



Special Article

Consensus Document on the Overlap Phenotype COPD–Asthma in COPD[☆]

Juan José Soler-Cataluña,^{a,*} Borja Cosío,^b José Luis Izquierdo,^c José Luis López-Campos,^d José M. Marín,^e Ramón Agüero,^f Adolfo Baloira,^g Santiago Carrizo,^e Cristóbal Esteban,^h Juan B. Galdiz,ⁱ M. Cruz González,^j Marc Miravittles,^k Eduard Monsó,^l Teodoro Montemayor,^m Josep Morera,ⁿ Francisco Ortega,^d Germán Peces-Barba,^o Luis Puente,^p José Miguel Rodríguez,^p Ernest Sala,^b Jaume Sauleda,^b Joan B. Soriano,^q José Luis Viejo^r

^a Hospital General de Requena, Requena, Valencia, Spain

^b Hospital Universitario Son Espases, Palma de Mallorca, Spain

^c Hospital Universitario de Guadalajara, Guadalajara, Spain

^d Hospital Virgen del Rocío, Sevilla, Spain

^e Hospital Universitario Miguel Servet, Zaragoza, Spain

^f Hospital Universitario Marqués de Valdecilla, Santander, Spain

^g Hospital de Montecelo, Pontevedra, Spain

^h Hospital de Galdakao-Usansolo, Bilbao, Spain

ⁱ Hospital de Cruces, Bilbao, Spain

^j Hospital Clínico Universitario, Valencia, Spain

^k Hospital Clínic, Barcelona, Spain

^l Hospital Parc Taulí, Sabadell, Barcelona, Spain

^m Hospital Virgen Macarena, Sevilla, Spain

ⁿ Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain

^o Fundación Jiménez Díaz CIBERES, Madrid, Spain

^p Hospital Gregorio Marañón, Madrid, Spain

^q Fundación Caubet-CIMERA, Bunyola, Mallorca, Spain

^r Hospital General Yagüe, Burgos, Spain

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ABSTRACT

Introduction: Although asthma and COPD are different pathologies, many patients share characteristics from both entities. These cases can have different evolutions and responses to treatment. Nevertheless, the evidence available is limited, and it is necessary to evaluate whether they represent a differential phenotype and provide recommendations about diagnosis and treatment, in addition to identifying possible gaps in our understanding of asthma and COPD.

Methods: A nation-wide consensus of experts in COPD in two stages: (1) during an initial meeting, the topics to be dealt with were established and a first draft of statement was elaborated with a structured “brainstorming” method; (2) consensus was reached with two rounds of e-mails, using a Likert-type scale.

Results: Consensus was reached about the existence of a differential clinical phenotype known as “Overlap Phenotype COPD–Asthma”, whose diagnosis is made when 2 major criteria and 2 minor criteria are met. The major criteria include very positive bronchodilator test (increase in FEV₁ ≥15% and ≥400 ml), eosinophilia in sputum and personal history of asthma. Minor criteria include high total IgE, personal history of atopy and positive bronchodilator test (increase in FEV₁ ≥12% and ≥200 ml) on two or more occasions. The early use of individually adjusted inhaled corticosteroids is recommended, and caution must be taken with their abrupt withdrawal. Meanwhile, in severe cases the use of triple therapy should be evaluated. Finally, there is an obvious lack of specific studies about the natural history and the treatment of these patients.

Conclusions: It is necessary to expand our knowledge about this phenotype in order to establish adequate guidelines and recommendations for its diagnosis and treatment.

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* Corresponding author.

E-mail address: jjsoler@telefonica.net (J.J. Soler-Cataluña).

Documento de consenso sobre el fenotipo mixto EPOC-asma en la EPOC

R E S U M E N

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Introducción: Aunque asma y EPOC son enfermedades distintas, muchos pacientes comparten características de ambas entidades. Estos casos pueden tener una evolución y una respuesta al tratamiento diferente. Sin embargo, la evidencia disponible es escasa, y es necesario valorar si representan un fenotipo diferencial y aportar recomendaciones sobre su diagnóstico y tratamiento, además de identificar posibles lagunas de conocimiento.

Método: Consenso nacional de expertos en EPOC en dos etapas: 1) Se establecieron los bloques temáticos a tratar y se elaboró una primera propuesta de aseveraciones, mediante una reunión presencial con metodología de «tormenta de ideas» estructurada. 2) Se realizaron dos rondas de consenso vía correo electrónico, utilizando una escala tipo Likert.

Resultados: Se consensua la existencia de un fenotipo clínico diferencial denominado «fenotipo mixto EPOC-asma», cuyo diagnóstico se realizará si se cumplen 2 criterios mayores o uno mayor y 2 menores (criterios mayores: prueba broncodilatadora muy positiva [aumento del FEV₁ ≥ 15% y ≥ 400 ml], eosinofilia en esputo y antecedentes personales de asma; criterios menores: IgE total elevada, antecedentes personales de atopia y prueba broncodilatadora positiva [aumento del FEV₁ ≥ 12% y ≥ 200 ml] en dos o más ocasiones). Se recomienda el uso precoz de corticoides inhalados (CI) ajustados individualmente, ser cautos con la retirada brusca de CI y, en casos graves, valorar el uso de la triple terapia. Finalmente, queda patente la falta de estudios específicos sobre la historia natural y el tratamiento de estos pacientes.

Conclusiones: Es preciso profundizar en el conocimiento de este fenotipo para establecer pautas y recomendaciones adecuadas para su diagnóstico y tratamiento.

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Introduction

Both chronic obstructive pulmonary disease (COPD) and bronchial asthma are chronic inflammatory diseases that affect the airway and are essentially characterized by the presence of bronchial obstruction. However, and despite these similarities, both the etiopathogenic base as well as the diagnostic, therapeutic or prognostic characteristics of both pathologies are different, and they therefore constitute nosologic entities. COPD is characterized by the presence of chronic obstruction and is not very reversible to airflow associated with an anomalous inflammatory reaction, mainly tobacco smoke.¹ The characteristic inflammatory infiltrate is mainly made up of macrophages, neutrophils and cytotoxic T lymphocytes (CD8+).¹ Contrarily, asthma is defined as a chronic inflammatory disease of the respiratory tract. It is partially conditioned by genetic factors and runs its course with bronchial hyperresponsiveness and airflow obstruction, which either totally or partially reverses spontaneously or by medicinal action. Unlike COPD, chronic inflammation of the airway is characterized by the activation of mast cells, an increase in the number of activated eosinophils, T lymphocyte cooperators with a profile of predominant Th2 cytokines and natural killer cells.²

In cases with typical presentation, the differential diagnosis between the two diseases is not usually difficult. COPD commonly appears after the age of 40, is associated with a previous history of smoking and generally presents airflow reversibility that is not very significant. In contrast, asthma usually presents at earlier ages, is not associated with smoking, has more variable symptoms (especially seasonal) and the obstruction is usually reversible. However, the clinical reality is more complicated, and we frequently see patients with a certain degree of overlapping, which leads to diagnostic and therapeutic doubts. Some asthma patients are smokers and they present characteristics similar to COPD, with greater neutrophilic inflammation, an accelerated decline in lung function or poorer response to bronchodilators or to corticosteroids.³ In the same way, we also see COPD patients who present characteristics that are traditionally attributable to asthma, such as a certain amount of eosinophilia in the sputum or an important reversibility after the administration of a bronchodilator.^{4,5} In fact, the UPLIFT study⁴ has recently demonstrated that somewhat more than 50% of COPD cases have significant reversibility. Siva et al.⁵ have also confirmed that treatment with inhaled corticosteroids in COPD

patients who presented eosinophilia in the sputum (defined as a presence of more than 3% of eosinophils) significantly reduces exacerbations, but not in patients without significant eosinophilia.

The patients in whom the characteristics of the two diseases overlap could potentially have different responses to treatment and evolutionary course.^{6,7} Nevertheless, until now they have usually been excluded from clinical assays, both for asthma as well as COPD; therefore, the existing scientific evidence about their diagnosis and treatment is scarce.⁸ Under these circumstances, the expert consensus opinion may be the first step towards the nosologic recognition of this entity and towards its detailed study in the future. In fact, the term COPD, which we now use with no restrictions, arose from a consensus of experts.⁹

The main objective of this consensus document was to learn the general opinion about the existence of a differential clinical phenotype in patients who share COPD and asthma characteristics. In addition, we proposed to establish a name for this entity, provide asseverations and recommendations for its diagnosis and treatment, and identify the main gaps in the research that would be recommendable to deal with in the future.

Methods

The consensus process was done in two phases. During the first phase, we established a coordinating group made up of 5 pulmonologists who are experts in COPD. These experts defined three topic areas of interest to deal with (existence and diagnosis of a different phenotype [COPD–asthma], treatment for this subgroup and research gaps). Later, a bibliographic search was completed in order to establish affirmations and recommendations for each of these areas. From this previous work, 5 asseverations arose for each area.

These 15 asseverations were presented and discussed at a meeting on March 12, 2011 with the attendance of 23 pulmonologists/COPD experts from all over Spain. Participants were selected according to their extensive clinical, research and/or teaching experience, in addition to their professional relevance in COPD, while also focusing on a certain degree of geographical distribution. Initially, a group of 30 pulmonology specialists were invited to participate, but 7 (23%) were unable to attend the meeting due to scheduling problems. For the group discussion, a structured brainstorming method was used (Metaplan technique).¹⁰ This technique

Table 1
Likert Scale Used for Assessing the Consensus Points.

1	2	3	4	5	6	7
"Block" Disagree	Disagree	Skeptical Uncertain	Don't know./Can't say.	Agree, with some reservations Agree	Agree, but with minor discrepancies	Agree

consists of obtaining ideas and structured knowledge from a group of experts. In this technique, the moderator poses previously established questions to the panel of experts who, after some minutes of individual reflection, write their answers on notecards. The ideas are then read aloud and debated by the group in order to obtain points of consensus and dissention.

During the second phase, we carried out 2 new rounds of consensus by e-mail. Each affirmation or point to be agreed on was sent to each pulmonologist for voting. A Likert-type scale was used, adapted by Kaner et al.,¹¹ with a scale from 1 to 7, 1 being total disagreement or a "block" and 7 total agreement with the idea proposed. In order to establish consensus, we grouped the scores into 3 groups: disagreement with the proposal (votes obtained between 1 and 2 points), uncertain (votes between 3 and 4) and agreement (votes between 5 and 7 points) (Table 1). For each group, the percentage of responses was calculated. It was agreed that consensus would be reached for ideas whose percentage in the agreement block were higher than $\geq 70\%$. This second phase tried to define major and minor diagnostic criteria.

In the first round, the question was in regard to the name of the clinical entity and the identification of its diagnostic criteria. For the identification of the name, each participant needed to evaluate three proposals and put them in order by preference.

In the second round, items that had nearly reached consensus in the first round were asked once again (percentages of response in the agreement group were between 60% and 70%). As for the diagnostic criteria selected (reaching more than 70% of agreement), each participant was asked to indicate which could be major criteria, and the criteria were considered major if the degree of agreement surpassed 70%. The criteria that did not reach consensus to be major criteria were defined as minor criteria. Once the diagnostic criteria were labeled as major or minor, we aimed to reach consensus to define the number of major and/or minor criteria necessary for recognizing this phenotype. In addition, this second round evaluated the asseverations presented on the first day of the meeting that had been reformulated according to the comments and results from said meeting.

For the data analysis, all the responses were transferred to a Microsoft Office Excel (2010) spreadsheet and the voting percentage was calculated for each point group on the scale used. As an exception, for the number of diagnostic criteria necessary for identifying the pathology, the average was used with the aim to reduce the number of diagnostic criteria necessary and to thus simplify the detection of this phenotype.

Results

All the participants agreed on the existence of a specific group of patients who share characteristics of both asthma and COPD, whose diagnosis and treatment may be different from the traditional approach used for COPD or asthma patients.

Identification of a Name for the Phenotype

Different proposals were presented: eosinophilic phenotype, hyperreactive phenotype and mixed COPD–asthma phenotype. Although there were two names with a consensus higher than 70%, the name that was chosen in the end was "mixed COPD–asthma phenotype" as it had obtained a consensus of 83%, and 72% of the

panel had prioritized this name as their first choice, as can be seen in Table 2.

Identification of the Diagnostic Characteristics of the Phenotype: Major and Minor Criteria

Table 3 shows the diagnostic criteria selected with the percentage of agreement obtained and those that were ruled out in the end. Table 4 presents the criteria considered as either major or minor. The major criteria selected were: *very positive bronchodilator test* (increase in FEV₁ $\geq 15\%$ and ≥ 400 ml over baseline value), *eosinophilia in sputum* and *personal history of asthma*. The minor criteria were: *total high IgE*, *personal history of atopy* and *positive bronchodilator test* (increase in FEV₁ $\geq 12\%$ and ≥ 200 ml over baseline value) on 2 or more occasions. In addition, it was agreed upon that it would be necessary for there to be 2 major criteria or 1 major and 2 minor criteria to correctly diagnose this clinical entity.

Consensus on Asseverations

Table 5 shows the degree of agreement reached for each of the affirmations related with the existence, treatment and gaps in understanding proposed for research in the first phase

Table 2
Proposed Names for the Clinical Entity Being Assessed: Percentages Agreeing With Each Name and the Assessment of the Top Position Over the Other Two Names.

Proposed Names	% Agreement	% in First Position
Eosinophilic phenotype	72	0
Hyperreactive phenotype	61	28
Mixed COPD/asthma	83	72

Table 3
Diagnostic Criteria of the Phenotype: Consensus Criteria.

Diagnostic Criteria of the Mixed COPD/Asthma Phenotype That Had Been Agreed Upon	% Agreement
Very positive bronchodilator test (increase in FEV ₁ $\geq 15\%$ and ≥ 400 ml over baseline)	94
Eosinophilia in sputum	94
Positive bronchodilator test (increase in FEV ₁ $\geq 12\%$ and ≥ 200 ml over baseline) on 2 or more occasions	89
Personal history of asthma (history before the age of 40)	78
High total IgE	78
Personal history of atopy	78
Criteria That Were NOT Agreed Upon as Diagnostic Characteristics of the Mixed COPD/Asthma Phenotype	% Agreement
Peripheral eosinophilia	67
Seasonal or unusual symptom variability	61
Positive skin prick tests	50
High FeNO	50
Positive methacholine test	50
Variability of (FEM) >20%	50
Family history of asthma and/or atopy	50
Rhinitis (any type)	44
Reversibility in current bronchodilator test	44
Positive oral corticosteroid test	44

FEM, maximal expiratory flow; FeNO, exhaled nitric oxide fraction; FEV₁, forced expiratory volume in one second.

Table 4
Major and Minor Criteria for the Identification of the Mixed COPD/Asthma Phenotype.

Diagnostic Criteria of the Mixed COPD/Asthma Phenotype That Were Agreed Upon ^a	% of Agreement in Order to Be Considered a Major Criterion ^b	Type of Criterion
Very positive bronchodilator test (increase of FEV ₁ ≥15% and ≥400 ml over baseline)	83	Major
Eosinophilia in sputum	78	Major
Personal history of asthma (history before the age of 40)	78	Major
High total IgE	50	Minor
Personal history of atopy	50	Minor
Positive bronchodilator test (increase in FEV ₁ ≥12% and ≥200 ml over baseline) on 2 or more occasions	39	Minor

^a This table only includes the criteria that the panel of experts considered to be diagnostic criteria for the mixed COPD–asthma phenotype, with a minimum response in the agreement block of 70%.

^b The criteria with a minimum of 70% agreement in order to be major diagnostic criteria were considered major criteria, and the rest were considered minor.

of the process and then reformulated in the second phase. It also cites the bibliographic reference from which each asseveration/recommendation had been adapted. Only two of the asseverations sent to the experts were not agreed upon.

Table 5
Summary of the Asseverations and Recommendations Agreed Upon by the Panel of Experts, Percentage of Agreement and Reference From Where It Was Adapted.

Consensus Asseveration	% Responses in the Agreement Block	Adapted From (Bibliographic Ref.)
<i>Existence of the phenotype</i>		
There is a COPD phenotype called mixed COPD–asthma that is occasionally difficult to separate from asthma with some of the following characteristics: eosinophilia in sputum, very positive bronchodilator test (increase in FEV ₁ ≥15% and ≥400 ml over baseline), positive bronchodilator test (increase in FEV ₁ ≥12% and ≥200 ml over baseline) on 2 or more occasions, personal history of asthma (history prior to the age of 40, including allergic rhinitis), high total IgE and personal history of atopy)	90	3,12
It cannot be ruled out that this subgroup may have a pathogenic base with some similarities with asthma, and that it is aggravated by smoking	100	13
This group of patients with mixed COPD–asthma phenotype has been systemically excluded from clinical assays (which usually include only typical COPD or asthma patients); therefore, the level of evidence about treatments and their effectiveness is very limited.	100	8
It is necessary to identify the mixed COPD–asthma phenotype by its symptoms, as its natural history, morbidity and mortality, prognosis and treatment may differ	100	5,14
Currently, and with the lack of contradictory evidence, these patients may benefit from a clinical management similar to asthma as the phenotype has clinical characteristics that suggest a greater effectiveness of anti-inflammatory treatment	85	5,15
<i>Treatment of the phenotype</i>		
In all the patients with mixed COPD–asthma phenotype, the early administration of inhaled corticosteroid treatment should be assessed	100	5,15
As in asthma, in patients with mixed COPD–asthma phenotype the dosage of inhaled corticosteroids should be adjusted according to the control of the symptoms, lung function and/or the presence of eosinophils in sputum	75	16
In severe cases of patients with COPD and mixed COPD–asthma phenotype, triple therapy with a long-acting anticholinergic, a long-acting beta-2 agonist and an inhaled corticosteroid may be indicated	90	17
In patients with COPD and mixed COPD–asthma phenotype, the abrupt withdrawal of maintenance treatment with inhaled corticosteroids may produce exacerbations in some patients, although there is not sufficient evidence in this type of patients	80	18,19
<i>Gaps in our understanding that should be researched</i>		
More evidence would be necessary to affirm that the mixed COPD–asthma phenotype treated with inhaled corticosteroids has fewer exacerbations or better survival than when not treated. However, the clinical experience leads one to believe that this asseveration is true	90	20
Unlike asthma or COPD, there are few controlled, randomized studies about the mixed COPD–asthma phenotype whose main objective is to reduce bronchial inflammation	95	3
The use of the exhaled fraction of nitric oxide to predict the response to corticosteroids in patients with COPD has shown contradictory results for evaluating heterogeneous COPD populations. However, its role in patients with mixed COPD–asthma phenotype and in the long-term is unknown	95	21–24
The presence of pneumonia should be studied in the mixed COPD–asthma phenotype due to the use of inhaled corticosteroids (and if this effect is dose- and molecule-dependent)	85	25
In patients with COPD and mixed COPD–asthma phenotype, the isolated use of long-acting bronchodilators should be watched because cases of increased mortality in bronchial asthma have been detected	60	26
<i>Gaps in our understanding that should be researched</i>		
Inflammation in the mixed COPD–asthma phenotype is partially resistant to corticosteroids	50	27

ND, not available (proposed by the expert panel).

Discussion

The insistence on adequately distinguishing between COPD and asthma and the obsession for systematically excluding patients with asthma from COPD studies, or vice versa, have blurred the ability to recognize a group of patients who share characteristics from both diseases, which translates into a notable lack of specific information. Under these circumstances, we believe that the consensus reached among experts constitutes the first step for the nosologic recognition of the phenotype. It is also a useful alternative for establishing recommendations that allow us to at least guide clinical decisions and/or establish research necessities. In this direction, and related with the present document, we should emphasize the high level of consensus reached for the majority of the affirmations or recommendations proposed, which are discussed below.

Existence of the Clinical Phenotype

The clinical phenotype in COPD is defined as the existence of certain characteristics of the disease, which either alone or combined describe differences between individuals with COPD regarding parameters that have clinical significance (symptoms, exacerbations, response to treatment, speed of progression of the disease or death).²⁸ Therefore, in order to be able to establish that the group of patients that present overlapping characteristics

of asthma and COPD constitute a specific clinical phenotype, it should be demonstrated that these patients present a differential behavior. Some data in the literature aim in this direction, but the scientific evidence is still limited. Hardin et al.,²⁹ in the heart of the COPDgene study, have recently observed that patients with COPD and a history of asthma present poorer health-related quality of life and a greater probability of having had severe exacerbations in the previous year or of presenting frequent exacerbations (OR=3.55; 95% CI: 2.19–5.75; $p<.001$). Although the study points out important differences between the group with COPD and asthma versus those who only have COPD, the design was cross-sectional. It is therefore unknown if both groups have a differential evolution. In this context, Hoppers et al.³⁰ demonstrated that the presence of bronchial hyperresponsiveness in COPD patients is associated with a poorer prognosis. However, the study has been criticized because the degree of bronchial hyperresponsiveness is related with airway diameter and the authors did not properly adjust the data for lung function. In a recent publication of the ECLIPSE study, it was observed that patients with bronchial hyperreactivity present a greater fall in FEV₁ over time.³¹ In another study, a British group of researchers demonstrated in a randomized, controlled clinical study that COPD patients who present eosinophilia in sputum have a better response to inhaled corticosteroids, which translates into a lower frequency of exacerbations.⁵ Despite this scarcity of studies, an almost unanimous consensus was detected for accepting the existence of this clinical phenotype, and it is believed that both its natural history as well as its morbidity and mortality, prognosis and treatment may be different. This opinion agrees with the proposal that was recently communicated by the GESEPOC workgroup (in the future Spanish clinical guidelines for COPD), which anticipates the existence of 3 clinically relevant phenotypes: the exacerbator phenotype, the emphysema-hyperinflated phenotype and, specifically, the *overlap* or mixed COPD–asthma phenotype.³²

Proposed Name: COPD–Asthma Mixed Phenotype

The name that was finally selected to define this differential entity was the “mixed COPD–asthma phenotype”. This term not only represents the preference expressed by the majority (82% of participants), but it also emphasizes the ambiguity of this phenotype. This is important to keep in mind in order to avoid these patients being pigeonholed into one group or the other. Other terms, like “asthma-like COPD”, “hyperactive COPD” or “eosinophilic COPD”, were rejected. The first of these was ruled out because it denoted a certain preponderance of the characteristics of one disease over the other. The other two were not appropriate because the name itself would require diagnostic tests, such as bronchial provocation or the determination of eosinophilia in sputum, which are not available at all health-care centers.

Diagnostic Criteria

For the clinical identification of this mixed phenotype, 6 diagnostic criteria were agreed upon and grouped as either major or minor, requiring a combination of 2 major diagnostic criteria, or instead one major and two minor criteria, in order to confirm diagnosis (Table 4). To select the diagnostic criteria, an agreement level of at least 70% was used. However, the average was used for selecting how many diagnostic criteria would be necessary for the identification of the pathology. In our opinion, this is an advantage because this way less necessary criteria are obtained than with the use of the arithmetical median, which may make recognizing this pathology easier, especially in primary care. An excessive requirement in the number of criteria to be used could lead to a lower detection of the phenotype in primary care, relegating its diagnosis to specialized care alone. We should promote its correct diagnosis

at the family medicine level to increase diagnosis and treatment at earlier phases of the pathology, reduce morbidity and improve the quality of life of these patients.

Treatment Recommendations

Most comments, discussion and contributions from the panel of experts had to do with treatment. Nevertheless, enough of a consensus was reached in order to establish that, currently, and without any scientific evidence to contradict it, these patients may benefit from a treatment similar to that of asthma as they have clinical characteristics that suggest greater effectiveness of the anti-inflammatory treatment. Thus, the document recommends using inhaled corticosteroids early on in all patients with the mixed COPD–asthma phenotype and, as in asthma, it also recommends adjusting the dosage according to the control of the symptoms, lung function and/or the presence of eosinophils in sputum. The dosage adjustment was initially proposed to be gradual or in steps, but the lack of sufficient scientific evidence to back this justified the modification of the affirmation (Table 5). Due to the nature of COPD itself and, unlike asthma, in all cases the use of corticosteroids should be associated with long-acting bronchodilators. In cases of worsened symptoms, the consensus also recommends assessing the triple association of inhaled corticosteroids, long-acting beta2-agonists and also long-acting muscarinic antagonists. Welte et al.¹⁷ have demonstrated good results after the use of triple therapy in patients with severe COPD, and many with great airflow reversibility. Thus, good results are foreseen with this combination in patients with the mixed phenotype in a more serious stage of the disease. Finally, and although a recent paper indicates the contrary,³³ consensus was reached to use caution when withdrawing inhaled corticosteroids in these patients, as this could cause new exacerbations.^{18,19}

Future Research

As has been widely commented, the existence of this mixed phenotype poses several unknowns that need to be evaluated scientifically. There is consensus for the need to identify these patients and to evaluate their long-term condition in order to confirm that they really behave as a specific clinical phenotype with differential clinical events (exacerbations, mortality, etc.). From a diagnostic point of view, it seems necessary to validate the consensus proposal and to review whether new diagnostic criteria should be incorporated. In this direction, it is expressly recommended to assess the utility of the exhaled fraction of nitric oxide (FeNO). The results obtained to date are contradictory, probably because the population selected is heterogeneous and does not include the mixed phenotype that is now proposed,^{21–24} which perhaps justifies not including FeNO as a current diagnostic criterion. As for future research in the field of therapy, it is recommended to specifically assess the inflammatory profile of these patients and their response to treatment. It is also recommended to evaluate whether these patients have a higher risk for pneumonia related with the use of inhaled corticosteroids or if the comorbidities are similar to those of the rest of COPD patients.

In closing, we hope that the tools provided by this document work as a stimulus and make it easier to detect patients with mixed COPD–asthma phenotype, both in our pulmonology consultations as well as in primary care. We also hope that this consensus is a base for promoting several studies directed at better understanding of this phenotype (prevalence, most appropriate treatment, prognosis, etc.), because there is an obvious lack of clinical evidence that would enable us to address many doubts.

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Conflict of Interests

- Juan José Soler-Cataluña has received fees for scientific consulting and/or for giving conferences from Almirall, AstraZeneca, Boehringer Ingelheim, Ferrer, GlaxoSmithKline, Laboratorios Esteve, Pfizer, Novartis, Merck Sharp & Dhome and Nycomed.
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