

COPD: Differential Diagnosis

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a high prevalent and impact socioeconomic disease. Although, cigarette smoking clearly fulfils all criteria to be classified as the etiology of COPD (Hill's criteria), the latest version of GOLD does not include this concept clearly, therefore half century of main documents has been culminated and they has never mentioned in the definition, tobacco or cigarette smoking as cause of COPD. American Thoracic Society and European Respiratory Society (ATS / ERS) in the definition of COPD include the phrase "primarily caused by cigarette smoking". Nevertheless, the next page smoking changes from the category of "cause" to simply a "risk factor"; in fact, smoking is included in table 2 as a risk factor under the column of "exposures", together with socioeconomic status, environmental pollution, disease in childhood, or diet, among other. A reason for not to refer to cigarette smoking as aetiology is that only 15% of smokers are susceptible to COPD, a concept wrongly attributed to Fletcher. Although not all subjects exposed to cigarette smoking develop COPD does not preclude such exposure is the cause, just as not all people infected with *Mycobacterium tuberculosis* develop Tuberculosis, but there is no doubt about the etiologic role of mycobacteria. Another reason for nor establish smoking to the category of etiological factor in COPD is the existence of COPD in non-smokers.

Therefore, when the aetiology is not part of the definition of the disease, it is usually replaced by a clinical description and the definition based on clinical findings are very poor, so a new definition of COPD is needed to ensure a more valid and accurate way to manage this worldwide condition.

In the Table 1 shows some of the criteria that different societies, guidelines and organizations have been used to diagnose COPD.

Actually COPD is defined as postbronchodilator FEV1/FVC ratio < 70%. Threshold of FEV1/FVC <70% is agedependent and will probably lead to a significant degree of overdiagnosis of COPD in the elderly and underdiagnose young adults. GOLD guidelines recommend that using the lower limit of normal (LLN) values for FEV1/FVC is a way to minimize the misclassification. But use LLN we also overdiagnose healthy subjects. Although use post-bronchodilator FEV1/FVC ratio <0.70 simplify the diagnosis of COPD, some pulmonologists, ever more, consider a diagnosis of COPD can not be based only on spirometry parameters; it is important to include the presence of respiratory symptoms and exposure to risk factors.

Society	Year	Criteria
ECCS	1983	FEV ₁ /VC or FEV ₁ / FVC<LLN
ATS	1987	FEV ₁ / FVC<0.75
ATS	1991	FEV ₁ / FVC<LLN
ECCS/ERS	1993	FEV ₁ /VC or FEV ₁ / FVC<LLN
ERS	1995	FEV ₁ /VC <88% predicted (men) or 89% (woman)
BTS	1997	FEV ₁ /FVC <0.70 and FEV ₁ <80% predicted
NLHEP	2000	FEV ₁ /FVC or FEV ₁ / FEV ₆ / \leq LLN and FEV ₁ <LLN
GOLD	2007	FEV ₁ /FVC<0.70 postbronchodilator
NICE	2004	FEV ₁ /FVC <0.70 and FEV ₁ <80% predicted
ATS/ERS	2004	FEV ₁ /FVC<0.70 postbronchodilator
ATS/ERS	2005	FEV ₁ /VC <LLN

ATS: American thoracic Society; BTS: British Thoracic Society; VC: Vital capacity; ECCS: European Community for Coal and Steel; ERS: European Respiratory Society; FEV₁/ FVC: ratio of forced expiratory volume in 1s to forced vital capacity; GOLD: Global Initiative for chronic obstructive lung disease; LLN: lower limit of normal (LLN); NICE: National Institute for health and clinical excellence; NLHEP: National Lung Health Education Program.

Table 1. Spirometry criteria to COPD in some guidelines Society

There are many diseases or processes that show a FEV₁ / FVC post-bronchodilator < 70%, these processes constitute the great chapter of what we call "disease" COPD.

Although nosological or semantically, definition of COPD as a syndrome is questionable, recently the term has come to be considered by other authors. Table 2 outlines a long list (not exhaustive) of entities that may be associated with airflow obstruction syndrome or COPD. Most of them are common such as pneumoconiosis and other occupational diseases, Airway obstruction in pulmonary tuberculosis, some clinical forms of asthma, etc and other less common such as lymphangioloeyomatosis, Bronchiolitis obliterans associated with consumption of *Sauropus androgynus* among others. This chapter will show a list of differential diagnosis, as complete as possible and some clues for the recognition of these processes vs COPD.

2. Smoking COPD

In 1950, smoking was established as a cause of COPD (chronic bronchitis and emphysema) and Fletcher and Peto corroborated its natural history. The relationship between smoking and COPD, probably influenced by genetic determinants poorly understood, is primarily a dose-effect relationship as demonstrated in multiple studies.

Findings have proven smoking cessation disrupts the natural history of COPD, but there are authors who have more controversial opinions about it and assert that in many cases, inflammation persists despite smoking cessation. The perpetuation of inflammation may be related to other factors, bacterial colonization has been proposed.

In the past, it was considered that only 15% of smokers were likely to develop COPD, when in fact it is known that this percentage is near 50% if they survive long enough. This

COPD from smoking COPD from alpha 1 antitrypsin deficiency COPD in non smokers Chronic Asthma (perennial) Aging Sequelae of tuberculosis Mitral stenosis Cardiac failure Anorexia nervosa Cystic fibrosis in adult Bronchiectasis Ambient exposure (biomass smoke) Marijuana smoking Sequelae accidental exposure (ammoniac) Occupational exposure <ul style="list-style-type: none"> • coal miners • pulmonary silicosis • byssinosis • pig farmers • cabinetmakers Others Endovenous exposure (heroin, cocain) Digestive exposure <ul style="list-style-type: none"> • (Sauropus androgynus) Bronchiolitis <ul style="list-style-type: none"> • Bronchiolitis obliterans • Diffuse panbronchiolitis • Obliterative bronchiolitis in microwave popcorn plant workers • bronchiolitis by rheumatoid arthritis • Others 	Sjogren syndrome Inflammatory bowel disease Wegener syndrome Sarcoidosis Extrinsic allergic alveolitis <ul style="list-style-type: none"> • Chronic Eosinophilic granuloma Lymphangiomyomatosis Neurofibromatosis Tuberous sclerosis Birt-Hogg-Dubé syndrome Scleroderma HIV AIDS (Pneumocistis jiroveci) Placental transmogrification Paraneoplastic Pemphigus Fabry disease Salla disease Amyloidosis Ligth chain deposition disease Relapsing polychondritis Tracheobronchomalacia Tracheobronchopathia achondropasia Ehler Danlos syndrome Tracheal stenosis Cord vocal paralysis Relapsing Polichondritis Traqueal neoplasia Papilomatosis tracheobronchopathia multiple Others
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Table 2. Causes of COPD syndrome

percentage of susceptibility increases if others methods, better than simple spirometry, have been used to detect COPD.

Although transfer of carbon monoxide (DLCO) and computed tomography (CT) with high resolution have demonstrated useful in early diagnosis of emphysema, they are underused.

Disadvantages for Chest CT and other imaging techniques are expensive and irradiation exposure.

3. Alpha-1-antitrypsin deficiency

There are excellent reviews about alpha 1 antitrypsin deficiency (AATD). AATD is associated with impaired pulmonary antiproteasas defenses leading to unopposed protease activity. ATTD is the best model of COPD and emphysema. The clinical course is accelerated mainly by the smoking, but also by air pollution, and phenotype well-known. Some cases are diagnosed as asthma or bronchiectasis for clinical manifestations. Others may be diagnosed by hepatologists if the first manifestation is liver findings. In recent years, the characteristics in

subjects over 60 years of age have been described. It is important the determination of the DLCO for evaluation of its prognosis and outcome, not only spirometry.

Heterozygous individuals have a higher susceptibility to develop COPD in the presence of smoking or cigarette exposure, and should be detected for a better affiliation of the syndrome. Therefore, measurement of alpha-1-antitrypsin should be practiced at least once in all patients with chronic airflow obstruction.

4. COPD syndrome by tuberculosis

Although Tuberculosis is considered as precursor in pulmonary specialty, airflow obstruction in pulmonary tuberculosis has been just considered few years ago. (Figure 1). In 1971, Snider et al had described Obstructive airway disease and pulmonary tuberculosis, and PLATINO study in Latin America has been updated this. In an environment where tuberculosis is or was common, the sequelae of tuberculosis are a major cause of chronic airflow obstruction in individuals who have never been smokers. Airway obstruction in pulmonary tuberculosis:

- do not correlate with the degree of the affected area, could coexist even if area of damage is small
- is presented in patients with treated pulmonary tuberculosis even healthy subjects
- is unusual progresses and
- is irreversible to bronchodilator.

5. Asthma chronic non-reversible perennial

Problems in the differential diagnosis of bronchial asthma not reversible and COPD are well known.

It is accepted that 30% of asthmatic patients are smokers, and this variant of overlap syndrome has been well described by various authors. There is evidence that smokers with asthma are more resistant to treatment. The natural history of patients with COPD asthmatic syndrome involves a fast loss of FEV1; they have a decreased life expectancy, though this aspect is not well known because many studies included as non-smokers and former smokers.

6. Aging

In the population over 80 or more years old, up to 50% of individuals may have a FEV1/FVC <70%. Although some analogies between COPD and elderly have already been highlighted, further studies are required. Hence tables with normal spirometric values for the elderly have just been available recently. Nevertheless, the presence of a FEV1/FVC <70% is clinical data that should not be neglected, because there has been a marker of reduced life expectancy, even in old age.

7. Heart disease

Classically, the chronic forms of valvular heart disease could present with airflow obstruction and / or reduction in DLCO. The decrease in the incidence of rheumatic fever and development of new cardiac diagnostic methods avoid this situation as a common

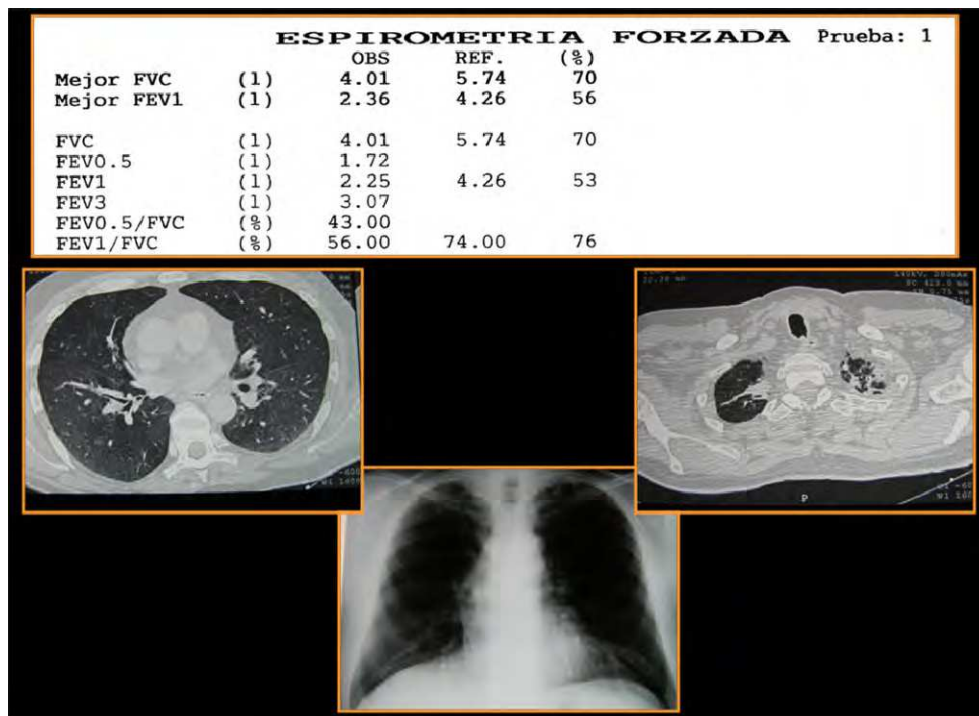


Fig. 1. A 55-year old woman, nonsmoker, was seen as outpatient in a check-up, a spirometry revealed the presence of obstructive patterns. A diagnosis of Pulmonary Tuberculosis had been made 25 year ago and antituberculosis treatment was completed. Diagnosis: sequelae of tuberculosis.

problem of differential diagnosis. The comorbidity of COPD and heart failure caused by smoking, metabolic syndrome, the syndrome of obstructive sleep apnea and aging, could hinder the diagnosis of COPD exacerbation vs heart failure. However, measurement of the natriuretic peptide can help in the differential diagnosis. Once patients have been discharged from hospital, they should be required to filial the impact of both processes. Studio ergometer should be made in outpatients in stable phase, although this is done in rare occasions.

8. No smoking COPD and antitissular antibody

To date, Birringer et al have perhaps been the only ones who have been systematically studied COPD in nonsmokers. Four hundred consecutive patients who visited for 2 years, Birringer found that 25% of them were smokers. Once discarded asthmatics, patients with bronchiectasis and a small subgroup with sputum eosinophilia, they were probably non-reversible asthma, a small percentage of 4% had common characteristics: they were preferably female, with age over 50 years, often with a history of Hashimoto's thyroiditis and / or antithyroid antibodies and / or antitissular antibodies or other features of autoimmune disease. Therefore, the measurement of antithyroid antibodies should be included in patients with features similar.

9. COPD from exposure to biomass smoke

It is considered that the population at risk of inhaling smoke from biomass could reach 3000 million people worldwide, mostly female. Anatomic pathology, COPD from inhalation of smoke from biomass has been becoming well known, has important similarities with COPD from smoking, but also significant differences.

Although its natural evolution is not well known yet, COPD from exposure to biomass smoke has some features in common with COPD from smoking. Romieu et al designed a study with methodology of trial in a group of Mexican women was divided into two groups: the control group cooking with the traditional open fire and the treatment group cooking with Patsari stove. After 6 years, confirmed a dramatic difference in the evolution of FEV1: the control group decline 62 ml FEV1 per year, while the intervention group only lost half. Orozco et al demonstrated that COPD in Spain by exposure to biomass smoke should be considered especially in older women from rural areas.

The impact of this disease is usually not epidemiologically relevant in developed countries, although some cases have been identified in countries as the United States, for example, in New Mexico, USA reported that 26% of subjects had been exposed to smoke from biomass fuel.

10. Other disease

Bronchiectasis, cystic fibrosis, bronchiolitis and alveolitis extrinsic allergic are disease or syndromes very often manifested with chronic airflow obstruction, as well as occupational exposures. Occupational exposures, in particular, are syndromes that constantly incorporating new disease. An example would be an extrinsic allergic alveolitis called hot tub, which is related to recreational activities whit contact hot water, as in water parks. *Mycobacterium avium* could have a main role.

Paradoxically, until recently it discussed the evidence that pneumoconiosis of miners could be the cause of pulmonary emphysema in the absence of smoking, which is currently shown. Other occupational exposure disease is obliterative bronchiolitis in microwave popcorn plant workers. It was observed when the additives to provide flavor was replaced. The patients had a very aggressive clinical course.

Another microepidemic is bronchiolitis obliterans associated with *Sauropus androgynus*, it also led to an extremely aggressive bronchiolitis and is not by respiratory exposure. The intention to lose weight was the reason of ingestion of extract of *Sauropus androgynus*.

Recently, CT scan has shown that patients with anorexia nervosa could be associated with emphysema. This observation was already known in the Nazi death camps. However, there is not evidence that emphysema cause by anorexia nervosa has airflow obstruction.

Patients infected with the human immunodeficiency virus (HIV) may have some respiratory disorders including pulmonary emphysema with airflow obstruction. It is accepted that the combination of smoking and inflammatory reactions caused by HIV accelerates the presentation of emphysema in 10 to 20 years. Recently it has tended to take an important role to *Pneumocystis jiroveci* in the obstruction of patients with HIV, but even this pathogen has been isolated in patients with COPD from smoking.

The eosinophilic granuloma, lymphangiomyomatosis (figure 2), histiocytosis X, tuberous sclerosis syndrome, Birt-Hogg-Dubé and deposition disease heavy chains are some orphan



	Pre-Bro			Post-Bro		
	Actual	Pred	%Pred	Actual	%Pred	%Chng
---- SPIROMETRY ----						
FVC (L)	3,32	3,64	91	3,32	91	-0
FEV1 (L)	1,39	3,00	46	1,51	50	8
FEV1/FVC (%)	42	83	51	45	55	8
FEF 25% (L/sec)	1,34	5,44	25	1,49	27	11
FEF 75% (L/sec)	0,21	1,72	12	0,22	13	5
FEF 25-75% (L/sec)	0,42	3,16	13	0,52	16	25
FEF Max (L/sec)	3,13	6,90	45	3,85	56	23
FIVC (L)	3,32			3,23		-3
FIF Max (L/sec)	3,10			2,92		-6
---- LUNG VOLUMES ----						
SVC (L)	3,41	3,64	94			
IC (L)	2,24	2,23	100			
ERV (L)	1,17	1,41	83			
FRC (N2) (L)	3,80	2,73	139			
RV (N2) (L)	2,62	1,51	174			
TLC (N2) (L)	6,03	4,96	122			
RV/TLC (N2) (%)	44	30	145			
Washout Time (min)	2,29					
---- DIFFUSION ----						
DLCOunc (ml/min/mmHg)	11,27	23,43	48			
DLCOcor (ml/min/mmHg)		23,43				
DL/VA (ml/min/mmHg/L)	2,28	4,72	48			
VA (L)	4,94	4,96	100			

Fig. 2. A 36-year old woman was seen in pneumology clinic because of dyspnea. She had a 5-pack-year history of smoking but had stopped smoking 4 year earlier CT: thin-walled cystic. Pulmonary function testing reveals an obstructive pattern. Lung biopsy: Lymphangioleiomyomatosis.

diseases, most of them genetic disease, they can cause airflow obstruction and pulmonary emphysema.

In half the cases, a rare disease such as vasculitis with urticaria and hypocomplementemia syndrome could present with severe emphysema. Its mechanism is could be local inactivation of alpha-1-antitrypsin.

Systemic diseases such as rheumatoid arthritis, lupus erythematosus, diffuse scleroderma, polymyositis and mixed connective tissue disease can cause bronchiolitis at some point in its evolution. Sjögren syndrome can provide images similar in CT of emphysema and additionally present with airflow obstruction.

Although, Sarcoidosis in advanced stages is present as pulmonary fibrosis, in the initial and/or mild stages is present as mild obstruction because hyperresponsiveness or involvement of the bronchial mucosa.

The connective tissue diseases such as Marfan syndrome and Ehlers-Danlos syndrome, among others, may present with lesions of emphysema, usually paraseptal. Simultaneously, may present with tracheobronchomegaly and hipercolapsabilidad tracheobronchial. CT and test of forced expiration have increased the diagnosis of bronchial hipercolapsabilidad. It probably is one of the main causes of airway obstruction in healthy people.

Likewise, tracheal tumors, the Wegener, vocal cord paralysis and vocal cord dysfunction also cause of airflow obstruction.

11. Special situations

Parentage of a patient with obstruction initially suffered from asthma and who subsequently becomes a smoker can be a clinical problem almost insoluble.

The combination of smoking and disease interstitial chronic or pulmonary fibrosis has been highlighted in several recent publications. A recent epidemiological study in area cardiology, MESA study, performing CT lung, indicates that this match will be anecdotal in the future.

Respiratory bronchiolitis with interstitial respiratory disease (RB / ILD) is another example of interstitial and bronchial disease secondary to smoking. Some patients who do not meet the criteria for COPD are patients with severe by accelerating their natural evolution. (Figure 3)

12. Comorbidity and differential diagnosis

Comorbidity in COPD is controversial. In fact, it has been so exaggerated to name as chronic inflammatory syndrome, including in the same process other systemic manifestations. It is much more common that the vascular comorbidity in patients with COPD due to chronic exposure to tobacco that systemic inflammation secondary to COPD. Table 3 lists the mechanisms of comorbidity and Table 4 summarizes the comorbidities of COPD.

Introduce comorbidity in the differential diagnosis have done difficult in many cases the appropriate affiliation to the patient. In a smoker of 65 years with a cumulative consumption of 40 pack / year comes to a vascular surgeon for a pulsatile abdominal mass is likely to

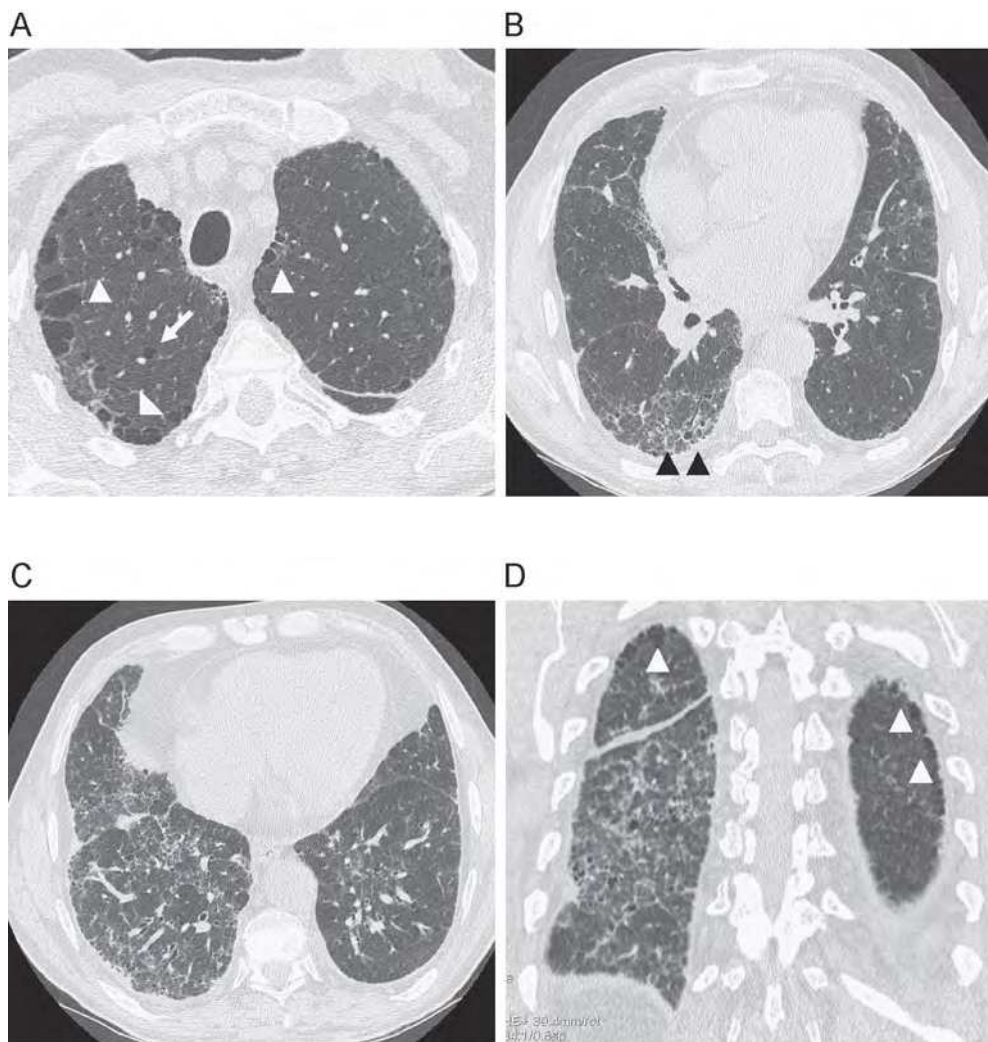


Fig. 3. High resolution computerized tomography (HRCT) of the same patient. A) Presence of paraseptal emphysema and subpleural bullae (white arrowheads) and centrilobular emphysema (arrows) in both upper lobes. B) Reticular interstitial disease with intralobular thickening and images of subpleural honeycombing and traction bronchiectasis (black arrowheads) C) Reticular interstitial disease in middle and right lower lobes, with interlobular septal thickening, subpleural honeycombing and traction bronchiectasis. D) Coronal reconstruction in the posterior regions of both lungs: Bilateral paraseptal emphysema (white arrowheads) and reticular interstitial disease and honeycombing in right lower lobe. (Used with permission MD Portillo)

Systemic features of cigarette smoking
Systemic features of COPD
Comorbidity of COPD
Extrapulmonary feature of COPD

Table 3. Mechanisms underlying the comorbidity of COPD

<p>Respiratory</p> <ul style="list-style-type: none"> • Bronchopulmonary carcinoma • Pulmonary arterial hypertension • Bronchiectasis • Pneumonia • <i>Pneumocystis pneumonia</i> • Obstructive sleep apnea • Invasive aspergillosis • Others <p>Cardiovascular</p> <ul style="list-style-type: none"> • Coronary disease • Auricular fibrillation • Cardiac failure • Carotid stenosis • Arritmia • Aneurysm of thoracoabdominal aorta • <i>Cor pulmonale</i> • Others <p>Neuropsychic</p> <ul style="list-style-type: none"> • Depressive disorder • Ictus • Lacunar infarct • Anxiety disorders • Orthostatic hypotension • Intracranial hypertension • Cognitive impairment • Others 	<p>Digestive</p> <ul style="list-style-type: none"> • Gastroesophageal reflux • Malabsorption • <i>Helicobacter pylori</i> infection • Others <p>Endocrine</p> <ul style="list-style-type: none"> • Diabetes • Hypogonadism • Others <p>Systemic</p> <ul style="list-style-type: none"> • Cachexia • Myopathia • Anemia • Osteoporosis • Polycythemia • Facial wrinkles • Hypercoagulable state • Others <p>Others</p> <ul style="list-style-type: none"> • Rhinitis • Cataracts • Inguinal hernia • Nephrotic syndrome • Periodontal disease, etc
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Table 4. Comorbidity of COPD

delay the practice of spirometry. Recently, Remy-Jardin et al have made an interesting proposal to TC (dual-energy) for the simultaneous evaluation of pulmonary and vascular damage smoking.

13. When should we suspect that COPD is not secondary to tobacco?

An example, a female patient over 70 who had lived much of her life in a rural area, who had never smoked, presents with cough, expectoration and airway obstruction would be a candidate that her disease was secondary to exposure biomass. We cannot be in accordance with a diagnosis of COPD in individuals who had smoked fewer than 10 packs / year,

unless they had simultaneous deficiency of alpha-1-antitrypsin disease. In obvious cases of airway obstruction in people younger than 40 years, it is unusual that this was secondary to smoking. If the annual decline of FEV₁ was greater than 75 ml, an additional cause should be suspected. A familial aggregation might suggest cystic fibrosis in adults. The coexistence of joint, skin or ophthalmic symptoms, mucosal dryness and thyroid disease should alert us about other causes of COPD. Bronchiectasis, mostly in women, with *Micobacterium avium complex* is associated with low body mass index. Finally, laboral and hobbies history should be complete in the first interview in pneumologic specialty. Table 5 shows signs and symptoms to help to exclude COPD.

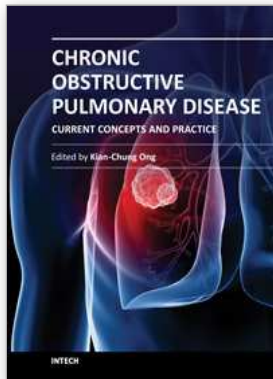
History of smoking <10 pack-year
Onset before 40 years old
Decline of FEV ₁ >75 mL per year
Autoimmune or collagenous disease
Ambiental exposure
Systemic symptoms
Progression of the obstruction years after smoking cessation

Table 5. Signs and symptoms to help to exclude COPD

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A decade or so ago, many clinicians were described as having an unnecessarily 'nihilistic' view of COPD. This has certainly changed over the years... This open access book on COPD provides a platform for scientists and clinicians from around the world to present their knowledge of the disease and up-to-date scientific findings, and avails the reader to a multitude of topics: from recent discoveries in the basic sciences to state-of-the-art interventions on COPD. Management of patients with COPD challenges the whole gamut of Respiratory Medicine - necessarily pushing frontiers in pulmonary function (and exercise) testing, radiologic imaging, pharmaceuticals, chest physiotherapy, intensive care with respiratory therapy, bronchology and thoracic surgery. In addition, multi-disciplinary inputs from other specialty fields such as cardiology, neuro-psychiatry, geriatric medicine and palliative care are often necessary for the comprehensive management of COPD. The recent progress and a multi-disciplinary approach in dealing with COPD certainly bode well for the future. Nonetheless, the final goal and ultimate outcome is in improving the health status and survival of patients with COPD.

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