

## Asthma, comorbidities, and aggravating circumstances.

### The GEMA-FORUM II task force

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi:

10.18176/jiaci.0460

**Key words:** Asthma, Comorbidities, Diagnosis, Monitoring, Treatment

**Palabras clave:** Asma, Comorbilidades, Diagnóstico, Monitorización, Tratamiento

The failure in asthma control can result from a complex interaction of variables, such as patient-related factors (i.e., adherence to treatment), some disease-related factors (i.e., comorbidities and aggravating factors), or a 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 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 objective of this study was to know and agree on the opinion of an expert panel using a modified Delphi consensus on the assessment and management of comorbidities and aggravating factors contributing to insufficient asthma control for which there is currently no strong opinion or evidence to support them. The project involved a scientific committee made up of three coordinators and 12 experts in pneumology, allergology, and primary care, and a panel of 60 experts selected by the scientific committee.

First, through the brainwriting methodology the scientific committee discussed some of the comorbidities and aggravating factors associated with insufficient asthma control

for which there is currently not enough evidence: pregnancy and menstruation, bronchiectasis, tracheobronchomalacia, anxiety and depression, nasal polyposis, functional dyspnea, vocal cord dysfunction, obesity, diabetes, gastroesophageal reflux, obstructive sleep apnea syndrome (OSA), and smoking [7-10]. Each one of the 12 experts of the scientific committee reviewed the available evidence on these comorbidities and presented the information in 12 face-to-face debate meetings throughout Spain. Five to eight medical professionals with experience in the management of asthma participated in each discussion meeting, whose objective was to identify the main controversies regarding the management of these comorbidities.

Based on the conclusions drawn from the discussion meetings, a questionnaire of 59 items was prepared for consensus by a panel made up of the 85 participants of the discussion meetings. To respond to the items, a unique 9 point ordinal Likert-type scale was proposed (1 to 3, interpreted as disagreement; 4 to 6, interpreted as no agreement or disagreement; and 7 to 9, interpreted as agreement). No consensus was reached when the scores of a third or more of the panelists were in the 1-3 range, and another third or more in the 7-9 range. On the other hand, there was consensus when two-thirds or more of the respondents scored within the 3-point range (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  $\geq 7$ , disagreement if the median was  $\leq 3$ , and uncertain if median was between 4-6).

After two rounds, a consensus was reached on 53 of 59 items (89.8%); all in agreement. The remaining 6 items (10.2%) did not show agreement or disagreement. Table 1 shows the items with the highest degree of consensus achieved by the experts after two rounds. The result obtained in the 59 items is shown in the supplementary material.

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

Other comorbidities that showed a high degree of consensus were bronchiectasis, tracheobronchomalacia, anxiety and depression, nasal polyposis, functional dyspnea, vocal cord dysfunction, and OSA. Most of the panelists agreed that these comorbidities should be considered in patients with asthma using the appropriate assessment, especially in patients with difficult-to-control asthma. A high-resolution computed tomography is recommended for bronchiectasis; fibrobronchoscopy is the gold standard for the diagnosis of tracheobronchomalacia and excessive dynamic airway collapse; specific questionnaires for anxiety and depression (HAD, STAI, and BDI); nasal endoscopy for the diagnosis of polyposis; stress test or the Nijmegen questionnaire for functional dyspnea; Pittsburg index questionnaire and laryngoscopy for vocal cord dysfunction; and STOP-Bang questionnaire for OSA screening. On the other hand, panelists did not reach consensus about the recommended diagnosis method 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 metacholine test as an objective methodology in these patients.

Management of these comorbidities also achieved a high degree of consensus. Panelists agreed the use of macrolides in asthmatic patients with bronchiectasis; respiratory reeducation techniques for functional dyspnea; speech therapy and

inspiratory muscles rehabilitation for vocal cord dysfunction; and proton pump inhibitors and anti-reflux 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 their efficacy in nasal polyposis. In addition, they agreed that in obese patients it is preferable to select biologic drugs adjustable according to 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 do not discontinue the 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. They agreed the most important aspects of the diagnosis and treatment of these comorbidities, but it is still necessary to increase the level of evidence on the treatment of some of them, especially through studies carried out in clinical practice.

## **Acknowledgments**

The authors wish to thank the Research Unit at Luzán5 (Madrid) for the design and coordination assistance; and Dr. Fernando Sánchez Barbero for the support on the preparation of this manuscript.

## **Funding**

Chiesi has sponsored this project without participating in any way in the design, data analysis or writing of this article.

## **Conflicts of interests**

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

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 for research projects from a variety of Government agencies and not-for-profit foundations, as well as AstraZeneca, Chiesi, and Menarini.

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.

José Serrano in the last three years received honoraria for speaking at sponsored meetings from Chiesi; received help assistance to meeting travel from Chiesi and Novartis; and act as a consultant for Astrazeneca, 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.

Alicia Padilla in the last three years has received fees for participating as a speaker in meetings sponsored by ALK-Abelló, Astrazeneca, GSK, TEVA, Zambon, Boehringer-Ingelheim, Chiesi, Mundipharma, and Novartis; received honoraria as a consultant for Astrazeneca, TEVA, Orion, and GSK; and received financial assistance for the attendance at congresses by ALK-Abelló, Chiesi, Menarini, Zambon, and Novartis.

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

Mar Mosteiro in the last three years received honoraria for speaking at sponsored meetings from Chiesi, GSK, Novartis, Astrazeneca, Menarini, and Boehringer-Ingelheim; and received financial assistance for the attendance at congresses by 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.

José María Olaguíbel Rivera reports personal fees from Astrazeneca, Chiesi, and ALK-Abelló and grants from Sanofi.

Julio Delgado in the last three years has received fees for lectures and scientific consultancy from GSK, Astrazeneca, Chiesi, Mundipharma, Sanofi, and TEVA.

Juan Luis García Rivero has no conflict of interests.

Carlos Martínez Rivera in the last three years has received fees for participating as speaker in meetings sponsored by Astrazeneca, GSK, Chiesi, Novartis, and Ferrer; received honoraria as a consultant for Astrazeneca, TEVA, Mundipharma, Novartis, Boehringer-Ingelheim, and GSK; and received funding/grant support for research projects from Astrazeneca, GSK, and TEVA.

Juan José Garrido in the last three years has received fees as speaker in scientific meetings sponsored by Zambon, Astrazeneca, GSK, Chiesi, and Novartis; received financial assistance for the attendance at congresses by Chiesi, Menarini, TEVA, and Novartis; and received funding support for research projects from Astrazeneca and GSK.

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

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

	Median (IQR)	% agreement
<b>Pregnancy and menstruation:</b> It is essential that pregnant women with asthma do not discontinue their asthma maintenance treatment and follow-up visits.	9 (0)	98.75
<b>Bronchiectasis:</b> Bronchiectasis should be suspected (and therefore chest HRCT requested) in patients with asthma and bronchial hypersecretion.	9 (1)	93.75
<b>Anxiety and depression:</b> In patients with associated psychomorbidity, adherence to anti-asthmatic therapy should be assessed as objectively as possible (by TAI and/or medication withdrawal record).	9 (1)	92.50
<b>Nasal polyposis:</b> All patients with severe asthma should be asked with specific questions about the presence of chronic rhinitis with or without polyposis.	9 (0)	100.00
<b>Functional dyspnea:</b> 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
<b>Obesity:</b> Obesity favors the overdiagnosis of asthma, making the use of objective diagnostic methodology essential.	9 (1)	95.00
<b>Gastroesophageal reflux:</b> 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
<b>Smoking:</b> During the anamnesis of any asthmatic patient should be asked about the habit of smoking, both in its conventional form and other forms of smoking (electronic cigarettes, hookahs, pipes...)	9 (0)	100.00

CPAP: Continuous Positive Airway Pressure; EDAC: Excessive Dynamic Airway Collapse; HRCT: high-resolution computed tomography; ILO: Inducible Laryngeal Obstruction; IRQ: interquartile range; OSA: obstructive sleep apnea syndrome; TAI: Test of Adherence to Inhalers; TBM: tracheobronchiomalacia.