
Asthma, Comorbidities, and Aggravating Circumstances: The GEMA-FORUM II Task Force

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Failure of asthma control can result from a complex interaction between variables such as patient-related factors

(ie, adherence to treatment), disease-related factors (ie, comorbidities and aggravating factors), and deficient diffusion and implementation of guidelines [1,2]. Asthma-associated comorbidities have a significant impact on patients' quality of life [2,3]. The coexistence of potentially worsening processes is frequent in asthmatic patients, especially in those with difficult-to-control asthma [4-6]. Therefore, clinicians should be prepared not only to treat asthma, but also to properly assess and treat associated comorbidities and aggravating factors, as recommended by clinical guidelines [7-10].

The objectives of this study were to establish a consensus opinion of an expert panel using a modified Delphi procedure and to study the assessment and management of comorbidities and aggravating factors contributing to poor control of asthma, for which there is currently no strong opinion or evidence to support them. The project involved a scientific committee made up of 3 coordinators and 12 experts in respiratory medicine, allergology, and primary care and a panel of 60 experts selected by the scientific committee.

Using the brainwriting methodology, the scientific committee discussed some of the comorbidities and aggravating factors associated with insufficient asthma control for which current evidence is insufficient: pregnancy and menstruation, bronchiectasis, tracheobronchomalacia, anxiety and depression, nasal polyposis, functional dyspnea, vocal cord dysfunction, obesity, diabetes, gastroesophageal reflux, obstructive sleep apnea (OSA) syndrome, and smoking [7-10]. Each of the 12 experts reviewed the available evidence on these comorbidities and presented the information in 12 face-to-face meetings throughout Spain. Five medical professionals with experience in the management of asthma participated in each meeting, whose

objective was to identify the main controversies regarding the management of these comorbidities.

Based on the conclusions drawn from the meetings, a questionnaire of 59 items was prepared for consensus by a panel made up of the 60 participants from the discussion meetings. A unique 9-point ordinal Likert-type scale was proposed to respond to the items (1 to 3, disagreement; 4 to 6, no agreement or disagreement; and 7 to 9, agreement). No consensus was defined as scores in the 1-3 range by a third or more of the panelists and in the 7-9 range by another third or more. Consensus was defined as scores within the 3-point range by two-thirds or more of the respondents (1-3 or 7-9) containing the median. The type of consensus achieved on each item was determined by the median value of the score (agreement if the median was ≥ 7 , disagreement if the median was ≤ 3 , and uncertainty if the median was between 4 and 6).

After 2 rounds, a consensus was reached on 53 of the 59 items (89.8%, all in agreement). There was neither agreement nor disagreement for the remaining 6 items (10.2%). The Table shows the items with the highest degree of consensus achieved by the experts after 2 rounds. The result obtained in the 59 items is shown in the supplementary material.

Consensus was high for most of the items proposed. All panelists agreed that it is necessary to ask asthmatic patients if they smoke. Although most panelists considered smoking to be a comorbidity that may be present in patients with asthma, they considered that not all smokers with asthma-compatible symptoms have asthma. All panelists also agreed that patients with severe asthma should be asked specific questions about the presence of chronic rhinitis with or without polyposis.

Other comorbidities for which there was a high degree of consensus included bronchiectasis, tracheobronchomalacia,

Table. Items With the Highest Degree of Consensus Achieved After the 2 Rounds

	Median (IQR)	Agreement, %
Pregnancy and menstruation: It is essential that pregnant women with asthma do not discontinue their asthma maintenance treatment and follow-up visits.	9 (0)	98.75
Bronchiectasis: Bronchiectasis should be suspected (and therefore chest HRCT requested) in patients with asthma and bronchial hypersecretion.	9 (1)	93.75
Anxiety and depression: In patients with associated psychomorbidity, adherence to antiasthmatic therapy should be assessed as objectively as possible (by TAI and/or medication withdrawal record).	9 (1)	92.50
Nasal polyposis: All patients with severe asthma should be asked specific questions about the presence of chronic rhinitis with or without polyposis.	9 (0)	100.00
Functional dyspnea: In the diagnostic evaluation of functional dyspnea as a cause of poorly controlled asthma, organic causes of poorly controlled asthma should be ruled out.	9 (1)	97.50
Obesity: Obesity favors the overdiagnosis of asthma, making the use of an objective diagnostic methodology essential.	9 (1)	95.00
Gastroesophageal reflux: Gastroesophageal reflux should be ruled out as part of the usual clinical practice of any asthmatic patient (especially in the cough variant of asthma, severe asthma, and poorly controlled asthma).	9 (1)	97.50
Smoking: When taking the clinical history, the physician should ask asthmatic patients about their smoking habit, both in its conventional form and in other forms (eg, electronic cigarettes, hookahs, pipes).	9 (0)	100.00

Abbreviations: HRCT, high-resolution computed tomography; TAI, test of adherence to inhalers.

anxiety and depression, nasal polyposis, functional dyspnea, vocal cord dysfunction, and OSA. Most of the panelists agreed that these comorbidities should be appropriately assessed in patients with asthma, especially in patients with difficult-to-control asthma, as follows: high-resolution computed tomography for bronchiectasis; fiberoptic bronchoscopy for diagnosis of tracheobronchomalacia and excessive dynamic airway collapse; specific questionnaires for anxiety and depression (Hospital Anxiety and Depression Scale, State-Trait Anxiety Inventory, and Beck Depression Inventory); nasal endoscopy for diagnosis of polyposis; stress test or the Nijmegen questionnaire for functional dyspnea; Pittsburg index questionnaire and laryngoscopy for vocal cord dysfunction; and the STOP-Bang questionnaire for OSA screening. On the other hand, panelists did not reach consensus on the recommended diagnostic methods for obesity and gastroesophageal reflux. Interestingly, while panelists agreed to use objective tests to diagnose asthma in obese patients, no agreement was reached on the recommendation to use the methacholine test as an objective methodology in this population.

A high degree of consensus was also achieved for management of these comorbidities. Panelists agreed on the following: use of macrolides in asthmatic patients with bronchiectasis; respiratory reeducation techniques for functional dyspnea; speech therapy and inspiratory muscle rehabilitation for vocal cord dysfunction; and proton pump inhibitors and antireflux measures for gastroesophageal reflux. Although most panelists agreed that patients with severe or uncontrolled asthma and at least moderate OSA should be treated with continuous positive airway pressure, they considered that there is not enough evidence to recommend this strategy in mild OSA. Panelists agreed that the choice of biological drug for patients with severe asthma and nasal polyposis is determined by its efficacy in nasal polyposis. In addition, they agreed that in obese patients, it is preferable to select biologic drugs that can be adjusted for weight. Most panelists also agreed that anxiolytics should not be withdrawn when the asthmatic patient has an exacerbation. They also agreed that in premenstrual asthma, the dose of maintenance therapy should be increased both in the days before and during menstruation and that pregnant women should not discontinue maintenance treatment for asthma.

The high degree of consensus reached by the panel of experts shows the importance of comorbidities in the control of asthma for the medical community. The panelists agreed on the most important aspects of the diagnosis and treatment of these comorbidities, although it is still necessary to increase the level of evidence with respect to treatment of some of them, especially through studies carried out in clinical practice.

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Conflicts of Interest

In the last 3 years, Juan Antonio Trigueros has received honoraria for speaking at sponsored meetings from Chiesi, GSK, Novartis, AstraZeneca, Mundipharma, and Boehringer-Ingelheim.

In the last 3 years, Vicente Plaza has received honoraria for speaking at sponsored meetings from AstraZeneca, Chiesi, GSK, and Novartis. He has also received travel assistance from Chiesi and Novartis, acted as a consultant for ALK, AstraZeneca, Boehringer-Ingelheim, Mundipharma, and Sanofi and received funding/grant support for research projects from a variety of government agencies and not-for-profit foundations, as well as from AstraZeneca, Chiesi, and Menarini.

In the last 3 years, Javier Domínguez-Ortega received fees as a consultant and as a speaker at meetings sponsored by ALK-Abelló, AstraZeneca, Chiesi, GSK, LETI, Novartis, Mundipharma, Stallergenes, and TEVA.

In the last 3 years, José Serrano has received honoraria for speaking at sponsored meetings from Chiesi and travel assistance from Chiesi and Novartis. He has also acted as a consultant for AstraZeneca and Boehringer-Ingelheim.

In the last 2 years, Carolina Cisneros has received assistance to attend congresses and honoraria for participating as a speaker at meetings or advisory boards from AstraZeneca, GSK, Novartis, Chiesi, Mundipharma, Menarini, and TEVA.

In the last 3 years, Alicia Padilla has received fees for participating as a speaker in meetings sponsored by ALK-Abelló, AstraZeneca, GSK, TEVA, Zambon, Boehringer-Ingelheim, Chiesi, Mundipharma, and Novartis. She has also received honoraria as a consultant for AstraZeneca, TEVA, Orion, and GSK and financial assistance for attending conferences from ALK-Abelló, Chiesi, Menarini, Zambon, and Novartis.

In the last 3 years, Mónica Antón Gironés has received fees for participating as a speaker in meetings sponsored by ALK-Abelló, AstraZeneca, GSK, and Novartis and honoraria as a consultant for AstraZeneca, Chiesi, Mundipharma, and GSK.

In the last 3 years, Mar Mosteiro has received honoraria for speaking at sponsored meetings from Chiesi, GSK, Novartis, AstraZeneca, Menarini, and Boehringer-Ingelheim. She has also received financial assistance for attending conferences from Chiesi, Novartis, TEVA, and Mundipharma.

Eva Martínez Moragón has been on advisory boards for and has received speaker's honoraria from AstraZeneca, GSK, Novartis, Chiesi, ALK-Abelló, Sanofi, and Boehringer-Ingelheim.

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

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