

REVIEW
XII PNEUMOLAB PROCEEDINGSRole and challenges of severe asthma services:
insights from the UK registryGiuseppe F. SFERRAZZA PAPA^{1, 2 *}, Manlio MILANESE³,
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ABSTRACT

Severe bronchial asthma affects at least 5% of the asthmatic population and remains a clinical challenge. Data from the UK National Registry for Severe Asthma suggest that dedicated centers may improve asthma control, quality of life, reduce healthcare use and oral steroid burden. A multidisciplinary approach through complete lung function evaluation, optimization of adherence to treatment and immunological characterization are key issues to improve patients' care. In this paper, we provide an overview of the challenges of managing patients with severe asthma and the role of dedicated services.

(Cite this article as: Sferrazza Papa GF, Milanese M, Facchini FM, Baiardini I. Role and challenges of severe asthma services: insights from the UK registry. Minerva Med 2017;108:13-7. DOI: 10.23736/S0026-4806.17.05323-X)

Key words: Quality of life - Asthma - Bronchial diseases.

Bronchial asthma is a syndrome which often defies definitions.¹ Currently, asthma is defined as severe when its treatment requires high-dose of inhaled corticosteroids and long-acting beta-agonists (or leukotriene modifier/theophylline) for the previous year or systemic corticosteroids for $\geq 50\%$ of the previous year to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy.² This unusual definition, based on therapy and clinical course, points out the lack of knowledge of why about 5% to 10% of asthmatic patients continues to remain sick despite treatment. This percentage becomes more relevant considering the global prevalence of asthma, which is about 300 million.³ Recently dedi-

cated guidelines have been published to shed light on evaluation and treatment of severe asthma.² Nevertheless, these patients remain a heterogeneous and difficult-to-treat group as the guidelines point out, uncontrolled symptoms and/or loss of pulmonary functionality might be due to the severity of the condition, but more frequently there are potentially controllable factors that are not addressed and are difficult to find or remove. Indeed, the British guidelines parallel the European definitions, but prefer the term "difficult-to-treat asthma" to describe those patients where asthma control has not been achieved and stresses that diagnosis should be confirmed and worsening factors should be worked out.⁴ In some cases

TABLE I.—*Alternative diagnosis for asthma.*

Chronic upper airways cough syndrome
Vocal cord dysfunction
Dysfunctional breathing
Bronchiectasis/airways stenosis
Inhaled foreign body
Lung cancer
Eosinophilic lymphoma
Chronic obstructive pulmonary disease
Cardiac failure
Interstitial lung diseases
Pulmonary embolism
Eosinophilic granulomatosis with polyangiitis (previously Churg-Strauss syndrome)
Bronchiolitis
Alpha-1 antitrypsin deficiency
Primary ciliary dyskinesia
Congenital heart disease
Bronchopulmonary dysplasia
Drug-induced cough

the challenge is to achieve a correct diagnosis (Table I). In other cases different conditions may mimic the disease, such as chronic cough due to other conditions, upper airway stenosis, vocal cord dysfunction, dysfunctional breathing, or chronic obstructive pulmonary disease (COPD) and congestive heart failure, inhaled foreign body, eosinophilic hematological conditions, eosinophilic granulomatosis with polyangiitis (formerly known as the Churg-Strauss syndrome), congenital/genetic airways diseases.⁵⁻⁸ Moreover, comorbidities such as rhinosinusitis, gastro-esophageal reflux disease, obstructive sleep apnea, obesity,^{2, 9-12} psychological/psychiatric disorders¹³ make asthma difficult to control (Table II). In other cases, as reported by Gamble *et al.*,¹⁴ a significant proportion of patients with severe

TABLE II.—*Main comorbidities and triggers of severe asthma.*

Comorbidities	Triggers
– Obesity	– Allergens
– Gastroesophageal reflux disease	– Respiratory infections
– Anxiety and depression	– Exercise
– Rhinitis, sinusitis, nasal polyps	– ASA and NSAID
– Obstructive sleep apnea syndrome	– Tobacco smoking
	– Exposure to other toxic agents/irritants

ASA: acetylsalicylic acid; NSAID: non-steroidal anti-inflammatory drugs.

uncontrolled asthma had poor inhaling technique¹⁵ or they revealed to be non-adherent to therapy; checking inhaling technique and measuring adherence should therefore be part of the assessment of difficult asthma patients, other patients cannot or will not be in the condition to avoid exposure to food allergens¹⁶ or inhaled allergens, for example mold, cat or dog dander,¹⁷ will be exposed to toxic/irritants^{18, 19} or will continue to smoke¹⁷ or asthma might be severe or uncontrolled because of their particular situation, such as pregnancy,²⁰ athletes,²¹ workers.²²

In several Countries, tertiary care dedicated services have been created with the purpose to manage severe asthma patients affected by higher morbidity and needs a high amount of healthcare resources. However, cost-effectiveness of this approach should be proved. Gibeon *et al.*²³ analyzed the National Registry for dedicated UK Difficult Asthma Services developed in 2006 and suggested that a systematic assessment is associated with an improved quality of life (QoL), asthma control and a reduction in healthcare use and oral steroid burden. Through the analysis of this paper, we aimed to provide an overview of the challenges of managing patients with severe asthma and the role of dedicated services.

Do dedicated asthma services improve patients' outcomes?

In 1993 Irwin *et al.*²⁴ firstly reported that a systematic management protocol reduced the proportion of asthmatic patients considered difficult-to-control. Over 20 years ago, the authors had already highlighted the role of adherence, inhaled corticosteroids therapy, and treatment of gastro-esophageal disease. Concerning adherence, Gamble *et al.*¹⁴ suggested the systematic evaluation of patient adherence in difficult asthma. Unfortunately, poor adherence is difficult to monitor. A simple strategy, using prescription refill records in a Severe Asthma Service²⁵ more recently allowed to identify about a third of non-adherent patients. The authors proved that, when poor adherence is identified, a targeted clinical intervention

resulted in a 37% improvement in patient adherence and in a reduction of rescue steroids courses and hospital admissions.²⁵

Gibeon *et al.*²³ confirmed that a systematic approach conducted in asthma services reduces the use of healthcare resources such as primary care or emergency departments visits and hospital admissions. Although the authors did not find a reduction in the percentage of patients requiring long-term oral corticosteroids, their maintenance dose and short bursts of steroids were slightly reduced. Severe asthma services spread also to improve the allocation of new drugs such as biologic agents. In the study by Gibeon *et al.* after patient evaluation in a dedicated service only 13.6% of patients were in therapy with anti-IgE (omalizumab). It is noteworthy that about 40% of the cohort continued to be treated with oral steroids. These percentages highlight that despite anti-IgE treatment may fit some patients, there is a need for other treatments for a wider population with uncontrolled disease. With a consistent amount of new therapies which will be readily available, such as new biologic agents, there is a strong need to identify patients who may benefit from these therapies. The burden of the disease (frequently affecting young patients) and the high costs of biologic drugs require treating clinicians to move towards a model of precision medicine. Tailoring drugs requires an in-depth comprehension of the disease and patient characterization. Regarding this issue there is ongoing research to achieve better understanding of the pathogenesis of asthma, and to find useful biomarkers to improve its clinical management.^{26, 27}

The role of severe asthma services in clinic and research

Severe asthma services seem to be cost-effective and clinically useful. These centers should point at achieving two aims: providing the best clinical care available and conducting high-quality research.

Both aspects are facilitated by centralization of severe cases and availability of dedicated physicians. Asthma Services should provide

promptly first and second level tests such as advanced spirometry with body plethysmography and lung diffusion measurement, skin prick tests, sputum analysis, exhaled nitric oxide measurement, blood eosinophil and total and specific IgE counts for inhalants and foods. In the near future inflammasome blood analysis^{9, 28} and gene expression²⁹ will contribute to further define asthma subgroups.

The evidence of the utility of third level techniques remains to be investigated. However, it is felt that centers should be of high-quality and with prompt diagnostic resources. Recently Lombardi *et al.*³⁰ proposed a model of appropriateness for the treatment of allergic respiratory diseases suitable for Italy in which asthma centers should be based on board certification, ability to deliver first and second level diagnostic tools, and availability for every 300,000-600,000 inhabitants. Research should be facilitated through cooperation with universities, dedicated teams and the possibility to follow a high number of selected patients. An essential feature is that adequate funding and resources will be allocated on this issue. This research field carries lofty expectations and could give the possibility of collaborations between universities and stakeholders with common aims; however, given the high economic burden of the disease the independence of researchers remains a critical factor.

Limitations of the study

The study by Gibeon *et al.*²³ is based on a clinical registry and, thus, on the clinical practice of different centers, however the seven centers enrolling patients in the UK National Register which were analyzed had all similar protocols and control groups. Therefore, the study does not provide information about the different protocols used to manage patients with severe asthma, but has demonstrated the efficacy of multidisciplinary and thorough approach to these cases. The evaluation of specific protocols was beyond the aim of this study and from this point of view results should be considered mainly as hypotheses generators which deserves further randomized studies.

The lack of shared protocols may question whether these results apply to other asthma services located outside the UK. However, the European Respiratory Society and American Thoracic Society guidelines fixed some key points in an integrated approach to evaluate and treat severe asthma patients, such as on the role of detecting comorbidities and using drugs.³¹

In the cohort analyzed by Gibeon it is noteworthy that 11% of the patients were current smokers and the mean Body Mass Index (BMI) was 30.8 kg/m². This underlines the necessity to address primary unsolved issues such as smoking cessation, weight reduction, and improving treatment of likely comorbidities such as gastro-esophageal reflux and oral steroids side effects. Given the complexity of treating these patients, a multidisciplinary approach, should be encouraged and made available in addition to specific lung treatment, focusing on improving nutrition, metabolic status and psychologic/psychiatric status; the last not only to highlight hidden reasons for poor asthma control, but also to manage the impact of this condition on patients' life.³²

Gibeon *et al.*²³ reported improvements in quality of life QoL (QoL) evaluated through validated questionnaires. However, as acknowledged by the author it is likely that a "placebo-type effect" might have played a role. Considering the package provided by a dedicated severe asthma service (in term of diagnosis, monitoring and treatment), we can hypothesize two different mechanisms that may modulate the disease perception: the placebo and the Hawthorn effect. As known, a placebo is not the inert treatment alone, but rather the entire therapeutic act.³³ A dedicated severe asthma center may represent a context inducing positive expectations of clinical improvement: its approach provides a multidisciplinary management, a targeted treatment, and, on average, more attention from the clinicians to patients' behavior (*i.e.*, smoking, adherence, inhaler technique) and an improved doctor-patient interaction. The Hawthorne effect³⁴ is used to describe any change in behavioral, clinical, and physiological variables that

occur in response to a participant's awareness of being under study. In other words, behaviors measured in the setting of an experimental study or of a dedicated approach, change in response to the attention received from study investigators.³⁵

Conclusions

In conclusion, the data from the UK National Registry for Severe Asthma suggest to invest in developing dedicated centers to face the challenge of severe asthma. A multidisciplinary assessment starting from objective lung function tests and immunological characterization are key issues to improve patients' care.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Manuscript accepted: June 29, 2017. - Manuscript received: June 23, 2017.