest high resolution computed tomography (HRCT) scan has been proposed as an additional tool for assessing pulmonary structural changes in long-standing diseases, such as asthma and COPD[35]. HRCT scan has been used to quantify abnormalities of the airways due to airway remodelling, and the HRCT scan score has been found to be correlated with the severity of asthma and airflow obstruction[35]. In addition, high-dimensional biological techniques (e.g., genomics, metabolomics) allow assessment of disease biomarker profiles[36], providing the possibility to discriminate disease entities based on composite molecular signatures, applicable to serum, BAL fluid, exhaled air and sputum[36-38].

CONCLUSIONS

The diagnosis of severe asthma should be reserved for those who have refractory asthma that persists after extensive re-evaluation and an appropriate observation period of at least 6 months. It is important that multiple objective independent outcomes are assessed, including health status, disease control[39], exacerbations, airway inflammation[40], lung function, BHR, atopy, and HRCT chest scan. These outcomes can facilitate the correct diagnosis and the distinction of particular disease phenotypes, and indicate the appropriate treatment.

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