# The Importance of Small Airway Dysfunction in Asthma. The GEMA-FORUM III Task Force

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Small airways are structures characterized by an internal diameter of 2 mm or less. They have shown to play an important role in asthma and other obstructive lung diseases, as their inflammation or smooth muscle contraction after inhalation of allergic and non-allergic irritants leads to a narrowing of their diameter, increasing the resistance in the airways of patients with these diseases [1-3].Peripheral airway obstruction, also known as small airways dysfunction (SAD),can occur at all severities of asthma, and its prevalence increases with asthma severity [1, 2, 4].In addition, SAD can greatly worsen the clinical expression and control of asthma, be associated with a higher number of exacerbations and more severe bronchial hype responsiveness, and require higher inhaled corticosteroids (ICS) dosage[1, 2, 5]. The main predictors of SAD are exercise-induced asthma, overweight, asthma-related night awakenings, smoking, and older age [5]. Although conventional spirometry measurements are unable to sensitively evaluate SAD, its combination with physiological tests, oscillometry, body plethysmography, chest computed tomography (CT) scan, multiple breath nitrogen washout, and nitric oxide would help to assess the complexity of this dysfunction and the response to drug therapy[4,6].

Taking into account the involvement of small airways in asthma, this region should be considered to be treated with small particle drug particles[7]. Nevertheless, the





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difficulties in exploring and studying small airways make them less well known than other aspects of respiratory diseases, especially asthma. In addition, due to the pandemic situation of the COVID-19 disease, many lung function examination procedures have been limited and new techniques for assessing SAD should be developed [8].

However, the evidence that justifies the assessment and specific treatment of SAD is not totally strength. This was the reason why the recent GEMA 5.0 (*Guía Española para el Manejo del Asma*v5.0) [9] does not include the possible role of the SAD in asthma disease. Thus, the GEMAFORUM task force proposed to debate and reach a consensus among a group of experts in asthma on this topic. The objective of the present study was to know the opinion of a multidisciplinary panel of experts on the assessment and treatment of SAD in patients with asthma. After reviewing the most recent literature, a scientific committee of 3 coordinators and 12 experts in pulmonology, allergology, and primary care, proposed a questionnaire of 50 items that addressed the main controversies regarding the diagnosis and treatment of SAD in patients with asthma (supplementary material). Following the same Delphi methodology described in the GEMA Forum II report [10], the items were sent to a panel of 87 pulmonologists and allergists involved in the care of asthma patients throughout Spain to express their degree of agreement. Briefly, there was consensus in agreement when more than two-thirds of the responders scored inside the 7-9 range of the Like rt-type scale (score median >7), and consensus in disagreement when three-thirds scored inside the 1-3 range (score median <3). Undetermined consensus if the score was in the 4-6 range (score median between 4-6).

After two rounds, a consensus was reached on 25 of 50 items (50.0%); all in agreement. The remaining 25 items (50.0%) did not show agreement or disagreement. Table 1



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shows the items with the highest degree of consensus achieved by the experts after two rounds. The results of the 50 items are shown in the supplementary material.

Of the 24 items related to the diagnosis of SAD, panelists agreed with 16 of them (66.7%). The remaining 8 items (33.3%) showed neither agreement nor disagreement. The item with the highest degree of agreement (87.2%) say that specific tools need to be developed to confirm SAD. Although the panelists are aware of the existence of different techniques to asses SAD, such as oscillometry, body plethysmography, or CT scan, they are not confident on them or consider these techniques only partially reliable[4-6]. Interestingly, although panelists did not agree on specific testing for suspected SAD in all patients with asthma, they did agree in patients with uncontrolled asthma where modifiable factors have been ruled out. Panelists explained that, due to the complexity of the tests to assess SAD, it is not necessary to perform them on patients with controlled asthma. Other items in which the panelists showed high agreement were that SAD is present at all levels of asthma severity (77.9%), and that the presence of symptoms requiring control treatment accompanied by normal lung function involves the small airways (75.6%). In addition, the panelists agreed that oscillometry should be incorporated into the pulmonary function laboratories (69.8%). Although nor in agreement nor in disagreement (indetermined consensus), the item related with diagnosis with the lower degree of agreement (16.3%) says that magnetic resonance imaging may play a more relevant role in assessing SAD if its costs are reduced and its use is widespread.

Of the 26 items related to treatment of SAD, panelists agreed with 9 (34.6%) and the remaining 17 (65.4%) showed neither agreement nor disagreement. The item with the highest degree of agreement (84.9%) states that a therapeutic trial with drugs capable of



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better reaching the distal airway should be performed if SAD is suspected. In this way, panelists agreed that extrafine particle ICS are more effective than non-extrafine particle ICS in treating SAD (66.3%). However, although a group of panelists considered that the use of extrafine particle drugs (ICS+LABA) could be considered from the beginning of treatment, others argued that there is not enough evidence to support such claim or that it would not be necessary in all patients, but only in some specific ones, which is why full consensus was not reached on this item. In addition, panelists agreed that device type, inhalation technique, inspiratory flow for each device, and patient preference for inhaler device should prevail over drug particle size. To assess treatment response for SAD, most of the panelists agreed that several methods should be used since only indirect methods are available(80.2%).This is in accordance with ATLATINS trial[4]. Measuring of FeNO, slow spirometry, plethysmography, chest CT, or dynamic hyperinflation after the 6-minute walk test (6MWT)did not reach consensus as sensitive methods for evaluating response to treatment for SAD by themselves. Although no consensus was reached, the item "The improvement of cough is a good marker of good response to treatment for SAD" obtained a 64.4% of agreement, and the item with the lowest degree of agreement say that "A decrease in the number of eosinophils in the peripheral blood is a marker of good response to treatment for SAD" (5.8%).

Despite the large consensus on the use of extrafine particle drugs when SAD is suspected, the lack of consensus or indetermination on many of the items in the study highlights the lack of available information on SAD. However, the lack of consensus on the items was due to the dispersion of opinions, not a polarization of them, which indicates that there is no controversy but indetermination. This suggests that more studies are needed to help clear up the experts' doubts. In addition, the lack of evidence





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has made SAD a relatively unknown topic among panelists involved in the treatment of asthma, or at least at a lower level than other asthma-related topics such as comorbidities. Fortunately, more and more scientific evidence is becoming available. In fact, some of the studies were published during the development of the consensus [4, 5]. The ATLANTIS study, in particular, is the largest study of SAD in patients with asthma of all levels of severity [4].

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**Conflicts of interests**

Vicente Plaza in the last three years received honoraria for speaking at sponsored meetings from AstraZeneca, Chiesi, GSK, and Novartis; received help assistance to meeting travel from Chiesi and Novartis; act as a consultant for ALK, AstraZeneca, Boehringer Ingelheim, Mundipharma, and Sanofi; and received funding/grant support





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Santiago Quirce has been on advisory boards for and has received speaker's honoraria from AstraZeneca, GlaxoSmithKline, MSD, Novartis, Chiesi, ALK, LETI, Sanofi, and Boehringer Ingelheim.

Juan Antonio Trigueros in the last three years received honoraria for speaking at sponsored meetings from Chiesi, GSK, Novartis, AstraZeneca, Mundipharma, and Boehringer Ingelheim.

Carolina Cisneros in the last two years has received help assistance to attend congresses, and honoraria for participating as a speaker at meetings or to participate in advisory boards from AstraZeneca, GSK, Novartis, Chiesi, Mundipharma, Menarini, and TEVA

Javier Domínguez-Ortega received fees in the past three years as a consultant and as a speaker at meetings sponsored by ALK-Abelló, AstraZeneca, Chiesi, GSK, LETI, Novartis, Mundipharma, Stallergenes, and TEVA.

Stefab Cimbollek has no conflict of interest.

Sara Fernández has been speaker or has received financial support for courses and congresses from Chiesi, Novartis, GSK, AstraZeneca, and ALK-Abelló.

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**Table 1**. Items with the highest degree of consensusachieved after the two rounds

| | Median (IQR) | % agreement |
|---|---|---|
| **Topic 1. Diagnosis** | | |
| SAD is present in asthmatics of all levels of severity. | 8 (1) | 77.9 |
| The presence of symptoms requiring control medication accompanied by normal lung function implies involvement of small airways. | 7 (0) | 75.6 |
| The development of specific tools is necessary to confirm SAD. | 9 (1) | 87.2 |
| Impulse oscillometry should be incorporated into pulmonary function units or laboratories. | 7 (2) | 69.8 |
| **Topic 2. Treatment** | | |
| If SAD is suspected, a therapeutic trial with drugs capable of better reaching the distal airway should be performed. | 8 (2) | 84.9 |
| Extrafine particle ICS are more effective in treating SAD than non-extrafine particle ICS. | 7 (2) | 66.3 |
| Extrafine particle size ensures more homogeneous pulmonary deposition than that obtained with non-extrafine particle size. | 7 (1) | 76.8 |
| Since only indirect methods are available, several of them should be used to evaluate response to treatment of SAD. | 8 (1) | 80.2 |

ICS: inhaled corticosteroids; SAD: small airway dysfunction.





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