Asthma-Chronic Obstructive Pulmonary Disease Overlap in Spain: Anything Special?

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ABSTRACT

The asthma-chronic obstructive pulmonary disease overlap (ACO) has recently attracted attention and triggered debate as evidenced by the proliferation of articles, reviews and editorials dedicated to this topic. Most of this debate is based on the lack of a consistent definition and the scarce knowledge of its underlying mechanisms. Spain has been very active in pursuing a better understanding of this topic and in developing a clearer definition to help clinicians identify and treat this condition correctly. This paper reviews the current evidence supporting its existence and the latest findings related to its mechanisms and it points out the limitations of using the classic labels to classify chronic airways diseases. (BRN Rev. 2018;4(4):245-57)

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THE CURRENT CONTROVERSY ON ASTHMA-CHRONIC OBSTRUCTIVE PULMONARY DISEASE OVERLAP

Chronic obstructive pulmonary disease (COPD) and asthma are two highly prevalent inflammatory diseases characterised by airflow obstruction that have different pathogenic mechanisms and different degrees of response to anti-inflammatory treatment. In the last decade, there has been increasing interest in an entity now named asthma-COPD overlap (ACO), which some authors have come to consider as the asthma-COPD overlap syndrome (ACOS), although even this concept has been refuted\(^1\). The term ACO has attracted much attention and triggered debate, as evidenced by the proliferation of reviews and editorials dedicated to this topic\(^2\)\(^-\)\(^4\), to the extent that some authors have claimed that even the acronym “chaos” might better describe the current situation of diverging definitions\(^5\). However, this interest is not new, and was already promoted by the studies of Burrows et al.\(^6\) in 1987, describing a group of patients who had a clinical evolution and a prognosis in between asthma and COPD that were named “asthmatiform bronchitis”, supporting the view of a common origin of asthma and COPD, the so-called Dutch hypothesis\(^7\). Recent studies of lung function trajectories in COPD also support the influence of early childhood asthma in early lung development\(^8\). The reason for this renewed interest has to do, on the one hand, with the proposal of identification of phenotypes with different prognosis and response to therapy in COPD and, on the other, with the warnings provoked by the indiscriminate use of inhaled corticosteroids (ICS) in patients with COPD that have led to an increased signal of pneumonia in some clinical trials.

Taking apart the academic discussions and, in keeping with Burrows’ observations, the reality is that some patients frequently appear with clinical characteristics that overlap both diseases. These real-life patients are not clearly represented in clinical trials and may have different evolution and prognosis, especially in the most severe forms, so their early identification is important. Biomarkers such as periostin\(^9\), eosinophilia in sputum and/or blood, bronchial hyperresponsiveness (BHR) or hyperreactivity or nitric oxide (NO) in exhaled air\(^10\) have shown equivocal results. There is some controversy regarding the clinical and prognostic influences of ACO, not to mention that there are authors that question its own existence, or the criteria used to define it. Some studies\(^11\)\(^,\)\(^12\) conclude that this situation leads to more frequent and serious exacerbations as well as worse health-related quality of life, while others indicate the opposite\(^13\). In this review we will try to clarify the impact that the presence of ACO may have, how to identify it in a simple way, and review its treatment.

ASTHMA-CHRONIC OBSTRUCTIVE PULMONARY DISEASE OVERLAP IN SPAIN

Spain has produced a major contribution in the development of the phenotype-based approach to COPD management. The Spanish Guideline for COPD (GeSEPOC) was a starting point that has been mimicked by other countries\(^14\), and it was the first to introduce a specific category for the overlap between asthma and COPD. This point, despite being controversial, has led to a fruitful scientific debate and international recognition of the
role of this innovative approach to guide COPD therapy. Moreover, some authors have suggested a new alphabet for COPD care, adding an “E” to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) ABCD, where “E” stands for “España” (Fig. 1). In keeping with this, the Characterization of ACO in Spain study (CHACOS), promoted by the Spanish Thoracic Society (SEPAR) and funded by the Spanish Health Institute Carlos III and Chiesi Spain, has been a cornerstone of this concept. It started from the hypothesis that the coincidence of COPD and asthma in the airway in the same patient should result in an inflammatory process that groups the biological characteristics of each of them. Therefore, its objective was to find clinical, functional or biomarker characteristics that would differentiate patients with ACO from others with COPD or with asthma and chronic airflow obstruction. With a cross-over design and the participation of researchers from 23 Spanish hospitals, CHACOS recruited 292 patients > 40 years with a post-bronchodilator ratio of forced expiratory volume in the one second over vital capacity (FEV₁/FVC) < 0.70, of which 94 were non-smoking asthmatics, 89 had COPD and 109 were qualified

**Figure 1.** A proposed new grading system for chronic obstructive pulmonary disease (COPD) management that includes an E box for asthma-COPD (ACO) (adapted from Young et al.15, reproduced with permission from the ©ERS 2018).

ACOS: Asthma-COPD syndrome; ICS: inhaled corticosteroids; LABA: long-acting β₂-agonist; LAMA; long-acting muscarinic antagonist; SABA; short-acting β₂-agonist; SAMA: short-acting muscarinic antagonist; SOB: shortness of breath.
as ACO according to two criteria: chronic airflow obstruction in patients with previous diagnosis of asthma and smoking history ≥ 20 pack-years (asthmatic smokers, 44 patients) or COPD with elevated eosinophils in blood ≥ 200 cells/μL (65 cases) which we call “eosinophilic COPD (e-COPD)”. In this review we aim to explain the current view of this controversial concept based on the evidence generated from different studies and the clinical experience of the authors.

**ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE: SIMILARITIES AND DIFFERENCES**

Chronic obstructive pulmonary disease and asthma share a series of clinical similarities that often make their differentiation complex, especially in smokers with a history of atopy. However, both processes can have a pathogenetic and pathophysiological basis easily differentiable in most cases (Fig. 2)¹⁵. The clinical characteristics shared by both diseases are based on inflammation and obstruction of the airways, the latter being poorly reversible and progressive in COPD and variable and reversible in asthma. Likewise, the location of the inflammatory response among these pathologies also has differences, being the predominant involvement of COPD in peripheral airways and lung parenchyma, in contrast to the lack of lung parenchyma damage and the pan-focal involvement of the airway in asthma. The cellular count obtained from the bronchial-alveolar lavage, induced sputum and bronchial biopsies in patients with COPD, demonstrate a predominant presence of neutrophils, CD8+ T lymphocytes and abundant macrophages, whereas in asthma, eosinophils, mast cells, CD4+ T lymphocytes and a smaller number of macrophages are the representative cells¹⁵. Inflammatory mediators also differ, with leukotriene-B4 (LTB4), interleukin-8 (IL-8) and tumour necrosis factor-alpha (TNF-α) among others, playing a predominant role in the case of COPD. Multiple inflammatory mediators have been found in asthma¹⁶, such as histamine, leukotrienes, IL-4, -5 and -13. The fraction of exhaled NO in patients with asthma is increased, reflecting the greater eosinophilic inflammation. The role of oxidative stress, although present in both situations, is more prevalent in COPD than in asthma, as a consequence of the increased activation of neutrophils and macrophages associated with the deleterious effect of cigarette smoke. The presence of BHR, defined as an “exaggerated bronchoconstrictor response to a variety of physical, chemical or biological stimuli”, is characteristic of asthma and is partially correlated with the severity of the disease and with markers of inflammation. In COPD, as

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**Figure 2.** The asthma-chronic obstructive pulmonary disease overlap (ACO) summary represented in a Venn diagram. AHR: airway hyperresponsiveness; COPD: chronic obstructive pulmonary disease.
we will discuss later, the presence of BHR is not considered a predominant finding\textsuperscript{17}. However, when analysing the behaviour of BHR in people older than 65 years, smokers and non-smokers, an association with excessive loss of lung function measured through FEV\textsubscript{1} was found\textsuperscript{18}. The consequence of the inflammatory cascade in both disorders causes a progressive and little reversible loss of lung function in COPD that is characterised by a bronchiolitis that evolves to fibrosis, where it is possible to observe areas of epithelial metaplasia of the mucus-producing cells. The remodelling of the airway present in asthma, due to the deposition of sub-epithelial collagen and the hypertrophy of the bronchial smooth muscle, may be responsible for the progression of the loss of lung function in persistent asthma. Despite these clear differences, both are heterogeneous disorders and they need to be differentiated into clinical phenotypes (exacerbator/non-exacerbator, chronic bronchitis/emphysema for COPD; early/late onset, T2-high/T2-low for asthma) to get a more precise management.

There are, however, situations in which the inflammatory profile of asthma and COPD are similar:

1. Severe asthma: the inflammatory pattern, unlike mild asthma, consists of predominance of neutrophils in the sputum, increased IL-8, TNF-\(\alpha\) and oxidative stress. From the therapeutic point of view, this condition presents a poor response to treatment with glucocorticoids. Unlike mild asthma in which the type 2 T helper (Th\textsubscript{2}) response predominates, in severe asthma there is a mixed Th\textsubscript{1} and Th\textsubscript{2} component in bronchial biopsies and an increase in CD8+ T lymphocytes. A pattern of neutrophilic inflammation similar to that of COPD is found in smoking asthmatic patients, who also have a poor response to both inhaled and systemic corticosteroids\textsuperscript{19}.

2. Chronic obstructive pulmonary disease with reversibility: this subgroup of patients with reversibility to bronchodilators have increased eosinophils in the induced sputum, increased levels of exhaled NO\textsuperscript{10} and better response to treatment with glucocorticoids\textsuperscript{16}, all characteristic of asthma.

3. Exacerbations: exacerbations of asthma and COPD can have common triggers (viruses, bacteria, environmental pollution, fumes). In both diseases exacerbations are associated with an increase in airway inflammation, an increase in the number of cells and higher concentrations of pro-inflammatory cytokines. Exacerbations of asthma triggered by viruses occur with an increase in neutrophils and eosinophils, whereas exacerbations of COPD may present eosinophilia in the sputum\textsuperscript{19}.

Despite being two inflammatory diseases that affect the airway, the response to anti-inflammatory treatment with glucocorticoids is not the same for both conditions, as a consequence of the different mechanisms and characteristics.

**IDENTIFICATION OF THE ASTHMA-CHRONIC OBSTRUCTIVE PULMONARY DISEASE OVERLAP AND ITS PREVALENCE**

The identification or definition of ACO has different approaches and it is therefore complex.
to estimate its prevalence, since it varies according the criteria used to define it\textsuperscript{6,18,19}. The Genetic epidemiology of COPD (COPDGene) study\textsuperscript{11} using the coexistence of the diagnostic code of asthma and COPD in the clinical history of the same patient found a prevalence of 13% of ACO. These patients may have a different natural history, with more frequent and severe exacerbations (odds ratio [OR]: 3.55), and a different response to treatment, which led to recommend the early introduction of ICS in these patients. These figures are similar to those reported in the Latin American Project for the Investigation of COPD (PLATINO)\textsuperscript{12} that used a similar definition: 12% prevalence of ACO and more risk of exacerbations in these patients (OR: 3.01). In Spain, an expert consensus\textsuperscript{20} proposed a series of major criteria (history of asthma, eosinophils in sputum > 5% or bronchodilator test > 400 ml and > 15%) and minor criteria (immunoglobulin E [IgE] > 100, allergy and two or more bronchodilator tests > 200 ml and 12%) that were later adopted by the Spanish COPD guidelines. Later on, a study in the COPD History Assessment In Spain (CHAIN) cohort found a very low prevalence of ACO using these criteria (0.5%) and proposed a modification of the major and minor criteria of the initial proposal of GeSEPOC including eosinophilia in peripheral blood (greater than 5%) as a minor criterion, finding a prevalence of 15% (Fig. 3). Using these modified criteria, ACO patients seemed to show lower mortality rates after one year of follow-up\textsuperscript{13}, the same that was shown by the Hokkaido cohort after 10 years of follow-up\textsuperscript{21}.

So, where should we go now? In case of doubt, we can always use guidelines. The Global Initiative for Chronic Obstructive Lung Disease includes a consensus document with the Global Initiative for Asthma (GINA), which defines ACO and proposes a different approach in which at least three characteristics of asthma and three of COPD, taken from a given list of symptoms and clinical characteristics, should be fulfilled in the same patient\textsuperscript{22}. The 2017 update of GesEPOC\textsuperscript{14}, recognises the existence of an ACO phenotype, and a joint commission with the Spanish Guideline for Asthma (GEMA) proposed a unified diagnostic algorithm\textsuperscript{23} (Fig. 4). According to this proposal, the diagnosis will be confirmed based on the following sequential evaluation:

1. Presence of chronic airflow limitation (post-bronchodilator FEV\textsubscript{1} / FVC < 0.70) in a patient ≥ 35 years old, smoker or ex-smoker with a smoking history of at least ten pack-years. In newly diagnosed patients, this criterion will be re-evaluated after treatment with a long-acting \(\beta\textsubscript{2}\)-agonist (LABA) and inhaled glucocorticoid and follow-up of at least six months; in some cases it is advisable to carry out a short course (15 days) of oral glucocorticoids as well. The reversal of spirometric obstruction after these treatments will rule out the diagnosis of ACO in favour of asthma.

2. Current diagnosis of asthma, that should include: a) history and/or symptoms of clinical suspicion: family history of asthma or personal history of asthma in childhood or personal history of atopy (sensitisation to certain allergens), with respiratory symptoms (wheezing, cough, chest tightness) of variable course, sometimes in the form of dyspnoea, crisis of also variable intensity, or inflammation of the upper airway (rhinosinusitis with or without nasal...
polyposis); and b) objective diagnostic confirmation of asthma with reversibility of airflow obstruction by spirometry or a bronchodilator test (BT) (≥ 12% and ≥ 200 ml), or a circadian variability of peak expiratory flow (PEF) ≥ 20% or an exhaled fraction of nitric oxide (FeNO) ≥ 50 part per billion (ppb).

3. In the event that the diagnosis of asthma cannot be established, the diagnosis of ACO will be confirmed in the presence of a very positive BT (≥ 15% and ≥ 400 ml); or, in the presence of eosinophilia in blood (≥ 300 eosinophils/μL) or both. These characteristics, although they are not diagnostic of asthma by themselves, point towards the existence of a high-Th₂ inflammatory pattern, which in a smoking patient with chronic airflow obstruction, allows to classify it as ACO.

However, we have recently evaluated these criteria in the CHACOS study population and it was found that patients with a diagnosis of ACO according to the criteria of this new consensus are indistinguishable from non-smoking asthmatics or COPD patients without eosinophilia²⁴. This finding strongly challenges the adequacy of the current algorithm, and even questions the existence of a specific phenotype with perceptible clinical

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**Figure 3.** Major and minor criteria using to diagnose asthma-chronic obstructive pulmonary disease (COPD) overlap (ACO) in a COPD population (reproduced from Cosío BG et al. with permission from Elsevier © 2016 American College of Chest Physicians. Published by Elsevier Inc. All rights reserved).

Eos: blood eosinophils; IgE: immunoglobulin E; PBD: post-bronchodilator test.
characteristics, even if it provides a reasonable classification of candidates for treatment with ICS.

**ASThma-CHRONIC OBSTRUCTIVE PULMONARY DISEASE OVERLAP IS A HETEROGENEOUS DISORDER**

As alluded to above, the problem with ACO is that it clusters two entities with different inflammatory substrate and clinical characteristics (smoking asthmatics (SA) and e-COPD), probably leading to a confused signal. Discrepant results when looking at clinical outcomes across the studies could be due to this uncertain clustering. An initial analysis of the CHACOS population showed that the clinical history of ACO patients did not differ significantly (symptoms measured by the Asthma Control Test [ACT] and COPD Assessment Test [CAT] or previous exacerbations) from patients with asthma or COPD, respectively. However, when patients were reclassified according to their inflammatory pattern as “Th2-high” (≥ 300 eosinophils/L in blood or ≥ 3% in sputum), or “Th2-low”, 2 groups of chronic airflow limitation patients emerged that did show different clinical characteristics (Fig. 5). Consequently, this new categorisation helped select patients who were candidates for therapies aimed at specific inflammatory patterns, such as ICS or biological agents. In a second study, we investigated the value and interactions of blood biomarkers of systemic inflammation (IL-6, IL-8, TNF-α,
IL-17) and Th₂ inflammation (periostin, IL-5, and IL-13) in patients with asthma, COPD, and ACO. A network analysis and a principal component analysis showed the inflammatory pattern of ACO to be a mixture of the patterns observed in asthma and COPD, but no single biomarkers nor any combination of biomarkers were identified that could safely differentiate ACO from asthma or COPD.

We also compared the clinical characteristics and the inflammatory profile of e-COPD and SA. Patients classified as e-COPD were older and more often male and showed significantly impaired pulmonary function, likely explained by a heavier smoking habit. On the contrary, SA had more atopic features, more reversibility of airflow obstruction and higher IgE levels. The concentrations of IL-5, IL-13, IL-8, IL-6, TNF-α, IL-17 in serum were similar between the two groups. However, Th₂-related biomarkers (periostin, FeNO and blood eosinophils) showed higher median values in e-COPD patients. Our findings reinforce the notion that ACO is a heterogeneous disorder and, as a consequence, it might be unacceptable to offer the same treatment for two related but different conditions.

Type 2 T helper cells are involved in what is called “humoral-mediated” immunity, which deals with bacteria, toxins, allergens... and these cells predominate in response to infestations by gastrointestinal nematodes. Type 2 T helper cells produce IL-4, IL-5, IL-10, and IL-13, which are responsible for strong antibody production, eosinophil activation, and inhibition of several macrophage functions, thus providing phagocyte-independent protective responses. In most asthmatics, type Th₂ is the underlying inflammatory response, but non-type 2 inflammatory mechanisms drive asthma in some subgroups of patients. Figure 6 summarises the asthma inflammatory process. Side A represents the asthmatic allergic response, characterised by specific IgE production during the sensitisation phase, which will bind to high-affinity IgE Fc receptors (FcεRI) on mast cells and basophils. Upon renewed contact, the allergen will bind cellular IgE. Crosslinking of FcεRI will lead to degranulation of mast cells and basophils. The chronic phase is characterised by a persisting inflammation and the presence of structural alterations in the airways through the action of several immune cells and mediators. It must be of note that near 50% of severe asthmatics show a neutrophilic phenotype as a result of changes in the microbiome, chronic infection, exposure to air pollutants or treatment with glucocorticoids. The molecular mechanisms of the neutrophilic asthmatic inflammation (namely Toll-like receptor, Th₁, Th₁₇, inflammasome) are currently under investigation. In the figure, side B represents non-allergic eosinophilic asthma: air pollutants and microbes induce the release of epithelium-derived cytokines, including IL-33, IL-25 and thymic stromal lymphopoietin (TSLP), which activate type-2 innate lymphoid cells (ILC2s) in an antigen-independent manner. These activated ILC2s produce high amounts of IL-5 and IL-13, leading to eosinophilia, mucous hypersecretion and airway hyperreactivity.

On the other hand, the underlying pattern of inflammation in COPD can vary; most often
it is predominated by neutrophils, cytotoxic CD8+ T cells, and alveolar macrophages, but approximately a third of patients with COPD has sputum eosinophilia and, importantly, sputum and/or blood eosinophilia in COPD may predict response to ICS for prevention of exacerbations\textsuperscript{31}. The role of eosinophils in the inflammatory network of these patients remains to be elucidated, but it seems that these cells are accompanied by other relevant Th\textsubscript{2} mediators such as IL-5 and IL-13\textsuperscript{26}.

These clinical and inflammatory differences may have direct therapeutic implications, since patients overlapping asthma and COPD would benefit from therapeutic intervention designed for each condition. Virtually all the pathways represented in the figure are potential therapeutic targets. Monoclonal antibodies (mAb) to IL-5 and to a combination of IL-4 and IL-13 have been developed and commercialised; a mAb to TSLP was recently tested in a clinical trial\textsuperscript{32}. More controversial results have been
obtained with anti-IL-5 treatment in COPD\textsuperscript{33,34} probably due to the mixed Th\textsubscript{1}/Th\textsubscript{2} inflammatory component. Additional monoclonal antibodies targeting both the innate and the adaptive immune Th\textsubscript{2} pathways are currently in development. However, a number of clinical trials directed against neutrophil-associated mediators (an antibody against TNF\textalpha, golimumab, an anti-IL-17 receptor antibody, brodalumab, and a CXC-chemokine receptor [CXCR]-2 antagonist) have not been successful in moderate-to-severe asthma\textsuperscript{35-37}.

There is an urgent need for easily measurable and reproducible biomarkers that are linked to underlying pathophysiologic disease mechanisms and can distinguish between the T2 eosinophilic/steroid responsive (T2-high) patients from the neutrophilic/steroid insensitive group (T2-low) endotype. Periostin was initially proposed as a systemic biomarker of airway eosinophilia in severe, uncontrolled asthmatics\textsuperscript{38}, but a subsequent study found that it was not able to distinguish eosinophilic from non-eosinophilic airway inflammation\textsuperscript{39}. Interestingly, serum periostin performed less well when compared with blood eosinophilia in this study and this might be related to whether it is the IL-5 or IL-13-mediated pathway that is driving the sputum eosinophilia. Blood eosinophilia is not sensitive enough in the most severe asthmatics because relationship between sputum and blood eosinophilia becomes weaker with increasing disease severity, especially in the glucocorticoid-dependent asthmatics\textsuperscript{40}. The F\textsubscript{E}{NO} might reflect ongoing epithelial cell activation driven by IL-13. However, it is not clear how F\textsubscript{E}{NO} can guide therapy with biologics, since anti-IL5 mAbs do not reduce this biomarker and, conversely, therapy directed against IgE\textsuperscript{41}, IL-13\textsuperscript{42} and IL4/13\textsuperscript{43} can reduce FeNO, suggesting that it might represent a T2-high sub-endotype with epithelial dysfunction. Combinations of these biomarkers did not improve their ability to predict sputum eosinophilia. On the other hand, it is evident that current biomarkers of neutrophilic asthma are not suitable for use in clinical trials. It is likely that in the near future “-omics” studies using a variety of biological samples will be used to identify underlying molecular pathways, but they will need to be validated for clinical efficacy.

**CONCLUSIONS**

Although not reaching a chaos, we think that ACO is a complex entity that leads to confusion. Much of this confusion can be explained by two ways of interpreting the same condition:

- The clinical approach tries to explain ACO in the light of several clinical or functional findings that were classically considered suggestive of COPD or asthma. However, in a recent multicentre and cross-sectional study carried out in Spain that included 292 patients with several types of chronic obstructive airways disease (COAD), we were unable to find clinical, demographic or functional variables – in solo or combined – capable of distinguishing ACO patients from other categories of COAD (COPD and asthma with bronchial obstruction)\textsuperscript{25}. Therefore, the classical labelling of COAD is useful to identify patients with well-defined forms of COPD and asthma, but it is less useful to describe those uncertain cases of COAD that show features of both entities\textsuperscript{44}. Accordingly, it will
be important to dismantle chronic airway disorders based on mechanisms, imaging and avoid terms such as asthma, COPD and obviously ACO in the future. Meanwhile, a personalised approach using treatable treats, such as airway obstruction and Th₂ inflammation could be appropriate⁴⁵,⁴⁶.

The biological approach is based on the assumption that, since both asthma and COPD are inflammatory diseases that affect the bronchial tree, it is to be expected to find, in patients with ACO, some evidence of the Th-1 pattern (characteristic of COPD) and some evidence of Th-2 pattern (characteristic of asthma). Under this approach, ACO can be diagnosed in patients without diagnostic criteria for asthma (those with eosinophilic COPD) and even in non-smoking asthmatics (those with mixed eosinophilic and neutrophilic pattern). In fact, the aforementioned Spanish study found that a classification based upon the inflammatory profile (Th₂-high and Th₂-low), irrespective of the taxonomy, provides a clearer distinction of COAD patients²⁵. This approach complies with the efforts to personalise medicine but these attempts collide with the limitations of current biomarkers of the bronchial inflammatory process. Likely, the unbiased systems biology approach to COAD diseases endotyping, which integrates “-omics” signatures and clinical data using large cohort studies may provide more comprehensive information than simple cellular measurements. Meanwhile, we might look for a change in the paradigm of obstructive airway diseases, as it happened to Einstein with the orbit of Mercury...⁴⁷

**CONFLICTS OF INTEREST**

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