

The management of asthma in the phenotype and biomarker era: the proposal of a new diagnostic-therapeutic model

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Abstract

Treatment goals in asthma patients are the achievement of a good control of symptoms and the reduction of the risk of exacerbation. However, a “one-size-fits-all” therapeutic strategy is no longer appropriate to effectively pursue these goals, due to the heterogeneity of asthma. To make the treatment scenario even more complex, asthma patients often present comorbidities which may alter response to therapy. In addition, adherence to asthma treatment is poor.

Given this complex and heterogeneous picture, the management of asthma is highly challenging. A clear diagnostic-therapeutic model of patients' care and the definition of the specific responsibilities of different healthcare providers appear necessary to improve clinical outcomes and better allocate healthcare resources. We present here a proposal for this model.

Keywords

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- [clinical decision](#),
- [diagnosis](#),
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Although asthma has historically been considered as an allergic condition affecting the smooth muscles in the bronchi, it is now widely considered an inflammatory chronic disease of multifactorial etiology. Nine years ago, in 2006, S.E. Wenzel stated that “*The common disease asthma is probably not a single disease, but rather a complex of multiple, separate syndromes that overlap*” [1]. The current Guidelines issued by the Global INitiative against Asthma (GINA) define asthma as a heterogeneous disease, usually characterized by chronic airway inflammation, with the presence of respiratory symptoms [2]. Treatment goals in asthma patients are the achievement of a good control of symptoms and the reduction of the risk of exacerbation [2]. However, a “one-size-fits-all” therapeutic strategy appears no longer appropriate to effectively pursue these goals given the heterogeneity of disease. To make the treatment scenario even more complex, asthma patients often present comorbidities which may alter response to therapy [3]. In addition, adherence to asthma treatment is poor, and modest compliance is associated with suboptimal clinical outcomes [4].

In line with the concept of heterogeneity of asthma, a number of disease phenotypes have been proposed over the last years [1,2], taking also into account the inflammatory bases of this condition [1]. Phenotypes can play a role in guiding treatment decisions, especially in more severe forms of asthma [2]. Importantly, patients with severe disease represent only 5–10% of the total number of subjects with asthma; however, this population consumes a disproportionate amount of the global asthma budget (~50%) due to unscheduled health care utilization in primary care, hospitalizations for severe exacerbations, and costs of pharmacotherapy [5,6].

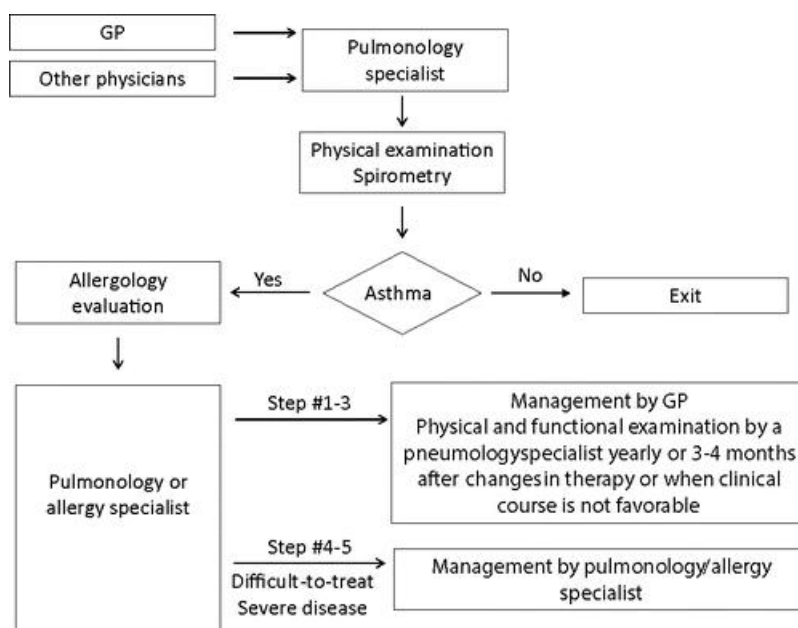
Efforts have therefore been taken to optimize asthma treatment, with a focus on severe forms of disease. In particular, clinical and laboratory research is active to identify reliable biomarkers able to predict response to therapy, in order to identify the patients who are more suitable to a given treatment [7,8]. “Omics” sciences like genomics and proteomics are providing new tools to facilitate discovery-driven studies on new biomarkers, and improve their clinical reliability [8]. New biological therapies are now available; they can modify specific pathogenic mechanisms on the basis of a precise genotype characterization in each single patient. This is the first step toward personalized therapy for asthma patients, especially for those with more severe disease [9,10].

Given this complex and heterogeneous picture, the management of asthma is highly challenging. Nowadays, about 2 out of 3 asthma patients are managed by general practitioners (GPs) [10]. However, complex diagnostic and therapeutic approaches such as genotype characterization or biological drugs require tools and skills which may not be immediately available to GPs or not-specialized hospital departments, but are rather more likely available in specialized pulmonology or allergology centers. At the same time, GPs must be involved in the daily management of every patient, given the high frequency of comorbidities associated with asthma [11]. Other specialists – e.g. pediatricians, ear-nose-throat specialists, and also experts of complementary and alternative medicine – are involved in the treatment of asthma as well.

A clear diagnostic-therapeutic model of patient's care and the definition of specific responsibilities appear necessary to improve clinical outcomes and better allocate healthcare resources. It is noteworthy that such a model should also aim at increasing patients' adherence, especially for difficult-to-treat patients who, paradoxically, have poorer compliance than subjects with less complex forms of disease [4].

A proposal for this model is displayed in [Figure 1](#). It specifically concerns the Italian scenario, but in line of principle it can be extended to other scenarios with some modifications to address the specific health system organization of each country.

Figure 1. Proposed diagnostic-therapeutic model of asthma management.



The model should necessarily start from the diagnosis process. The diagnosis of asthma is based on history of previous respiratory symptoms, physical examination and functional evaluation (spirometry with or without methacholine challenge). Functional evaluation must be performed in every patient at the time of diagnosis. When possible, the GP or any other physician following the patient – or the Emergency Department when appropriate - should therefore refer each patient with a suspect diagnosis of asthma to a pulmonologist, in order to perform the necessary examinations. If the diagnosis of asthma is not confirmed, the patient leaves the model. If the diagnosis is confirmed, the patient is referred to an allergy specialist for specific evaluations.

The therapy of asthma patient should adhere to the GINA stepwise approach [2]. After the evaluation by the pulmonologist and/or the allergy specialist, who should confirm the diagnosis and propose the first treatment approach, the GP can manage patients who are in steps of treatment #1–3. In these patients, also the pharmacist might have a key role in monitoring adherence and controlling the onset of “red-flags” which may prompt further evaluation [12,13]. The pulmonary specialist assists the GP in the management of each patient: a pulmonology visit with physical and functional evaluations must be performed yearly, or within 3–4 months from each modification in the therapy plan, or every time the clinical course of the disease is not favorable.

On the other hand, therapy of patients in GINA steps of treatment #4–5, those who are difficult-to-treat, or subjects with severe disease should be followed directly by the pulmonology or allergy specialist, possibly in a dedicated center. Specialized pulmonology or allergology centers will likely have mounting importance in the next years, since biological therapies which require specific management and dedicated genotyping tools have been introduced into the market. To this end, and in the perspective of cost-saving, different pulmonology and allergology centers in the same geographic area can be joined into a network and share a common model of clinical record. In addition, a strategic program linking GPs, local pulmonary units and referral asthma centers should be promoted in each region, in order to optimize diagnosis, phenotyping and treatment decision in every single patient.

The application of the above-described model into clinical practice may allow the optimization of healthcare resources by avoiding unnecessary specialist visits and promoting patient's adherence. To this end, it has been shown that the optimal selection of the inhaler device to ensure optimal aerosolisation performance and consistency in efficacy can further optimize patient's compliance [14,15]. For instance, the use of patient-friendly devices with an inhalation counter – which shows the actual number of inhaled doses – can be useful in increasing adherence. In addition, adherence can be further enhanced by using drug-device systems which allow a uniform distribution of drug particles in the entire bronchial tree, with the aim to optimize drug delivery [16]. Last, drug/device systems able to permit the modulation of the number of inhalations according to symptoms improvement can allow a better control of therapy [17,18].

Although simplified, we believe that this model can represent a general approach, which should be tailored to the specific local scenarios also with the involvement of scientific societies.

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References

- 1. Wenzel SE. Asthma: defining of the persistent adult phenotypes. *Lancet*. 2006;368:804–813. [CrossRef], [PubMed], [Web of Science ®]
- 2. GINA report 2014. Available at http://www.ginasthma.org/local/uploads/files/GINA_Report_2014_Aug12.pdf. Last accessed 24th January 2015.
- 3. Boulet LP. Influence of comorbid conditions on asthma. *Eur Respir J*. 2009;33:897–906. [CrossRef], [PubMed], [Web of Science ®]
- 4. Murphy AC, Proeschal A, Brightling CE, et al. The relationship between clinical outcomes and medication adherence in difficult-to-control asthma. *Thorax*. 2012;67:751–753. [CrossRef], [PubMed], [Web of Science ®]
- 5. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43:343–373. [CrossRef], [PubMed], [Web of Science ®]
- 6. Siddiqui S, Gonem S, Wardlaw AJ. Advances in the management of severe asthma. *Semin Respir Crit Care Med*. 2012;33:666–684. [CrossRef], [PubMed], [Web of Science ®]
- 7. Leung TF, Ko FW, Wong GW. Recent advances in asthma biomarker research. *Ther Adv Respir Dis*. 2013;7:297–308. [CrossRef], [PubMed], [Web of Science ®]
- 8. Rossi R, De Palma A, Benazzi L, et al. Biomarker discovery in asthma and COPD by proteomic approaches. *Proteomics Clin Appl*. 2014;8:901–915. [CrossRef], [PubMed], [Web of Science ®]
- 9. Braido F, Holgate S, Canonica GW. From “blockbusters” to “biosimilars”: an opportunity for patients, medical specialists and health care providers. *Pulm Pharmacol Ther*. 2012;25:483–486. [CrossRef], [PubMed], [Web of Science ®]
- 10. Drazen JM. A step toward personalized asthma treatment. *N Engl J Med*. 2011;365:1245–1246. [CrossRef], [PubMed], [Web of Science ®]
- 11. Cazzola M, Calzetta L, Bettoncelli G, et al. Asthma and comorbid medical illness. *Eur Respir J*. 2011;38:42–49. [CrossRef], [PubMed], [Web of Science ®]
- 12. Turner-Bowker DM, Saris-Baglama RN, Derosa MA, et al. Using Qualitative Research to Inform the Development of a Comprehensive Outcomes Assessment for Asthma. *Patient*. 2009;2:269–282. [CrossRef]

- **13.** Ng MC, How CH. Recurrent wheeze and cough in young children: is it asthma? Singapore Med J. 2014;55:236–241. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **14.** Lavorini F, Fontana GA, Usmani OS. New inhaler devices - the good, the bad and the ugly. Respiration. 2014;88:3–15. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **15.** Scichilone N, Contino A, Figlioli GB, et al. Patient perspectives in the management of asthma: improving patient outcomes through critical selection of treatment options. Patient Prefer Adherence. 2010;4:17–23. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **16.** Price D, Small I, Haughney J, et al. Clinical and cost effectiveness of switching asthma patients from fluticasone-salmeterol to extra-fine particle beclometasone-formoterol: a retrospective matched observational study of real-world patients. Prim Care Respir J. 2013;22:439–448. [\[CrossRef\]](#), [\[PubMed\]](#)
- **17.** Papi A, Corradi M, Pigeon-Francisco C, et al. Beclometasone-formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial. Lancet Respir Med. 2013;1:23–31. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **18.** Braidó F, Baiardini I, Compalati E, et al. Towards the Grade of Recommendations, Assessment, Development and Evaluation system: methods and results of budesonide/formoterol maintenance and reliever therapy research. Curr Opin Allergy Clin Immunol. 2011;11:361–374. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)