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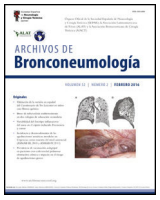

PRO/CON debate

Etiotypes in COPD: a pro/con debate

Introduction

Chronic obstructive pulmonary disease (COPD) has traditionally been considered a "single" disease caused by tobacco smoking.[1] Yet, recent research has shown that about a third of COPD patients around the globe are never smokers,[2] indicating that there must be other causes of COPD ("*etiotypes*") apart from tobacco smoking.[3–5] The Editor of *Archivos de Bronconeumologia* invited the two authors of this article to a pro/con debate on etiotypes of COPD. Each was asked to develop a PRO (Alvar Agusti) or a CON (Marc Miravitlles) position independently and then they were given the opportunity for some joint conclusions.

PRO

The 2024 Global Initiative for Obstructive Lung Disease (GOLD) document states that COPD is *"a heterogeneous lung condition that results from gene (G)-environment (E) interactions occurring over the lifetime (T) of the individual (GETomics) that can damage the lungs and/or alter their normal development/aging processes"*.[5] Following this statement, GOLD proposes the existence of several etiotypes (Fig. 1). Importantly, GOLD explicitly states that *"this proposal has relatively little impact on current clinical practice, other than illuminating this so-far ignored aspect of COPD, but it is of the outmost importance to highlight the need to explore current and future therapies in these other etiotypes of COPD"*.[5] With this caveat in mind, the following comments may be of interest.

COPD-G

Alpha-1 antitrypsin deficiency is the best-known genetic cause of emphysema (hence COPD), albeit its prevalence in the population is low.[5] Yet, now more than 100 genetic variants that can also increase the risk of COPD have been identified, but their individual effect size is small, and thus, several of these variants need to coexist in the same individual to have a measurable clinical impact.[6] Of note, very recent research has shown that a polygenic risk score identified in adult patients with COPD is also associated with lower lung function in childhood and up to adulthood.[7] This provides strong support for a, still poorly understood, genetic (and epigenetic) basis of COPD.[8]

COPD-D

It is now well established that due to a variety of early-life factors, including prematurity, low birth weight, maternal smoking, poor diet, and repeated infections, among others,[9] can impair lung development before and after birth in a substantial number of people, so between 4 and 12% of the general population do not reach normal peak lung function at the age of 20–25 years.[10,11] These individuals suffer a higher prevalence and incidence of cardiovascular and metabolic diseases, and die prematurely.[12] It is therefore important to identify these abnormal lung function trajectories as soon as possible in order to prevent them and, if possible, intervene promptly.[13]

COPD-C

All previous randomized clinical trials (RCTs) in COPD required cigarette smoking (normally, more than 10 pack-year of cumulative smoking exposure) as an inclusion criterion, and therefore, COPD-C has been extensively studied. In fact, all our current management recommendations refer to COPD-C.[5] This is good because cigarette smoking is the main environmental risk factor of COPD. However, epidemiological research has shown that about 30% of patients with COPD in the world are never smokers,[2] so other etiotypes (Fig. 1) must play a role and require and deserve research. It is also of note that the mean age of participants in all available RCTs is COPD-C is around 64 years and younger individuals with COPD (see COPD-D above) are normally not included. Understanding COPD in young people (whether caused by smoking or other etiotypes) is an important knowledge gap that requires research since therapeutic intervention at younger ages can likely provide better outcomes.[13]

COPD-P

Exposure to household pollution, ambient air pollution, wildfire smoke and some occupations are well recognized, but much less studied, risk factors of COPD.[14] Importantly, many of these factors can alter lung development in children leading to reduced peak lung function and morbidity later in life.[9]

COPD-I

Repeated childhood infections, tuberculosis *sequelae* and HIV infection can lead to COPD in adulthood, but their prevention and management is much less understood. Their relevance is likely to be higher in low-middle income countries,[5] but this is a good example of the importance of identifying different COPD etiotypes, so new research and public health measures can be initiated or implemented.

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Classification	Description
Genetically determined COPD (COPD-G)	Alpha-1 antitrypsin deficiency (AATD) Other genetic variants with smaller effects acting in combination
COPD due to abnormal lung development (COPD-D)	Early life events, including premature birth and low birthweight, among others
Environmental COPD	
Cigarette smoking COPD (COPD-C)	• Exposure to tobacco smoke, including *in utero* or via passive smoking • Vaping or e-cigarette use • Cannabis
Biomass and pollution exposure COPD (COPD-P)	Exposure to household pollution, ambient air pollution, wildfire smoke, occupational hazards
COPD due to infections (COPD-I)	Childhood infections, tuberculosis-associated COPD, HIV-associated COPD
COPD & asthma (COPD-A)	Particularly childhood asthma
COPD of unknown cause (COPD-U)	

Fig. 1. Proposed taxonomy (Etiotypes) for COPD.
Reproduced with permission from GOLD. For further explanations, see text.

COPD-A

The intersect between asthma and COPD has been the subject of numerous discussions and proposals (e.g. ACOS[15]). Of note, symptoms of asthma in infancy are non-specific and may be due to abnormal lung development and not to a specific disease such as asthma. If so, treatment may be completely different. This is an area that requires research.[9]

COPD-U

It is always important to leave the door open to future, currently unknown, etiotypes of COPD such as, perhaps, vaping or radon exposures, among others, in order to undertake preventive measures as soon as evidence emerges.

In conclusion, GOLD 2024 appropriately highlights that COPD is not a "single" disease, and that although tobacco smoking is the main environmental risk factor for COPD, there are also multiple other causes ("etiotypes") of this devastating disease that require and deserve research and, eventually, implementation of appropriate preventive and therapeutic strategies. GOLD acknowledges that, today, this proposal is still far from being implemented in clinical practice but the only way to get it into mainstream practice is to identify the problem and encourage and support appropriate research.

CON

The continuous and endless use of new terms to try to define the heterogeneity of COPD only creates more and more confusion to clinicians. Basically, the conflict is caused by the use of the term COPD as a synonym of chronic airflow limitation (CAL). Chronic airflow limitation is not a disease and is not even a syndrome, but rather it is a physiological definition obtained from a diagnostic test and, as such, it may help diagnose a suspected disease, for example COPD, in an adult individual with respiratory symptoms and significant exposure to smoking or other similar toxics.[16] However, epidemiological studies classify every participant with a post-bronchodilator $FEV_1/FVC < 0.7$ (or below the lower limit of normal (LLN)) as having COPD, even in the absence of any respiratory symptoms or exposures.[17] Is a ratio $FEV_1/FVC < 0.7$ a disease? It may or it may not be. According to the presence of etiologic factors, clinical manifestations and the histopathological findings, it may be a consequence of not just one, but several diseases: from asthma to bronchiectasis, sequelae of tuberculosis and many others; or even no disease at all, because a ratio < 0.7 may be physiologic in elderly subjects (or <LLN can be found in 5% of normal subjects, by definition).[18,19]

In order to avoid these misconceptions and misclassifications, we should follow the advice of Scadding, formulated some 65 years ago: "*when the current state of knowledge permits more than one possible basis of definition of a disease, an etiological basis will usually be more useful than a pathological, and a pathological more than a syndromal*".[20] The etiology of more than 70% of cases of CAL in developed countries is well known: tobacco smoking.[17,21] Therefore, we should define COPD as CAL caused by smoking, with all its associated signs and symptoms, and provide specific names to the remaining forms of CAL due to other causes.[22–24] Instead, the Lancet Commission[4] and the last GOLD document[5] have introduced the concept of etiotypes of COPD to define different forms of the so-called "COPDs". The term etiotype is, in itself, confusing, because the characteristic that best defines a disease is its etiology; therefore, different etiologies should correspond to different diseases. For example, COPD-A, described as COPD & asthma, and particularly childhood asthma,[4,5] is (and has always been) asthma. In a child with severe asthma who develops CAL in adult life the disease has not changed; it is still asthma and not a type (or etiotype) of COPD and must be treated as asthma. The introduction of the term COPD-A may create confusion, and these patients might be erroneously treated as COPD instead of asthma. Another example is COPD-I; sequelae of tuberculosis or childhood infections may result in CAL, but can we define this disease as COPD? Is there any evidence that these individuals respond to COPD medications? Is their evolution or prognosis similar to smoking-related COPD? Wouldn't it be better to call this tuberculosis-associated CAL instead of COPD-I? On the other hand, the promising concept of phenotype of COPD

was abandoned because it was argued that several patients shared different phenotypes, which is exactly the same with the etiotypes. It is not difficult to imagine a patient who had asthma during youth, who smoked 30 pack-years and suffered a destructive tuberculosis (and perhaps was diagnosed with alpha-1 antitrypsin deficiency), but which is his etiotype? In a recent study including a sample of 3476 COPD patients, Jo et al.[25] identified only 987 (28.4%) with a non-overlapping etiotype.

One of the reasons for the introduction of these etiotypes was to create awareness of non-smoking COPD (although we should call it non-smoking-related CAL instead). It is true that in all epidemiological studies in developed countries up to 25% of cases of COPD (or rather CAL) are diagnosed as never smokers.[17,26,27] However, we should not forget that the important message is that 75% of cases of CAL (or COPD) are due to smoking. Furthermore, non-smoking COPD generally presents mild-to-moderate airflow limitation, corresponding to GOLD grades 1 and 2, whereas the great majority of severe COPD cases are smoking-related.[26,27] Moreover, non-smokers with COPD have long term outcomes similar to or even better than subjects without CAL.[19] Nevertheless, research in non-smoking CAL must be stimulated, but if we want to have a real impact on public health, we need to significantly increase our investment in smoking-related COPD. In fact, paradoxically, the concept of a COPD etiotype may hinder investment in research of different etiotypes. For example, alpha-1 antitrypsin deficiency is considered a rare disease and pharma industry can apply for an orphan drug designation to facilitate the development of new therapies; however, this might not apply for patients with "COPD-G".

The use of new and useless terminology is not restricted to stable COPD. In the field of exacerbations of COPD, a recent publication defined etiotypes, endotypes and phenotypes of exacerbations.[28] However, careful reading of the descriptions of these new terms suggests that there is no novelty in the concepts behind the words. Etiotypes is exactly the same as the classical term etiology, endotypes as pathophysiology and phenotypes as clinical manifestations. There is no need to invent new words that contribute to the increasing confusion of the clinicians if they do not provide any new concept that improves clinical management.

Finally, if we really want to clarify the field of obstructive lung diseases, we should use the etiologies to define diseases, as postulated by Scadding,[20] and reserve the term COPD for the most frequent and severe form of CAL caused by smoking. With this approach, COPD would finally have the status of a disease with a known etiology, and the remaining 25% of individuals with non-smoking-related CAL should be carefully assessed to identify the etiologic factors and classify them accordingly. By doing so, we will be able to emulate Birring et al.,[29] who identified only 25 cases or 5.7% of the total referrals to their center for COPD as being non-smokers. They found that 86% of the "non-smoking COPD" patients were women, with mild airflow obstruction and after careful investigation all of them were offered an alternative diagnosis.[29] Not using etiologies to define diseases, only creates more confusion and increases the risk of misdiagnosis and inadequate treatment.

Conclusions

Needless to say, CAL is not exclusive of COPD. In fact, GOLD indicates that CAL diagnoses COPD "*in the appropriate clinical context*"[5] and, indeed, the term etiotype precisely intends to recognize these different "clinical contexts".[5] Eventually, when the pathobiology and treatment of each of these etiotypes can be unveiled by future research, they can become diseases themselves, as it was the case for α1 antitrypsin deficiency or cystic fibrosis, both of which are also often associated with CAL. The main argument to sustain the concept of etiotypes is to highlight the need for research beyond smoking-related COPD. From this perspective, this pro/con debate is basically semantic.[3]

On the other hand, although everybody agrees that COPD is very heterogeneous, there is no consensus on how to address this heterogeneity. One option is to include all forms of CAL in adults under the umbrella of COPD and identify the different etiotypes, and the opposite would be to reserve the term COPD for the most frequent type of CAL, associated with smoking, and individualize all other types of CAL as single different entities. Which option would better serve better our patients? Time will tell.

Conflict of Interests

The authors state that they have no conflict of interests.

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