







Time for a change: anticipating the diagnosis and treatment of COPD

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COPD is often not diagnosed, or is diagnosed too late. It is time for a change that anticipates both diagnosis and treatment. <https://bit.ly/2BrDSv1>

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Introduction

COPD is a major public health problem because of its high prevalence (about 10% of the adult population), rising incidence (likely related to the ageing of the population), associated morbi-mortality (it is currently the third leading cause of death globally), and personal, social and economic costs [1]. The traditional way to address this problem has been to reduce smoking exposure, the main environmental risk factor for COPD [1]. Although this was, is and will be, a key public-health strategy, we argue here that it is not enough. If we want to eradicate COPD [2], it is time for a change that anticipates the diagnosis and treatment of the disease.

Rationale

COPD has been traditionally considered a disease of old people, self-inflicted by tobacco smoking [3]. Yet, research over the past few years is changing this paradigm (figure 1). Well-conducted epidemiological studies have shown that close to 30% of subjects with airflow limitation consistent with COPD have never smoked [4]. Yet, by and large, the evidence available today on the natural history and therapeutic management of COPD focuses almost exclusively on smoking-related COPD, essentially ignoring COPD in never smokers [4]. We also know that there are subjects with similar risk factors and clinical manifestations, but normal spirometry [5]. Likewise, it is clear now that impaired lung development also plays an important role in the pathogenesis of COPD [6, 7], that there are many different factors beyond smoking that influence lung function through life (figure 2) [8], and that low lung function in early adulthood is associated with multi-morbidity and premature death [9]. Because undiagnosed patients have

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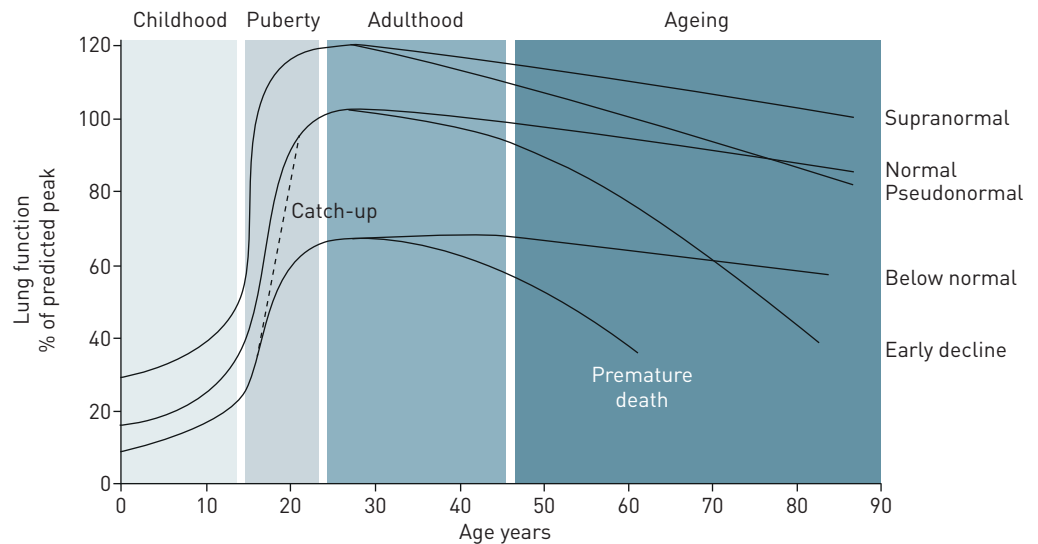


FIGURE 1 Lung function trajectories from birth to death. Both abnormal lung development and an increased rate of lung-function decline with age can lead to COPD in adulthood. These two mechanisms can coexist. For further explanations, see text. Reprinted from [7] with permission from the publisher.

poor outcomes [10, 11], anticipating the diagnosis and treatment of COPD is likely to reduce disease burden, both individually and collectively [12, 13].

Time for a change: the ANTES programme

To anticipate the diagnosis and treatment of COPD, several centres in Spain have agreed to collaborate on a research initiative named ANTES (“Earlier” in Spanish). Below, we discuss the five initial working areas where to develop specific research projects aimed at achieving the strategic goals of ANTES. Collaborations with other research centres are welcome.

1) Improve COPD underdiagnosis

Currently, more than 75% of COPD patients in the community have not been diagnosed, so they may not have been treated adequately [14]. Improving COPD underdiagnosis is therefore a key goal in ANTES. Spirometry is required for the diagnosis of COPD [1]. Although it is noninvasive, inexpensive, reproducible and easy to perform, and despite many years of intensive educational efforts, it is often not used in clinical practice. It is therefore time to implement novel strategies. One involves the use of questionnaires combined with micro-spirometers or peak flow meters [15–17]. Another may take advantage of the built-in microphones that are available in most smartphones to analyse breathing sounds, which may in turn provide lung function estimates [18]. Likewise, there are novel ways that use artificial intelligence to detect COPD on computed tomography scans obtained for different reasons [19]. A final alternative may involve access to lung function centres to refer individuals with respiratory symptoms for spirometry and specialised assessment [20]. All in all, this goes beyond the much debated concept of “COPD” screening [21] and proposes a new approach for “lung health” screening (figure 1) [8, 12], which, as discussed above, is associated with prevention of early comorbidities and premature death [9]. As a result, the current definition and taxonomy of COPD may need to be reconsidered [22].

2) Act earlier

Over the past few years there has been an increasing interest in the concept of “early” COPD [6, 9, 23–25]. It has been defined, somewhat arbitrarily, as chronic airflow limitation in subjects younger than 50 years exposed to tobacco smoke or other pollutants [26, 27]. Yet, there is evidence that there are detectable structural and functional abnormalities in much younger individuals [6, 8, 9, 12, 25]. Therefore, efforts should be made to look for younger patients or subjects at risk. Initiatives to test lung function in schools, universities, and during examination for a driving licence [12] are under way in ANTES.

3) Early therapeutic optimisation

Anticipating the diagnosis and treatment of COPD does not only mean to diagnose and treat “younger” patients with COPD, but also to explore if early therapeutic optimisation results in better outcomes [28].

	6 to <15 yrs	15 to <30 yrs	30 to <45 yrs	45 to <60 yrs	60 to 82 yrs
	n=981	n=2012	n=2404	n=3010	n=2972
Prevalence pre-BD FEV ₁ <LLN	6.6%	7.2%	7.4%	7.5%	8.5%
Age	1.5				
Low education status		1.03			
Wheezing			3.0	2.0	1.8
Coughing				2.0	
Dyspnoea				2.0	2.0
Asthma	7.5	2.8	2.9		3.3
COPD/chronic bronchitis	43.3		2.9	3.5	4.1
Sinusitis/nasal polyps			4.9		
Pneumonia, ever				1.6	
Low fat free mass index	3.9	2.2	1.6		2.3
Central obesity					1.8
Diabetes					2.0
Positive skin prick test	2.5				
Low hand grip test			1.9		
Current smoking	NA			1.7	1.8
≥20 pack years	NA	81.8			2.9
Sugary drinks, >1 per day			1.5	1.7	
Fruits/vegetables, <2 per day		1.8			
High traffic level near home			1.6		
Parenteral asthma/COPD					1.8
Elevated hsCRP	3.8				
Elevated eosinophils					2.1

FIGURE 2 Prevalence of low lung function (forced expiratory volume in 1 s (FEV₁) less than the lower limit of normal (LLN)) in different age bins and heatmap of significantly associated factors identified by multivariate regression analysis in the LEAD cohort in Austria. Figures in cells indicate odd ratios (blue, lowest OR; red, highest OR); white cells indicate absence of a significant relationship. NA: not available. Reproduced from [8] with permission from the publisher.

This is a different strategy from current guideline recommendations that propose a step-up approach for the pharmacological management of COPD [1]. For instance, there is evidence that the initial use of dual bronchodilator therapy in patients with mild airflow limitation decreases the rate of lung function deterioration [29]. This is currently being explored further in the on-going RETHINC trial (<https://clinicaltrials.gov/ct2/show/NCT02867761>), that compares dual bronchodilation *versus* placebo in symptomatic smokers without airflow limitation (forced expiratory volume in 1 s to forced vital capacity ratio >0.70). Although this trial will not be able to compare dual *versus* single bronchodilation, it will offer important new knowledge in this setting. Yet, other pragmatic, real-life studies will still be needed in this

area to define the potential risks and benefits associated with an early therapeutic optimisation strategy. The recent severe acute respiratory syndrome coronavirus 2 pandemic has opened new questions on the potential role of respiratory medications on the outcome of coronavirus disease 2019 patients with COPD that will have to be further investigated [30].

4) Exacerbation zero

COPD exacerbations worsen health status, accelerate lung function decline, increase mortality and generate important costs [31–33]. Preventing exacerbations is, therefore, a key objective of COPD management [1]. Current recommendations require that the patient should have suffered two or more exacerbations in the previous year (despite appropriate bronchodilator treatment) to escalate therapy in order to prevent future exacerbations [1]. In these patients, the combination of two bronchodilators or the addition of inhaled corticosteroids (ICS), phosphodiesterase-4 inhibitors or macrolides to one or two bronchodilators reduce the number and severity of future exacerbations [1]. This raises the question on why we must wait until the patient has suffered two or more exacerbations to initiate effective preventive treatment. This approach is not applied in patients with other chronic conditions, such as cardiovascular diseases. In these patients, preventive measures are not delayed until the patient has suffered two acute coronary events or strokes, and we postulate that this should not be the case either in patients with COPD. In ANTES, we argue that we need to be more ambitious and aim for an “exacerbation zero” goal. The ideal way to achieve this ambitious goal would be primary prevention of the disease [12]. Once the disease has developed, though, it may probably need to be reshaped into a “severe exacerbation zero” goal. To this end, several potential strategies may be conceived. First, smoking cessation, regular physical activity, appropriate diet and adequate vaccination [1]. Second, although pharmacology can certainly contribute to it, perhaps we should reconsider the currently recommended strategy [1]. For instance, adding ICS to chronic bronchodilator therapy at the onset of an upper respiratory tract infection decreases the severity of exacerbation that may follow [34]. Unfortunately, the use of personalised risk scores to predict and prevent the likelihood of future exacerbations is not yet ready for prime time [35]. In part, this is related to the lack of objective diagnostic markers of a COPD exacerbation [36]. ANTES envisage to define and validate a definition of COPD exacerbation based on objective, measurable and validated biomarkers as a necessary intermediate step to achieve the “exacerbation zero” goal.

5) Improve survival

Improving survival is one of the key therapeutic goals of many human chronic diseases [37]. The traditional, nihilistic approach that prognosis cannot be improved in COPD must be abandoned, since several interventions have proven it wrong. Smoking cessation, vaccinations, regular exercise and appropriate dietary programmes must be enforced in all people, including COPD patients, as they all have well known health consequences. Besides, several specific COPD interventions have also shown conclusively to improve survival in these patients, including oxygen supplementation to hypoxaemic COPD patients and lung volume reduction in patients with severe functional limitation and upper lung lobe inhomogeneous emphysema [1]. Likewise, the fact that comorbid diseases, such as cardiovascular diseases and lung cancer [38], are highly prevalent in patients with COPD, and that they are often their cause of death, particularly in patients with mild to moderate airflow limitation [39], pinpoints towards another important area where effective treatment can reduce mortality, so every COPD patient should be evaluated for their presence, because these diseases are treatable. For instance, as indicated by one of the anonymous reviewers of this paper, in patients with COPD and cardiovascular disease, the effectiveness of an early treatment that combines dual bronchodilation and β -blockade should be assessed.

Respiratory pharmacotherapy using long-acting bronchodilators alone or combined with ICS can also potentially reduce the risk of death in COPD [40]. It is true that the two pharmacological studies that were powered on mortality (TORCH [41] and SUMMIT [42]) did not achieve statistical significance, albeit TORCH was close (the hazard ratio for death in the combination therapy group *versus* placebo after adjustment for the fact that an interim analyses was done during the course of the study was 0.825, with 95% CI 0.681–1.002; $p=0.052$) [41]. Numerically speaking, though, both studies showed a 17.5% and 12% relative risk reduction in mortality *versus* placebo, respectively [41, 42], thus providing some encouraging signal. In fact, other studies where mortality was a secondary outcome, such as the 4-year UPLIFT trial that compared tiotropium *versus* placebo, did indeed show a benefit in mortality [33]. Further, a numerical reduction in mortality was also seen in a *post hoc* stratified pooled analysis of the effects of the extra-fine triple combination, albeit differences did not achieve statistical significance except, interestingly, for mortality due to non-respiratory events [43]. Finally, the recent IMPACT study confirmed prospectively that triple combination of ICS/long-acting β -agonist/long-acting muscarinic antagonist significantly reduced mortality in COPD, albeit mortality was a pre-specified secondary (not primary) outcome of the study [44]. Likewise, very recently, the ETHOS study has confirmed that triple therapy reduces mortality significantly

in patients with moderate-to-very-severe COPD and at least one exacerbation in the past year [45]. Considered together, these studies suggest that pharmacotherapy may indeed reduce mortality in some selected patients with COPD [40]. It is possible, and ANTES will address this issue, that by identifying the subset of patients most likely to respond and/or prove that a pharmacological intervention may reduce the risk of death in patients with COPD will provide the necessary impetus to develop novel treatment strategies aimed at achieving this ultimate goal [40].

Conclusions

ANTES is an ambitious, multicentre, research initiative based on the concept that anticipating the diagnosis and treatment of COPD will reduce its public-health impact by improving its prevention, treatment and prognosis.

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