NICOLAE TESTEMITANU STATE UNIVERSITY OF MEDICINE
AND PHARMACY OF THE REPUBLIC OF MODOVA

CORLĂTEANU ALEXANDRU

MULTIDIMENSIONAL ASSESSMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

CHIȘINĂU
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CONTENTS

SUMMARY

Chronic obstructive pulmonary disease (COPD) is a complex systemic pathology, which cannot be characterized, diagnosed or assessed only by the evaluation of pulmonary function. Last years were developed new approaches in evaluation COPD. In this book we review the most recent multidimensional classification of COPD, based on analysis of functional and physiologic parameters, health status and risk of exacerbations. The A, B, C, D system elaborated by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) permits a more accurate assessment and risk stratification of COPD. In addition, new trends in evaluation of COPD are presented: from phenotypes, multidimensional indices, scale-free networks and diseasome to radical concept of P4 medicine (Personalized, Predictive, Preventive, and Participatory elements) and also precision medicine.

The diagnosis and management of COPD in every patient should be personalized, and guided by symptoms, exacerbations, pulmonary function tests, imaging variables and chronic comorbidities.

In addition, are presented up-to-date overview of the prevalence and disease burden of the comorbidities that are often associated with COPD, as well as their interaction with, and impact on COPD exacerbations. The monograph summarizes the most current aspects of the non-pharmacological and pharmacological treatment of stable COPD.

ADNOTARE

EVALUAREA MULTIDIMENSIONALĂ A BRONHOPNEUMOPATIEI CRONICE OBSTRUCTIVE

Sumarul compartimentelor monografiei

În **introducere** este argumentată actualitatea problemei cercetate.

Capitolul 1 conţine o sinteză a rezultatelor expuse în literatura de specialitate privind bronhopneumopatia cronică obstructivă.

Bronhopneumopatia cronică obstructivă (BPOC) rămane una dintre cauzele majore de mortalitate din întreaga lume.În pofida faptului că este cea mai studiată maladie indusă de fumat, încă nu sunt date concludente în privinţa aspectelor fiziopatologice şi a tratamentului, chiar dacă au fost determinate efectele dăunătoare ale diversităţii de molecule implicate şi au fost propuse câteva terapii fezabile pentru diminuarea secreţiei acestora. Studiile actuale se axează preponderent pe originea autoimună a BPOC şi pe modificările epigenetice. Ideea de autoimunitate în BPOC indus de fumat a prins contur odată cu identificarea autoanticorpilor în serul pacientului, pe când unele studii consideră complexele de anticorpi localizate în plămâni mai importante pentru viitoarele cercetări. Investigarea aspectelor autoimune ale BPOC va permite selectarea unor strategii de tratament mai concrete. Pregnanţa modificărilor epigenetice din acest domeniu poate fi apreciată pornind de la existenţa unei conexiuni dintre modificările epigenetice induse de fumatul matern şi dezvoltarea ulterioară a BPOC. Aceasta explică tendinţa savanţilor pentru medicamentele capabile să restabilească aceste transformări precum agenţii de deacetilare, care posibil că previn şi rezistenţa către steroizi. Totuşi stoparea fumatului rămâne a fi abordarea indispensabilă pentru tratamentul şi prevenţia BPOC.

În **Capitolul 2** sunt sunt relatate principalele particularităţi ale pacientului cu BPOC: clinice şi paraclinice. BPOC este patologia asociată cu efecte sistemice majore (pierderea ponderală, disfuncţia musculaturii scheletice, boala cardiovasculară, anemia, depresia şi osteoporoza), care

au consecinţe clinice importante, contribuie la limitarea capacităţii de efort, la declinul stării de sănătate şi la agravarea prognosticului.

În acest capitol sunt reflectate comorbidităţile, care semnificativ influenţează evoluţia, severitatea şi prognosticul BPCO.

În **Capitolul 3** Este descrisă şi argumentată necesitatea evaluarii multidimensionale (parametrii funcţionali, dispneea, calitatea vieţii, exacerbările) a pacientiilor cu BPOC.

Există trei abordări bine-cunoscute şi acceptate pe scară largă pentru evaluarea BPOC: evaluarea GOLD a severităţii, evaluarea multilaterală şi fenotiparea.

Cel mai citat în literatura de specialitate este indicele BODE, care a fost propus de Celli şi Cote în 2004. În BODE au fost incluse trei variabile care sunt predictori mai bune de mortalitate decat VEMS (IMC, dispnea evaluată cu scara Medical Research Council, şi toleranta la efort fizic evaluată prin testul de mers de 6 minute). Indicele BODE a fost dovedit a fi mai bun decât VEMS in estimarea riscului de deces la pacientii cu BPOC. De asemenea, indicele BODE este sensibil pentru evaluarea exacerbarilor şi poate fi ca un marker surogat al rezultatelor viitoare, după intervenţii, cum ar fi o intervenţie chirurgicală de reducere a volumului pulmonar sau de reabilitare pulmonara. Indicele BODE ca expresie adecvată a severităţii bolii a fost propus pentru o nouă abordare în managementul şi tratamentul pacienţilor cu BPOC.

Indicele multidimensional BODE şi alţi indici includ validitatea predictivă a celor mai bune surogate potentiale pentru mortalitatea si exacerbarile intr-o singura masura de severitate BPOC si de supravieţuire.

Indicele BODE şi alte instrumente de evaluare multilaterala se pot dovedi a fi valoroase instrumente nu numai în evaluarea severităţii şi progresia bolii, dar, de asemenea, în evaluarea răspunsului la intervenţiile terapeutice. Sunt necesare studii de implementare pentru a determina valoarea clinică a instrumentelor de evaluarea multilaterala.

Managementul BPOC la fiecare pacient trebuie să fie personalizat şi ghidat de simptome, exacerbări, funcţie pulmonară şi comorbidităţi.

În **Capitolul 4** sunt trecute în revistă particularităţile de tratament farmacologic al BPOC. Sunt analizate studiile populaţionale majore cele mai recente.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) represents a major problem for public health worldwide, an important cause of morbidity and mortality at the global level and its burden is expected to increase in the next decade. COPD is one of the major non-communicable diseases (NCDs), which will be the predominant health problem of the 21st century. COPD remains the fourth leading cause of chronic morbidity and mortality at the global level, and it represents a major problem for public health (1). The burden of COPD it is likely to increase over the next several years. Some authors have predicted that the prevalence of COPD will continuously increase, and that it will become the third leading cause of death by 2020 (2) after coronary heart disease and stroke (3, 4). The complex pathophysiology of COPD and its heterogeneous, multisystemic manifestations and multiple comorbidities were recognized in the last years.

In order to increase awareness about chronic lung conditions, and in particular COPD throughout the world, the Global Initiative for Chronic Obstructive Lung Disease (GOLD), in collaboration with thousands of health care professionals and patient groups, have organized the *World COPD Day*. The 2016 theme for the World COPD Day is *Breathe in the Knowledge*. In 2016, the World COPD Day was hold Wednesday, November 16th.

The main question, that those of us dealing with patients with respiratory issues ask on regular basis, is why COPD remains such an important illness for the lay person community? Unfortunately, COPD is still underestimated by the general public and commonly underdiagnosed by healthcare professionals, and therefore, undertreated. In addition, another unmet need in COPD, is that only early diagnosis of disease and smoking cessation, are the most efficient methods to stop the decline of lung function and progression of this devastating illness.

From a clinical and basic science standpoint, COPD is now recognized as a systemic disease with multicomponent pathophysiology, and

heterogeneous and multisystem manifestations (5, 6). Over the past decade, the assessment of COPD was revolutionized by the development of new strategies in its management: from a simplistic approach, based exclusively on spirometry, to a complex system of evaluation which include clinical markers, functional parameters, health related quality of life, biomarkers, imaging, etc.

To date, there are three, well-known, and widely-accepted approaches in the assessment of COPD: GOLD assessment of severity, multilateral evaluation, and phenotyping (7).

GOLD assessment of severity, was developed in 1997, and initially was based exclusively on evaluation of lung function by FEV1. In 2011 was introduced the ABCD system based on evaluation of lung function, rate of COPD exacerbations, and symptomatic scores (MRC or CAT test). Finally in 2017, evaluation of lung function was excluded from classification ABCD system, and remained for diagnosis and follow up.

The most cited in the medical literature is the *BODE index*, which was proposed by Celli and Cote in 2004 (8). This index incorporates three variables, which are better predictors of mortality than the forced expiratory volume in one second - FEV1 (body mass index [BMI], dyspnea [assessed by Medical Research Council scale], and exercise capacity evaluated by 6-minute walking test). Moreover, the BODE index is useful in exacerbations, and more importantly, acts as a surrogate marker of future outcome after interventions, such as lung volume reduction surgery or pulmonary rehabilitation. The BODE index is considered excellent in understanding the severity of illness. This scoring system allowed new approaches in the management of COPD patients.

The BODE index and other multilateral staging tools have shown to be valuable tools, not only in the evaluation of severity and progression of disease, but also in the response to therapeutic interventions.

A newer assessment/indexing approach has recently been proposed, and includes different components of COPD, such as: *severity* (functional impairment, including airflow limitation, hyperinflation, arterial hypoxemia and reduced exercise capacity), *activity* (exacerbations, FEV_1 decline, and weight loss), and *impact* (individual patient's perception of disease severity and activity) (9).

The diagnosis and management of COPD in every patient should be personalized, and guided by symptoms, exacerbations, pulmonary function studies, imaging variables and other chronic comorbidities.

Health care providers must understand that the management of these patients is a "moving target". Unless we personalize treatment, our outcomes will remain dismal. A single day a year ("COPD World Day") should not be the only time of the year when we think about this epidemic illness. Clinicians caring for patient with COPD or at risk of developing it, need to continue to pursue diagnostic tools and therapeutic interventions aimed to improve the quality of life of these patients as well as to stop the exponential increase in the number of cases.

The incidence of COPD comorbidities increases later in life, decreasing the quality of life of patients with COPD, as well as complicating the management of the disease. The most frequently described comorbidities include skeletal muscle wasting, cachexia (loss of fat-free mass), lung cancer (small cell or non-small cell), pulmonary hypertension, ischemic heart disease, hyperlipidemia, congestive heart failure, normocytic anemia, diabetes, metabolic syndrome, osteoporosis, obstructive sleep apnea, depression, and arthritis (4, 10). Apart from these comorbid conditions, there are data suggesting that a significant number of other medical problems are seen more frequently among patients with COPD, and professional healthcare providers must be aware of them.

Unfortunately, COPD remains largely underperceived by patients and underdiagnosed by doctors, and as a result undertreated (1).

CHAPTER I. COPD DEFINITIONS AND ETIOLOGY

Definitions

In 1997 Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) was launched. GOLD was launched in collaboration with the National Heart, Lung, and Blood Institute, National Institutes of Health, USA, and the World Health Organization. GOLD's program is determined and its guidelines for COPD care are shaped by committees made up of leading experts from around the world.

GOLD Objectives are:

- Recommend effective COPD management and prevention strategies for use in all countries.
- Increase awareness of the medical community, public health officials and the general public that COPD is a public health problem.
- Decrease morbidity and mortality from COPD through implementation and evaluation of effective programs for diagnosis and management.
- Promote study into reasons for increasing prevalence of COPD including relationship with environment.
- Implement effective programs to prevent COPD.

In 1997, GOLD formed to promote COPD education and help set universal standards of diagnosis and treatment of COPD. GOLD tries to stem the tide of COPD cases and promote increased patient understanding.

For the first time management strategy for COPD was presented in the original GOLD document in 2001. Proposed original definition proposed by GOLD committee was: COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.

GOLD in 2011 suggested the definition: COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases (2).

In the GOLD 2011 report (11), the scientific committee proposed the following definition of COPD: a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients. This definition of COPD remains unchangeable last 5 years in GOLD guidelines: from 2011 till 2016.

If we compare old definition of COPD of 2001 with the new definition of 2011, then we can state that the complexity of disease and its heterogeneous and systemic character were finally recognized by respiratory physicians (1). In plus, the term "abnormal" inflammatory answer has been replaced by the "enhanced chronic" inflammatory response after the proposal of Siafakas et al (12).

In the GOLD 2017 report, last updated version of the guidelines (1), the scientific committee proposed the following revised definition of COPD: a common, preventable and treatable disease, that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.

Classic COPD classification

All classic classifications of COPD were based exclusively on the single parameter post-bronchodilator forced expiratory volume in one second (FEV1) as a expression of airflow obstruction (2, 13). Also FEV1 was considered as "golden standard" and used widely for diagnosis, treatment of COPD and was one of the most of important outcomes in large clinical studies (*Table 1*). After the appearance in literature of the first serious evidences that COPD is a complex disease with multiple pulmonary and extrapulmonary manifestations, it became evident that old COPD classifications cannot reflect complexity of disease. COPD patients cannot be described by only using the severity of airflow limitation.

Table 1

Classification of Severity of Airflow Limitation in COPD by Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) 2001-2010

SEVERITY	FEV1	FEV1/FVC
GOLD 1: Mild	$\geq$ 80% predicted	< 0.70
GOLD 2: Moderate	50% $\leq$ FEV_1 < 80% predicted	
GOLD 3: Severe	30% $\leq$ FEV_1 < 50% predicted	
GOLD 4: Very Severe	FEV_1 < 30% predicted	

*Based on Post-Bronchodilator FEV1
FEV1 - Forced expiratory volume in one second
FVC - Forced vital capacity

Smoking as a major risk factor for COPD

There is an indisputable connection between COPD and smoking since approximatively 40% of those who developed the disease are smokers or ex-smokers (14). In a recent study there was even found a correlation that current smokers with reduced time to first cigarette after waking are more prone for COPD development related to those with prolonged one (15). There is mounting evidence relating to a higher nicotine dependence between smokers with COPD than amidst smokers without this condition (14). Some studies scored this dependence using Fagerström Test for Nicotine Dependence and it was also determined that for every point of this test there is a raise of 11 % of the probability to develop COPD (16). Unfortunately the risk of developing COPD is high enough not only for current cigarette smokers but might form in early childhood as a result of maternal smoking (17).

This part of chapter represents a brief review of particular aspects related to the link between cigarette smoking and COPD.

Impact of smoking on pathogenesis of COPD

Smoking has deleterious actions especially on lungs through varied mechanisms. According to common views the major ones are: inflammation, oxidative stress and the increase of the protease activity, the last two maintain and increment the first one. Smoking's detrimental effects on lung include mucous glands hyperplasia, inflammatory infiltrate and the obstruction of the airways, especially the smallest ones (in COPD airways with a diameter of < 2 mm being the dominant site of obstruction), number of vibratile cilia's reduction, alveolar destruction, metaplasia and reduction of small arteries diameter (5). Oxidative stress determines lung components

lesion such as epithelium, airways and alveoli also it leads toward the increase of proteases that degrade lung's matrix (18-20).

Speaking about the inflammatory process induced by cigarette smoking that will further degenerate into COPD there has been studied the role of various cells like: macrophages, neutrophils, different subsets of T and B lymphocytes and dendritic cells (18). Hoetzenecker et al provided data concerning the part of CD4+ cells in preserving the inflammatory alteration in COPD patients by displaying a proliferative response toward elastin and collagen exquisitely of lung origin (21). Another study concluded that CD(+)(8)T-lymphocytes infiltration is responsible for pulmonary inflammation that later induces COPD (22).

It was settled that the direction toward a pro-inflammatory versus anti-inflammatory response in COPD patients is established by specific shifts in the equilibrium of Th17/Treg cells (23). Probably dioxins contained in smoke, which exhibit the function of ligands for the aryl hydrocarbon receptor might be implied in this shift since this receptor has controlling effects on Treg/Th17 balance (24). Supplementary to the beforehand presented studies is the evidence that there is a consistent increasing of IL-17A in severe to very severe COPD (GOLD III/IV) related to smokers and never-smokers without COPD (25). Along with an increase in IL-17 there is a raise in an extensive variety of other molecules such as: TNF-alpha, IL-1beta, granulocyte-macrophage colony-stimulating factor (GM-CSF), transforming growth factor (TGF)-beta1, MCP-1, LTB4, IL-8 elaborated by pulmonary epithelium (26), (27); chemotactic chemokines like CXCL9, CXCL10, and CXCL11 secreted by macrophages (28); also proteolytic enzymes MMP-2, MMP-9, MMP-12, and cathepsins (29).

The release of these molecules activates a complex reaction cascade that urges lung matrix's degeneration and directs toward COPD. Likewise there has been discovered that smokers with COPD develop fragmentation of the reticular basement membrane in lungs, a feature that potentially exposes them to greater extension of the inflammation process (30). That defines the relevance of therapies directed toward reducing the production of all these molecules that do not only initiate but also preserve smoke induced inflammation in lungs. According to a novel study accomplished on mice IL-8 production might be diminished by AMP-activated protein kinase (31). By suppressing cytokine production not only the inflammation diminishes but also the regenerative process can be initiated there. Among other novel treatments implicated

in epithelial regeneration is azithromycin - capable of reversing vascular endothelial growth factor (VEGF) aberrant expression mostly induced by smoking and it also inhibits the production of reactive oxygen species (32). To this drug also has been attributed the role of suppressing the CD8 T cell granzyme B in COPD patients (33).

An innovative facet in COPD pathophysiology induced by cigarette smoking is CC16 (a marker of lung epithelial injury produced by Clara cells) that are found in a diminished proportion in COPD might exhibit a regenerative action towards airway epithelium (34).

An earlier research paper stated that chronic cigarette smoke exposure directs toward the waste of CD28 and to the up-regulation of NK cell receptor expression on T cells (35) with common views comes another study that identified a decrease of CD4+ and CD8+ T cells during acute exacerbations of COPD (36). In discord with this the review article that points out that there is an augmentation of CD8+T-cells in the lungs of COPD patients that are meanwhile current smokers (37),(38) as well as another study that spotted an increment in the percentage of CD8+CD45RA+ T-lymphocytes, that possess greater destruction potential for lung tissue as long as they have accomplished the final maturation-activation state (39).

A possible autoimmune origin of smoking induced COPD

During the last years the idea of the autoimmune component in COPD is intensively speculated. That is why Faner et al tried to match Witebsky postulates (criteria for autoimmune diseases) in order to consider a disease of autoimmune origin and accomplished their goal by grabbing direct, indirect and circumstantial evidence from a considerable number of studies. Also they presumed that dendritic cells in smokers are partially activated in healthy subjects' lungs by autoimmune antigens not by DAMPs that explains the induced tolerance to them comparative to COPD patients where these cells maturation is thorough by autoimmune agents and DAMPs (40).

Among the studies debating the autoimmune origin of COPD one found out that CD8/CD28(null) T cells produce co-stimulatory molecules that might wield a part in the autoimmune responses in COPD (41). Another evidence demonstrating the autoimmune nature of COPD could be considered it's association with 18 autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, psoriasis and other diseases (42). Also there are various researches debating the

presence of ubiquitous autoantigens and subsequently autoantibodies that also serve as an evidence for the autoimmune component of COPD. Along with studies in regard to autoantibodies against lung matrix proteins performed on mice (43) are researches which operated with COPD patients and identified diverse kinds of antibodies like: antiendothelial cell antibodies (44), also autoantibodies to thyroid-specific antigens, thyroid peroxidase (TPO), thyroglobulin, carbonyl modified self-protein, etc (45). What is intriguing about antibodies against carbonyl modified self-protein is that they have a tendency toward IgG1 profile and their titer inversely correlates with the severity of COPD. At least this was established in a single study and needs further confirmation. The study assumes that it might be possible to ascertain the status and phenotype of the disease by determining the antibody profile (46). A different view is projected in an investigation where they suppose that future studies need to be directed toward antibody complexes that reside in the lung tissue comparatively to circulating ones because they did not identify any difference between COPD and control subjects after adjusting anti-elastin antibody levels (47).

Amidst other mechanism involved in autoimmunity is incriminated the peroxynitrite radical which is generated in great amount in the lower airways of COPD patients and it might potentially induce the elaboration of neo-autoantigens (18). In consonance with antecedent research that spotted a modification in the CD4 phenotype concretely in lungs, owing to smoking exposure (48) the disclosure of a peculiar Th17 cell subset and precisely of the T cells that display chemokine receptor CCR6 could gain its place in the autoimmunity origin of COPD (49).

Epigenetics changes determined by smoking in COPD

Taking into consideration the fact that exclusively a proportion of 20% of smokers will develop COPD there emerges the idea that there have to be additional factors implied in the pathogenesis of the disease. A common element of COPD's formation is the genetic predisposition. A substantial genetic contributor is the nicotinic acetylcholine receptor gene cluster CHRNA5-A3-B4 that acts by modifying smoking behavior. This explains the aspect of smokers who possess the rs16969968 risk allele in CHRNA5 of smoking heavier than the others and of being predisposed to a greater risk for the advance of COPD (50). Also a high risk for developing COPD exists in patients with the rs1051730 allele in CHRNA determining them to attain airway obstruction and destruction of lung parenchyma (51).

Some studies hypothesized that there might stand a central mechanism that exerts adjustments in the transcription of the airway basal cell genes affected by cigarette smoking which potentially can lead to COPD. This much the discovery of this mechanism could help in identifying a way to restore the molecular phenotype of the smokers' airway basal cells (52). But certainly first-rate solution for COPD prevention is smoking cessation (53). Also there are important evidences supporting smoking cessation as one of the best solutions for COPD patients because it leads to a lower level of bronchial epithelial remodeling but only after a prolonged period as it was stated in a study >3.5 years (54).

There prevail even tighter connections between epigenetic modifications provoked by smoking that could potentially lead to COPD (50). The idea of epigenetic changes implicated in COPD pathogenesis came after there was established that those single-nucleotide polymorphisms distinguished through genome-wide association studies connected with COPD cannot reveal the frequency of the disease manifestation (19). Explained differently there is an exceeding number of COPD patients that lack risk alleles implicated in this disease pathology so there has to be another factor to blame for the development of this disease.

According to recent studies the most frequent epigenetic modifications entangled with COPD development are: DNA methylation, histone acetylation and deacetylation, phosphorylation and ubiquitination (55). Epigenetic alterations are not only incriminated in inflammation but also in cellular senescence and steroid resistance. For example diminution of the HDAC2 (histone deacetylase) leads not only to inflammatory response but also to steroid resistance and senescence in lung (56). So it can be cogitated that a cause of glucocorticosteroid treatment's inefficacy in COPD might be histone deacetylase. What is even more curious is the idea of other epigenetic modifications in COPD's therapy resistance that is why by overcoming these changes it will be possible to improve patients' outcome. Modifications in the activity of histone deacetylase and DNA-methylation patterns could be induced even to fetus by its exposure to maternal smoking during pregnancy (17). Maternal smoking during pregnancy is also associated with transformations in DNA methylation of CpG dinucleotides of distinct gene regions. The DNA methylation status is linked not only with the existence of COPD and other lung disorders but conjointly to their severity (57).

Furthermore in some studies there is reflected the idea that epigenetic changes are incriminated for disturbing the balance amidst patho-

genic and commensal pathogens determining the exhibition of neo-epitopes (50). These neo-epitopes serve for autoantibody elaboration and sustain lung inflammation. Even more strikingly remains the fact that cigarette smoking promotes epigenetic changes in different cells. For example an intriguing paper related about a prevalent down-regulation of multiple microRNAs (miRNAs), precisely in lung macrophages and hypothesized that it might serve as a predominant manager of the disease-promoting macrophage phenotype (58).

It is very important to add that these epigenetic changes can reverse after smoking cessation. Toward the probable time of reverse most of the researchers agree on long period of smoking cessation while a quite novel study found that there is possible to observe specific loci methylation modifications towards non-smoking status within 12 weeks of smoking arrest (59). (14)[5]

Conclusions

Current researches in regard to the association between cigarette smoking and COPD did not reveal a broad area of unknown aspects that require further investigation. Alongside confirming some of the existing theories there were determined new associations. To be more precise the evidences about the autoimmune origin of COPD gained more ground and the relevance of epigenetic changes in COPD pathogenesis.

Undeterred by the fact that autoimmunity represents a black box full of surprises identifying an autoimmune origin in COPD induced by smoking might serve not only as a starting point for new research but also strengthens the relevance of smoking cessation in such patients. By establishing tighter connections amidst smoking and the autoimmune origin of COPD similar to well defined autoimmune diseases there will be achievable to direct COPD's therapy toward different classes of medicine.

Along with these come the discoveries concerning epigenetics modifications induced by smoking, more importantly being the fact that they can be induced even by maternal smoking predisposing the child to future lung pathology. Studies in regard to histone deacetylation that induced steroid resistance in COPD patients direct research toward novel strategy therapies able to overcome such epigenetic changes.

What concerns the available approaches toward smokers with COPD remains smoking cessation as the vital step in defeating the disease and preventing other deleterious effects of cigarette smoking.

CHAPTER II. OUTCOMES FOR ASSESSMENT OF COPD

Outcomes

Spirometry is the golden standard for the diagnosis of COPD, but its value is limited by the presence of a large range of clinical and functional variability in patients with COPD (especially the elderly patients), which is supported by the results of numerous studies that pointed out the lack of correlation between pulmonary function assessed by FEV1 and the symptoms (dyspnea, considered the chief symptom); the frequency of exacerbations, effort tolerance (assessed by the distance completed in the 6-minute-walk test); the quality of life (evaluated by St. George's Respiratory Questionnaire - SGRQ); the post-operative risk; the mortality risk.

The multidimensional approach of chronic respiratory diseases required the quantification of the quality of life, given that the functional evaluation does not strongly correlate with the degree of dyspnea and the quality of daily life of the patients.

St. George's Respiratory Questionnaire (SGRQ) currently represents the most applied questionnaire in the evaluation of the quality of life in the chronic respiratory diseases. The administration of SGRQ questionnaire can detect changes in the quality of life in the absence of significant modifications of FEV1. The conducted studies prove that this instrument is reproducible, valid and sensitive. The scores of the SGRQ questionnaire significantly correlate with different parameters, thus: the score of the symptoms with the frequency of the wheezing ($r = 0.32$, $p < 0.0001$), the activity score with the 6-minute-walking distance.

The quantification of the degree of dyspnea imposed the description and validation of some scores, among which the MRC (Medical Research Council) score is the most common for the patients with COPD. The MRC dyspnea scale is a validated, easy-to-use instrument, 4 points being the maximal rate of severity.

Developed by Celli and colleagues in 2004, the BODE index is a complex system that assesses the mortality risk in patients with COPD. Its creation primarily included the identification of four risk factors for mortality of the patients with COPD, then their validation took place (60).

Conventionally, the classification of COPD severity (61, 62) was based on the grade of airways obstruction evaluated by FEV1 (GOLD, ATS/ERS), which was used as a standard indicator for determining the disease progression and for appreciating the need for treatment, but it is not as useful for assessing the effect of therapeutic interventions (63). Also, COPD is associated with a list of clinical manifestations, which are not caused directly by the limitation of the airflow (progressive dyspnea, reduction of effort tolerance, pulmonary hypertension, peripheral muscle weakness and malnutrition) (64, 65). Moreover, the latest studies proved that FEV1 is not the only exclusive predictor of the prognosis, other risk factors being also identified (hypoxemia, hypercapnia, 6-minute-walk distance, low BMI) (66).

It was proved that the only measure that slows down the decline of the pulmonary function is the quitting of smoking (62, 67-69). Randomized controlled trials have proved that there is no medication that, compared to *placebo*, exerts a more significant influence on FEV1 on the long term (62). All these measures lead to the necessity to define new parameters for the assessment of the disease progression (70-74). Nowadays, there are many parameters that can be used for the appreciation of the disease progression: inspiratory capacity (IC), dyspnea, health related quality of life, BODE index and frequency of COPD exacerbations (63, 75-77).

In *Table 2* presented potential outcomes which can be used for assessment of COPD. They can be classified in 4 major groups: clinical or symptomatic, functional or physiologic, biological markers and radiological markers.

Table 2

Potential outcomes for assessment of COPD

Clinical Markers	Functional parameters	Biomarkers	Radiological Markers
Dyspnea (MRC) Health Related Quality of Life (SQRQ, CAT, CCQ) Exacerbations (rate and type)	Spirometry (FEV1, FVC, FEV1/ FVC) Bodypletismography Sleep (AHI)	Expectorated markers of inflammation (cellular and soluble) Expired gases and air condensate CRP Procalcitonin Anemia	HRCT (quantification of emphysema, quantification of airways disease)

Functional (Physiological) parameters

Being the mainstay of the diagnosis and staging of COPD, spirometry has been studied thoroughly. FEV1 is negatively correlated with the survival of COPD patients and the frequency of exacerbations. Forced expiratory flow (FEF) 25%-75% reflects the degree of small airways disease and is an early marker of COPD. Reversibility of airflow limitation with bronchodilators suggests asthma-COPD overlap. TLCO can differentiate between predominantly bronchitic versus emphysematous patients.

Although the determination of the inspiratory capacity (IC) is widely used for appreciating dynamic and static hyperinflation in patients with COPD, there are no longitudinal studies that demonstrate the changes of IC over time (78-80). In a study including 689 patients with COPD, it was proved that pulmonary hyperinflation, measured by the *inspiratory capacity - to - total lung capacity ratio* (IC/TLC), is an important and independent mortality predictor. The death risk was critical when the IC/TLC ratio was under 25% (81).

Longitudinal and transversal studies have shown that the effort capacity decreases with age in healthy subjects. Oga and colleagues (82) have proved that the decline of the annual capacity of the oxygen intake (VO2 max) is 0.5 higher (SD ± 0.3 ml/kg/minute) in elderly patients (69 ± 1 years old, FEV1 = 46% ± 1) with the initial maximal VO2 being 14,8 (SD ± 0.3 ml/kg/minute).

The functional capacity is appreciated with the 6-minute-walk test (6MWT) (83-87), which represents a simple, reliable, standardized,

inexpensive test, that can be employed successfully in people of a certain age (88, 89). Pinto-Plata and colleagues (90) have been monitorising patients with COPD for 2 years, pointing out that the decline of the walked distance during the 6-minute-walk test (6MWD) amounted 26 (SD ± 37) m/year, while in healthy people of a similar age the distance increased by 12 (SD ± 25) m/year.

The first large long-term observational study, in which reference equations and 6MWT results of major clinical impact were applied and validated and the association with mortality was assessed, was finished in 2008 by C. Cote and colleagues (91, 92). This study confirmed the clinical relevance of the 6MWT and, also, the role of 6MWD as the predictor of survival (93). It was proved that the absolute value of the 6MWD is a better mortality predictor for COPD patients, compared to FEV1 and BMI. The 6MWD result under 350 meters was associated with a poor prognosis of the disease. In this study, the statistically significant correlation between the mortality and the 6MWT was observed, both in women ($r = -0.49$, $p < 0.0001$) and in men ($r = -0.38$, $p < 0.0001$) (91).

Clinical Markers

Increased BMI is associated with predominantly bronchitic changes, higher level of pulmonary and extra-pulmonary inflammation and higher oxidative status (94), more frequent exacerbations, but also with reduced lung hyperinflation (95). Exercise capacity can precisely predict severe COPD exacerbations and mortality. ECLIPSE study demonstrated that less than 334 metres in 6 minutes walking distance (6MWD) is suggestive of high risk of death and less than 357 meters predicts severe exacerbation needing hospitalisation, during the following year (96). Sputum quantity is associated with worse airflow limitation, respiratory symptoms, quality of life and less emphysema (97). In addition, the presence of different comorbid diseases poses an additional burden to these patients and represents different markers.

Dyspnea

The perception of dyspnea varies greatly among patients with COPD, especially in persons of a certain age (98-100). There are two major goals in the measurement of dyspnea in patients of a certain age suffering from COPD: assessment of the dyspnea severity and dynamic evaluation of the dyspnea of a given patient (101).

There are many questionnaires for dyspnea quantification. These surveys can be used for evaluating dyspnea triggering stimuli, for the dyspnea daily activity relationship and for the dyspnea physical activity tests ratio (102).

There are three big groups of surveys: unidimensional, that can be used for evaluating dyspnea triggering stimuli (OCD - *Oxygen Cost Diagram*, Modified Borg, Borg CR 10, Borg RPE Scale, VAS - *Visual Analogue Scale*); specific for dyspnea - MRC - *Medical Research Council*, *Feinstein Index of Dyspnoea*, *The Cancer Dyspnoea Scale* (CDS), *Dyspnoea Exertion Scale*, *Dyspnoea Assessment Questionnaire*, *Breathlessness Assessment Guide*, *Cincinnati Dyspnea Questionnaire*, *Baseline Dyspnoea Index/Transition Dyspnoea Index* (BDI/TDI), specific for the disease - *Chronic respiratory disease questionnaire*, *St.George's Respiratory Questionnaire* (SGRQ), *Seattle Obstructive Lung Disease Questionnaire*, *Lung Cancer Symptom Scale*, *revised ALS Functional Rating Scale* (99, 103, 104).

Baseline Dyspnoea Index / Transition Dyspnoea Index (BDI/TDI) is a multidimensional clinic instrument, which was developed for the exhaustive assessment of the severity of the dyspnea in patients with chronic pulmonary diseases. *Baseline dyspnea index* (BDI) includes 3 compartments: activities that cannot be completed, the amplitudes of the load and effort that trigger dyspnea (103). *Transition dyspnea index* (TDI) determines the changes of these data over time. A minimal clinically significant change is a point.

The MRC - *Medical Research Council* dyspnoea scale (see *Table*) has been in use for many years for grading the effect of breathlessness on daily activities of the patients. This scale measures perceived respiratory disability, the MRC dyspnoea scale is simple to administer as it allows the patients to indicate the extent to which their breathlessness affects their mobility. Over the time were proposed some changes in the MRC dyspnoea scale and was developed the modified Medical Research Council (mMRC) scale (see *Table 4*). Recently was proposed The extended Medical Research Council Dyspnoea score (eMRCD), which permits assessment of dyspnea in the last 3 months (*Table*).

Jones and colleagues (105) and Oga (82), demonstrated that the MRC score changes by 0.1 unit per year in two different patient cohorts. In the cohort consisting of 76 patients with COPD, Mahler and

his colleagues (102) described a decreasing of 0.7 (SD ± 2.9) of the TDI in 2 years. The same drop rate of the TDI was demonstrated by Casaburi in the research including 325 patients, who received placebo, as part of a randomized controlled study with tiotropium bromide (106).

The clinical appreciation of the dyspnea is a key part of the clinical examination of the patients with chronic pulmonary diseases, because dyspnea is one of the major complaints of the patients with COPD, also being the sum of the impact of pathophysiological and psychological factors (68, 103, 107, 108). By standard evaluation of dyspnea, the doctor can appreciate the severity of dyspnea and its impact on the functional status of the patient (109-111).

The gradation of dyspnea is also useful for establishing the effectiveness of the drug treatment (108, 109, 112, 113). Enough evidence about the effectiveness of the treatment in stopping the decline of the pulmonary function has not been obtained yet, therefore the main goal of the drug treatment continues to be the amelioration of clinical symptoms, especially the dyspnea (113, 114).

Also, the dyspnea is a survival predictor in patients suffering from COPD. In a prospective, multicentric trial, conducted by Nishimura and his colleagues on 227 patients with COPD (115), the survival rate was not significantly associated with the staging of COPD, based on FEV1, and the dyspnea appreciated by the MRC scale was a better survival predictor ($p < 0.001$).

Table 3

Medical Research Council (MRC) Dyspnoea Scale (116)

Severity	Degree of breathlessness related to activity
Grade 1	Not troubled by breathless except on strenuous exercise
Grade 2	Short of breath when hurrying on a level or when walking up a slight hill
Grade 3	Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace
Grade 4	Stops for breath after walking 100 yards, or after a few minutes on level ground
Grade 5	Too breathless to leave the house, or breathless when dressing/undressing

Table 4

The modified Medical Research Council (mMRC) scale

Severity	Description of Breathlessness
Grade 0	I only get breathless with strenuous exercise
Grade 1	I get short of breath when hurrying on level ground or walking up a slight hill
Grade 2	On level ground, I walk slower than people of the same age because of breathlessness, or I have to stop for breath when walking at my own pace on the level
Grade 3	I stop for breath after walking about 100 yards or after a few minutes on level ground
Grade 4	I am too breathless to leave the house or I am breathless when dressing

Table 5

The extended Medical Research Council Dyspnoea score (eMRCD) (117)

eMRCD score 'In the past 3 months, when you were feeling at your best, which of the following statements best describes your level of breathlessness?'	(Circle)
Only breathless on strenuous exertion	1
Breathless hurrying on the level or walking up a slight hill	2
Walks slower than contemporaries, or stops after walking on the level for 15 min	3
Stops for breath after walking 100 m, or for a few minutes, on the level	4
Too breathless to leave the house unassisted but independent in washing and/or dressing	5a
Too breathless to leave the house unassisted and requires help with washing and dressing	5b
Guidance notes: *Remember that you are asking the patient about their level of breathlessness on a good day over the preceding 3 months, not breathlessness during an exacerbation/on admission. A patient only achieves a higher grade if they are as breathless as defined in that higher grade.*	

Health Related Quality of Life

World Health Organization defined the quality of life as "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (68, 118, 119). The quality of life can be defined in many ways and can have various meanings for each person.

More specifically, by the quality of life in medicine we understand physical, psychic and social well-being, as well as the patients' capacity to exert their regular duties, on a daily basis. Kaplan (120) suggests a common definition: the quality of life reflects preferences for certain states of health that allow the amelioration of morbidities and mortalities and that are expressed by one single weighted index – standardized age, depending on the quality of life.

Health Related Quality of Life (HRQL) in terms of healthcare has been of great interest for the last 10 years, determining the development of surveys as working instruments for its assessment. Measuring the HRQL is important for evaluating the impact of the disease on the life of the patient, but it can also assess the consequence of a therapeutic procedure (pharmacological or non-pharmacological, for long term oxygen therapy, pulmonary rehabilitation, pulmonary transplant), eventually comparative, with classic measurements of the severity of the disease (e.g. FEV1). Many factors, such as age, the socioeconomic and social status can affect many aspects of the HRQL (109, 121).

HRQL assessment allows to determine the degree of limitation of the normal existence under the influence of the disease and to develop the optimal treatment strategy with the justification of individual characteristics of the patient (122). Also, the assessment of HRQL allows to determine the effectiveness of therapeutic measures and of disease management (118, 123, 124).

There are many questionnaires that can be used to quantify the quality of life, both as *generic* instruments that apply to several groups of subjects, to evaluate all types of diseases or conditions, applicable to any medical facility or even in general population (*The MOS 36/Item Short/Form Health Survey* - SF/36, *Sickness Impact Profile* - SIP, *European Quality of Life* - EuroHRQL, WHO *Quality of Life* - WHOHRQL/100, *Nottinham Health Profile*), and as *specific* instruments for chronic respiratory diseases (*Asthma Quality of Life Questionnaire* - AQLQ, *Asthma Quality of Life Questionnaire Marks* - AQLQ/M, *St. Georges Respiratory Questionnaire* - SGRQ, *Clinical COPD Questionnaire* - CCQ, *Living with Asthma Questionnaire* – LWAQ, *Respiratory Quality of Life Questionnaire*) (125).

Generic questionnaires are designed to assess the health status of the population, regardless of a concrete nosology, can be used in healthy or sick people. More often, they are used in epidemiological

studies. A disadvantage of generic questionnaires is low sensitivity to changes in the health status within a specific pathology: they are more sensitive to deterioration than to improvement of the quality of life.

Specific questionnaires are used to assess the health related quality of life of patients with a specific disease. It is rational to use specific questionnaires for assessment of the efficacy of the treatment a certain nosology.

St. George's Questionnaire (SGRQ) developed by professor P. Jones in 1991 consists of 76 questions, structured into 2 parts: one part reflects the symptoms and the second part - activity and impact. The total score is also generated, which is 100 points (126).

St. George's Questionnaire is a tool for assessing the quality of life of patients with COPD, which is valid, reliable and sensitive. Using SGRQ can capture changes in the HRQL without significant changes to FEV1. In a study, Kuzniar and his colleagues showed significant correlations between SGRQ and symptoms, self-evaluation of health status and the degree of depression (105). St. George's Questionnaire also has prognostic properties. It was proved that it is the true predictor of visits to the doctor (127). SGRQ allows a more accurate emphasis of the patient groups with different degrees of bronchial obstruction (128). Comparative analysis of the HRQL of patients with moderate and severe stages of COPD showed a weak correlation between FEV1 (or PEF) and SGRQ scores.

Incalzi R. (129) proved that COPD has a greater impact than asthma on the quality of life of elderly patients in stable clinical conditions. In previous studies, after investigating the impact of the obstructive ventilator defect on the HRQL of the elderly, conflicting results were obtained (130-132).

Some authors have shown improvement of HRQL with age in patients with COPD, which was explained by the restriction of daily activities by patients (133). In contrast, another group of authors proved the persistence of HRQL deterioration with age (119, 130, 134). Peruzza S., Sergi G. and colleagues suggested that COPD is the most frequent cause of severe deterioration of the HRQL, of the physical activity and of the functional status in elderly patients, and that the degree of deterioration depends on the severity of bronchial obstruction (130).

Although both asthma and COPD cause airflow limitation similarly COPD is linked to a more significant deterioration of lung functions, greater degree of airway obstruction and overall health problems (135, 136). Besides that COPD tends to cause psychiatric disorders and sleep dis-

turbances further deteriorating life quality of the patient (137). Patients with COPD often tend to suffer from other comorbidities which in combination further affect their HRQL. Frequent exacerbations of COPD also present a risk since they are linked to sudden cardiac death which shows that COPD is no longer the disease that affects only the respiratory system (138).

In our study (139) the patients were divided arbitrarily into two groups according to the age: to elderly ≥ 65 years and "younger" COPD patients < 65 years. The first group consisted of 87 patients with mean age 73.1±5.5 years, 57 were males (65.5%) and 30 were females (34.5 %). The second group consisted of 93 patients with mean age 54.8±3.1 years, 60 were males (64.5%) and 33 were females (35.5 %).

The demographical and general data of the patients is shown in *Table* . The weight, the height, and thus body mass index were similar in both groups. In the groups was similar FEV1: in the first group FEV1 (% from predicted) was 41.7±11.7 % and in the second group FEV1 was 41.8±13.3 % ($p > 0.05$). Rate of COPD exacerbations was assessed retrospectively and was similar in both groups: 4.1 ± 0.7 versus 4.5 ± 0.6 ($p > 0.05$). Charlson index was higher in elderly COPD patients (2.8 ± 0.7 points), the most frequent comorbidities were heart failure (67%), systemic hypertension (53%) and coronary heart disease (30%). Charlson index in "younger" COPD patients was 1.5 ± 0.7 points, the most frequent comorbidities were systemic hypertension (38%), heart failure (25%), and anemia (23%).

The total SGRQ score was higher in the elderly group (*Table 7*), in comparison with the younger patients (69.7 points versus 57.4 points, $p < 0.0001$). The SGRQ „activity" and SGRQ „impact" scores were higher in elderly (65.7 points versus 53.7 points, $p < 0.05$ and 67.1 points versus 55.7 points, $p < 0.05$), wheras the difference between SGRQ „simptoms" score was not statistically significant (79.1 points versus 82.7 points, $p > 0.05$). There is a tendency for the „symptoms" score to increase in "younger" adults which may be explained by the higher impact of COPD on their lives.

The quality of life assessed by CCQ also showed to be more affected in elderly patients: total CCQ score 3.3 versus 3, $p < 0.05$, the functional and mental domain scores were more elevated in elderly 2.7 versus 2.3, $p < 0.05$, and 4.1 versus 3.5, $p < 0.05$ respectively, but the symptoms domain score was similar in both groups (3.3 in "younger" versus 3.4 in elderly patients, $p > 0.05$). It is important to mention that the mental score al-

so tends to be affected which is usually underestimated in clinical practice.

At the same time it is crucial to evaluate the HRQL of the patients depending on their COPD stage. It was demonstrated that the HRQL in COPD patients decreases with the progression of the disease. Therefore each COPD stage can be characterized not only by functional parameters, but also using the HRQL (see *Table 8*).

The analysis of the links between the HRQL scores in 180 patients showed that patients with severe obstruction (IV GOLD stage) had a higher score ($p < 0.01$) than those with II and III GOLD stages. The total SGRQ score in elderly COPD patients group with IV GOLD stage was 74.7±11.7 points, whereas II and III GOLD stages, 57.1±11.1 points and 68.5±11.8 points respectively. In the "younger" COPD patients group the highest total value of SGRQ score was in patients with COPD who had IV stage of the disease (66.7±12.3 points).

Pearson correlation coefficient analysis demonstrates in elderly COPD patients a significant positive correlation between the BODE and the total scores of the CCQ ($r=0.6$, $p<0.01$) and SGRQ ($r=0.45$, $p<0.01$). Pearson correlation coefficient analysis shows in "younger" COPD patients a significant positive correlation between the BODE and the total scores of the CCQ ($r=0.6$, $p<0.01$) and SGRQ ($r=0.4$, $p<0.01$).

The multivariate logistic regression method (forward stepwise regression) was applied for identifying of the independent predictors in elderly and "younger" COPD patients for HRQL deterioration. The results of the statistical analysis for the both groups are presented in *Table 9*, *Table 10*, *Table 11* and *Table 12*. The forward stepwise regression analysis shows that the BODE index, Charlson index and rate of exacerbations are the important predictors of deterioration of HRQL in COPD elderly patients which explains 29% of the SGRQ total score. In the "younger" COPD patients the coefficient of determination R^2 was 0.27, while BODE index and the rate of exacerbations were the predictors for HRQL deterioration.

One of the main goals of our study was to investigate the impact of COPD on HRQL. Elderly patients with COPD have a deterioration of psychosocial aspects of life as well as a decline of the daily physical activity, therefore it is essential to establish a link between COPD and HRQL in elderly patients.

The previous studies that investigated how obstructive ventilatory defect affects the HRQL in elderly patients had some controversial

results. Several authors showed a better HRQL in elderly patient with COPD, which may be explained by the restriction of some of the daily physical activities (140). Other researchers, on the contrary, have found a persistent deterioration of HRQL to be associated with age (141).

In our study HRQL was affected more in COPD elderly patients in comparison with "younger" COPD patients, the fact confirming that COPD has a huge impact on HRQL in elderly patients. In other studies (128, 130) bronchial obstruction was shown to have an important role, mainly by the relationship between the values of FEV1 and SGRQ, and it was attested by logistic regression analysis.

Our data suggests that COPD is a major factor for severe deterioration of HRQL, limitation of physical activity (good correlation between 6 MWD and FEV1 – $r = 0.6$, $p < 0.01$) and functional status in elderly patients with COPD and this influence largely depends on the severity of airway obstruction. It was demonstrated that with the disease progression the HRQL and physical activity tends to decline, thus elderly patients with more severe stage of COPD have a lower HRQL in comparison with COPD patients with moderate stage of the disease.

Due to the conducted research it was revealed that there is a significant correlation between the SGRQ and CCQ domains and BODE index in elderly and "younger" adult patients which is stronger if compared to the correlation with the severity of airway obstruction. In elderly patients BODE index had a strong correlation with the total SGRQ score ($r = 0.45$), but not as strong as in the "younger" adults ($r = 0.6$).

Besides, a correlation between the health related quality of life, evaluated by SGRQ questionnaire, and BODE index was pointed out (142). Ong and colegues describes a weak to moderate correlation between the SGRQ questionnaire and BODE index ($r = 0.27$-0.46), whereas the correlation between COPD stages and some of the SGRQ questionnaire domains (total, impact and activity) was weaker ($r = 0.27$-0.28). Higher BODE indexes are associated with higher total SGRQ scores. Some very strong correlations were found between BODE quartiles and total SGRQ scores ($r = 0.914$; $p < 0.01$). In contrast, GOLD stages showed moderate correlation with total SGRQ scores (143). There is an association between health-related quality of life, as assessed by the SGRQ and the BODE index within the entire spectrum of COPD severity. Even in early disease stages and BODE index zero, health-related quality of life is already impaired (144).

Conclusion

Elderly patients with COPD have a more severe deterioration of the quality of life. The BODE index, Charlson index and rate of exacerbations were found to be the major determinants of quality of life in COPD elderly patients, while BODE index and the rate of exacerbations serve as main determinant factors in "younger" COPD patients.

Table 6

Caracteristics of patients with COPD according to age

Variable	Younger COPD Patients (n = 93)	Elderly COPD patients (n = 87)	p
Age, years	54.8±3.1	73.1±5.5	<0.01
Weight, kg	78.3±17.3	73.7±17.7	>0.05
Height, m	1.67±0.07	1.66±0.08	>0.05
BMI	26.7±5.6	25.8±5.8	>0.05
FEV_1, %	41.7±11.7	39.9±13.2	>0.05
FVC, %	49.4±16.5	47.2±20.9	>0.05
FEV_1/FVC ratio	57.5±10.7	59.5±8.5	>0.05
mMRC score	3.2±0.7	3.7±0.63	<0.01
6MWD, m	267.5±87.2	203.7±81.9	<0.01
BODE score	5.3±1.8	6.8±1.5	<0.01
Pack-years	31±15.7	33.5±16.7	>0.05
Rate of exacerbations	4.1±0.7	4.5±0.6	>0.05
Charlson index	1.5±0.7	2.8±0.7	0.0001
Values are means ± SD BMI = Body mass index.			

Table 7

HRQL in the younger and elderly COPD groups

Variable	Younger COPD patients	Elderly COPD patients	p
SGRQ symptoms score	79.1±11.7	82.7±12.9	>0.05
SGRQ activity score	53.7±13.4	65.7±12.5	<0.05
SGRQ impact score	55.7±11.4	67.1±12.4	<0.05
SGRQ total score	57.4±12.7	69.7±11.4	<0.05
CCQ symptoms score	3.3±0.9	3.4±0.8	>0.05
CCQ functional domain score	2.3±0.8	2.7±0.7	<0.05
CCQ mental domain score	3.5±1.1	4.1±0.9	<0.05
CCQ total score	3±0.7	3.3±0.6	<0.05
Values are means ± SD			

Table 8

Comparison between grades of COPD severity regarding SGRQ and CCQ scores in younger and elderly COPD patients

	Younger COPD patients				Elderly COPD patients			
COPD stage	**moderate**	**severe**	**very severe**	**p value**	**moderate**	**severe**	**very severe**	**p valu**
Patients	25	30	32		23	38	32	
SGRQ symptoms score	69.5±12.3	76.3±10.8	86.7±9.8	≤0.01	74.9±13	82±9.6	86.2±11	≤0.01
SGRQ activity score	47±9.9	48.7±12.1	57.7±16.9	≤0.01	54.5±13	64±14.6	71±14.5	≤0.01
SGRQ impact score	53.7±9.7	55.8±8.9	63±15.1	≤0.01	56.7±12	68.1±11	71.5±14	≤0.01
SGRQ total score	54.3±9	57.1±9.1	66.7±12.3	≤0.01	57.1±11.1	68.5±11.8	74.7±12.3	≤0.01
CCQ symptoms score	2.8±0.6	3.14±0.8	3.99±0.8	≤0.01	2.6±0.5	3.3±0.7	3.8±0.5	≤0.01
CCQ functional domain score	1.78±0.4	2.1±0.8	3.1±0.9	≤0.01	2.2±0.4	2.6±0.6	2.9±0.5	≤0.01
CCQ mental domain score	2.25±0.6	2.7±1.2	3.79±1.3	≤0.01	3.5±0.6	4.1±0.7	4.5±0.6	≤0.01
CCQ total score	2.28±0.5	2.64±0.8	3.6±0.9	≤0.01	2.6±0.4	3.2±0.5	3.6±0.5	≤0.01

Table 9

Multiple regression analysis: factors predicting SGRQ total score in elderly COPD patients

	β	SE	B	SE	95% CI	R^2	t	p
Interceptor			35.7	6.0	23.7, 47.78		5.9	0
BODE	0.25	0.11	1.8	0.8	0.24, 3.4	0.18	2.3	0.02
Rate of exacerbations	0.29	0.11	3.7	1.4	1, 6.5	0.06	2.7	0.008
Charlson index	0.23	0.1	2.2	0.9	0.34, 4.1	0.05	2.3	0.02
Total $R^2 = 0.29$								

Table 10

Multiple regression analysis: factors predicting SGRQ total score in younger COPD patients

	β	SE	B	SE	95% CI	R^2	t	p
Interceptor			37.9	4.4	29.2, 46.8		8.6	0
BODE	0.26	0.12	1.4	0.6	0.1, 2.6	0.19	2.2	0.02
Rate of exacerbations	0.3	0.12	3.3	1.3	0.7, 5.97	0.06	2.5	0.01
Total $R^2 = 0.27$								

Table 11

Multiple regression analysis: factors predicting CCQ total score in elderly COPD patients

	B	SE	B	SE	R^2	95% CI	t	p
Interceptor			3.5	2.1		–0.68, 7.7	1.66	0.09
BODE	0.4	0.1	0.14	0.04	0.38	0.07, 0.2	3.88	0.0002
Rate of exacerbations	0.33	0.09	0.2	0.06	0.09	0.08, 0.3	3.5	0.0007
Charlson index	0.15	0.08	0.07	0.04	0.02	–0.07, 0.1	1.79	0.05
SaO_2	–0.1	0.1	–0.02	0.02	0.008	–0.06, 0.02	–1.1	0.27

Table 12

Multiple regression analysis: factors predicting CCQ total score in younger COPD patients

	β	SE	B	SE	R^2	95% CI	t	p
Interceptor			6.4	3.1		–0.29, 12.6	2.1	0.04
BODE	0.43	0.12	0.18	0.05	0.36	0.08, 0.27	3.65	0.0005
SaO_2	–0.18	0.11	–0.05	0.03	0.03	–0.1, 0.01	–1.7	0.1
Rate of exacerbations	0.14	0.1	0.12	0.09	0.01	–0.06, 0.32	1.3	0.2

Exacerbations

Frequently, COPD is associated with periods of exacerbation of symptoms. Usually, the patient makes 1-4 COPD exacerbations per year (145). The exacerbations are rare in the mild stages of COPD, being more characteristic for moderate and severe stages of COPD (146, 147).

The most common primary causes of exacerbations are tracheobronchial tree infections (bacterial or viral) and air pollution. Other ("secondary") causes are pneumonia, pulmonary thromboembolism, pneumothorax, chest trauma, misuse of narcotics, sedatives and non-selective beta-blockers, left and right heart failure or arrhythmias. But in about 1/3 of cases the cause of exacerbations remains unidentified (62).

The most typical pathogenic microorganisms for exacerbations are *Haemophilus pneumonia, Pseudomonas aeruginosa, Streprococcus pneumonia* and *Moraxella catarrhalis*.

So far, there is no clear and universally accepted definition of COPD exacerbation by the experts (61, 109, 148, 149). Exacerbations in a patient with COPD is considered, by some experts, to be an analog of the acute coronary syndrome in the patients with coronary heart disease (148). Coronary heart disease is similar to COPD, because it also contains in the natural progression of the disease a long asymptomatic phase, when preventive treatment is highly effective. COPD patients may become symptomatic and unstable (unstable COPD, similar to unstable angina pectoris in IC, which would require the change of the therapeutic tactics and further review) (148).

Traditionally, the diagnosis of COPD exacerbations is based on the classic Anthonisen criteria (63, 150):

- major criteria: increased dyspnea, sputum volume and purulent sputum;
- minor criteria: cough, sibilant rales, rhinorrhea, angina or fever.

According to Anthonisen criteria, there are three types of exacerbations: type I - when three major criteria are present, type II - two major criteria are present, type III – 1 major criterion +/- 1 minor (109).

Assessment of the severity of an exacerbation of COPD is based on the anamnesis, his previous medical history of COPD exacerbations, symptoms, physical examination, pulmonary function tests, measurement of the partial pressures of gases in the arterial blood and other laboratory tests (62, 151-154).

Frequent COPD exacerbations are associated with a rapid decline in lung function, worsening of the quality of life and decreased survival rate (147, 154-156). Recently was proposed new COPD phenotype – frequent exacerbator, which is characterized by frequent exacerbations and bad prognosis.

Cote and colleagues (2007) demonstrated in a study on 205 patients with COPD the impact of COPD exacerbations on the functional status (157). The patients have been followed up for 2 years: at the beginning of the study, the patients in exacerbation had a higher BODE index compared to patients during the stable phase of the disease (4.2 ± 2.1 versus 3.57 ± 2.3, respectively, $p < 0.03$). During exacerbations, the BODE index increased by 1.38 points, and remained increased by 0.8 and 1.1 points, compared to the initial BODE, over 1 and 2 years respectively. COPD exacerbations have a negative impact on the BODE index and this sensitive indicator can be used for estimating the impact of exacerbations and for monitoring the progression of COPD (157).

Anemia

The association of the COPD with anemia is widely discussed in literature (158, 159) during the last years. It happens because COPD is a disease that was traditionally considered as an inductor of polycythemia (160, 161).

The connection between the anemia and important clinical parameters in patients with COPD is also characteristic for the other chronic conditions (162). Therefore, the strong association between the anemia and morbidity, increased mortality and decreased health related quality of life is well studied in such pathologies like chronic kidney disease, cancer, congestive heart failure and HIV/AIDS infection (163, 164). Moreover, numerous studies have demonstrated the advantages of anemia correction in patients with these chronic diseases that leads to the improvement of the functional state and exercise tolerance, dyspnea decrease and amelioration of the quality of life (165, 166). Regarding COPD there were recently made just several minor studies, in which the role of anemia correction concerning the clinic parameters was examined (167).

Objectives of our study (168) were the evaluation of the anemia impact on the functional state in the older and young adult patients with COPD and the determination of the predictors of dyspnea and physical activity tolerance in patients with COPD.

Totally, 158 patients were included in the study, 111 (70%) of which were males and 47 (30%) – females, aged between 44 and 80 years, the average age being 64.6 ± 8.9 years.

The positive diagnosis of COPD was established according to the GOLD classification, 2006 and ATS / ERS, 2004 (13, 169). The COPD diagnosis was based on the patient history of exposure to risk factors and presence of the obstructive syndrome, partially reversible or irreversible, with or without the presence of the symptoms. There were analyzed spirometry data, BODE index, physical activity tolerance and quality of life indices.

Statistical analysis: the correlation of the parameters was determined by Spearman correlation coefficient (R) appreciation. Multiple logistic regression (forward stepwise regression) has been also used for calculation.

All the patients with COPD were divided into three groups according to the plasmatic level of the hemoglobin: 1 – patients with anemia (hemoglobin level below 130 g/l for both males and females); 2 – patients with polycythemia (hemoglobin level over 170 g/l for males and over 150 g/l for females); 3 – patients with normal level of hemoglobin. Low level of hemoglobin was determined in 22 of 78 young adults (28%) with COPD and in 25 of 80 elderly patients (31%) with COPD.

The groups of young adult patients and older patients were divided according to the presence of anemia (*Table 13* and *Table 14*).

In the young adult patients group the average level of hemoglobin and number of erythrocytes in anemic and non-anemic patients was 118.9 ± 9.8 g/l and $4.2 \pm 0.4 \times 10^{12}$ and 147.8 ± 14.6 g/l and $4.9 \pm 0.5 \times 10^{12}$ respectively ($p < 0{,}0001$). It is important to mention that both groups of patients had the similar age ($p > 0.05$) and grade of airway obstruction ($p > 0.05$).

Young adult patients with anemia showed more severe dyspnea that was quantified according to the MRC breathlessness scale in comparison to the patients without anemia (3.8 ± 1.13 versus 3.1 ± 0.65 points respectively, $p < 0.05$). Anemic patients showed more comorbidities: Charlson index was 2.36 ± 1.3 versus 1.9 ± 1.2 in non-anemic patients ($p < 0.05$). Besides, the BODE index was higher in anemic patients (5.9 ± 2.04 versus 5.0 ± 2.3 points) ($p < 0.05$).

The exercise capacity quantified with the help of the 6-minute walk test was shorter in the patients with the low level of hemoglobin. The traversed distance in the 6-minute walk test was noticeably reduced in the anemic patients (226.3 ± 80.8 m versus 266.8 ± 95.1 m in non-anemic patients) ($p < 0.05$).

Table 13

Young adult patients with COPD characteristics according to the presence of anemia

	Anemic patients n=22		Non-anemic patients n=56		p
	Mean	SD	Mean	SD	
Age, years	57.1	3.76	56.7	4.04	> 0.05
FEV1, l/s	1.4	0.5	1.4	0.53	> 0,05
FEV1, %	45.4	14.09	41.6	14.56	> 0.05
Erythrocytes, $x10^{12}$	4.2	0.39	4.9	0.52	0.0001
Hb, g/l	118.9	9.77	147.8	14.58	0.0001
BMI, kg/m^2	25.8	6.32	28.7	6.54	> 0.05
MRC, points	3.8	1.13	3.1	0.65	< 0.05
6MWT, m	226.3	80.79	266.8	95.16	< 0.05
BODE, points	5.9	2.04	5.0	2.3	< 0.05
Charlson index, points	2.36	1.3	1.86	1.21	< 0.05

The older patients with anemia showed a severe dyspnea level, so the MRC scale was 4.04 ± 0.74 versus 3.73 ± 0.59 points in non-anemic patients ($p = 0.04$).

In the group of older patients with COPD, as well as in the group of young adult patients, the number of comorbidities and BODE index were increased in patients with anemia: Charlson index was 3.16 ± 1.18 versus 2.76 ± 1.37 ($p < 0.05$) in non-anemic patients; index BODE was higher in anemic patients (7.3 ± 1.5 versus 6.8 ± 1.8) ($p < 0.05$).

The traversed distance in the 6-minute walk test was shorter (181.4 ± 69.2 m versus 220.8 ± 85.9 m) ($p < 0.05$). The level of dyspnea, evaluated by the MRC breathlessness scale was as well higher in anemic patients (4.04 ± 0.7 versus 3.73 ± 0.6, $p < 0.05$).

The aim of the multiple regression (term used by Pearson, 1908) is to detect the relation between a dependent variable (the dyspnea level that is quantified by the MRC breathlessness scale) and a majority of independent variables (age, FEV1, level of hemoglobin, BMI, presence of comorbidities assessed by Charlson index and CDS index).

vigorous activity of the bone marrow. However, the bone marrow cannot respond adequately. This is caused by a relative erythropoietin resistance due to an attenuated ability of red blood cells progenitors to respond to erythropoietin. An attenuated mobilization of reticuloendothelial iron stores is an additional pathophysiologic factor (173).

The main limitation of our research can be considered an insufficient amount of the analyzed sample size. Our study didn't have the objective to examine how the anemia treatment can affect the major clinic parameters in patients with COPD, but the obtained results reconfirm the hypothesis that the anemia in patients with COPD is associated with many serious consequences. In spite of the fact that anemia represents a possible systemic manifestation of COPD it could be also an associated phenomenon, that marks patients with severe disease. In addition, the hypothesis about the amelioration of the clinical parameters after anemia correction seems to be rational. However, this hypothesis needs to be verified in the further clinic studies.

Conclusions

In our research the anemia prevalence was 28% in the group of the young adult patients with COPD and 31% in older patients with COPD. Anemia in COPD is an independent risk factor for worsening of dyspnoea and reducing the functional capacity.

Biomarkers

Apart from the well established clinical phenotypes which will be discussed in the next chapter, multiple biomarkers are currently evaluated as potential cut points for novel phenotypes, in order to provide COPD patients the most appropriate treatment, minimising the side effects simultaneously (5). Different studies suggest different biomarkers/phenotypes which should be evaluated according to the degree of association with clinically meaningful outcomes and their complexity, associated risks and price which may limit their use in daily practice. Different biomarkers assess stable COPD and/or the outcomes of an exacerbation.

We can classify markers (161) into molecular markers, which include inflammatory mediators and cells seen in the blood, bronchoalveolar lavage (BALF), phlegm or exhaled air, radiological markers, with main representative the emphysematic changes, clinical characte-

ristics, such as the frequent exacerbations or the comorbid diseases, and physiological markers, which include spirometry (5).

Molecular markers

Numerous studies have suggested different inflammatory molecules or cells as potential biomarkers for COPD. Serum eosinophilia predicts responsiveness to inhaled corticosteroids, as mentioned previously. Neutrophil-to-lymphocytes ration has been suggested as a marker of inflammation and disease activity (174). High sensitivity serum CRP is significantly higher in stable COPD compared to healthy patients, independently of the smoking status (175). A concentration of more than 3 mg/l is associated with a very poor prognosis (176). Serum CRP is also negatively associated with pulmonary function and exercise capacity (177). A prospective cohort of 6,574 patients followed for a median time of four years showed that the combination of elevated CRP, fibrinogen and leukocyte count in COPD patients can predict frequent exacerbations (178). High sensitivity troponin T is also elevated in patients with COPD and associated with the severity of disease and with immune activation (a high inflammatory status of the patient) (179). Fibrinogen has been strongly associated with worse pulmonary function and increased mortality in a large cohort from NHANES III study of 8,507 patients and 3,290 documented deaths during follow-up (180). In addition, fibrinogen level was positive correlated with frequent exacerbations of COPD and may identify persons with a higher risk of mortality (181).

COPD is characterized by prominent neutrophilic inflammation and raised IFN-γ production at both bronchial and systemic level. Serum levels of tumour necrosis factor-α (TNF-a) is strongly correlated with disease severity and inversely with body mass index (182). This is supported by a study which showed that etanercept, a TNF-α antagonist, may decrease the frequency of severe COPD exacerbations (183). TNF-α indicates an enhanced systematic inflammatory status, as suggested by ECLIPSE study, and is correlated with lean body mass loss (184) and osteoporosis (185). Increased serum IL-6, which reflects persistent and progressive systemic inflammatory process, suggests increased mortality and limited physical performance (186). The results presented in Moy et al study suggest the conceptual basis to study whether an intervention to promote walking will reduce systemic inflammation in people with COPD

(187). Less supported associations have been suggested for the serum levels of other interleukins, adiponectin, matrix metalloproteinases, the brain natriuretic peptide, tumour markers and several other molecules (5).

The levels of inflammatory molecules and cells in sputum and BALF have also been suggested as potential biomarkers. ECLIPSE study suggested that sputum neutrophil levels are significantly but weakly related to FEV1 and Quality of Life (188), while another study also correlated sputum neutrophils to chronic expectoration (189). Sputum eosinophilia characterises patients with specific phenotype asthma COPD overlap syndrome and can predict the responsiveness to ICS (190). High sputum eosinophil counts and bronchial wall thickening on chest high-resolution computed tomography might therefore be a good predictor of response to ICS (190). Eosinophilic cationic protein, eosinophil peroxidase (191), IL-5 (192) and exhaled nitric oxide (193) are markers of sputum eosinophilia and can also predict responsiveness to ICS. Leukotriene B4 in the sputum can predict deterioration of COPD and an exacerbation up to a week before the onset of symptoms (194). This would be of great value for the patient, who may be a subject for early treatment and thereby avoid a progression of the disease and the complications (194). Finally, ECLIPSE also identified genetic loci in the inflammatory cells of the sputum that are associated with the spirometric severity of COPD and degree of emphysema (195).

Exhaled breath condensate (EBC), obtaining from cooling down exhaled air, is another source of biomarkers. EBC pH, which is a simple and cheap marker, is strongly, negatively correlated to disease severity (196), sputum eosinophilia, level of oxidative stress and, consequently, the level of inflammatory activity (197). However, it cannot differentiate COPD patients from healthy smokers. Several other markers of *oxidative stress and inflammation, such as hydrogen peroxide, nitrates* and nitrites have been proposed by different studies.

Exhaled nitric oxide (FeNO) is another simple biomarker of inflammation. It is now possible to estimate the predominant airway site of increased FeNO large versus peripheral airway/alveoli, and its potential pathologic and physiologic role in obstructive lung disease (198). The main advantage of FeNO is the ability to estimate the predominant site of inflammation (central versus peripheral airways) (198). Potential uses in COPD are currently under investigation. It appears that FeNO is an early but not specific marker of COPD inflammation, which may precede spi-

rometric ventilatory defect (199). Moreover, FeNO is more pronouncedly increased in patients with unstable COPD, although smoking, which has been found to decrease FeNO, may be a confounding factor.

Procalcitonin, the prohormone of calcitonin, is released in different tissues, in response to bacterial but not viral infections (200). For this reason, procalcitonin is a promising biomarker, which is currently used in the diagnosis of bacterial infections in different settings (201-204). Such a biomarker could be very useful in the differentiation between bacterially induced and other types of COPD exacerbations. Nevertheless, its use in COPD could be more challenging, due to the chronically elevated baseline inflammatory status and the chronic bacterial colonization of the airways (205) and needs to be carefully assessed. Some randomized controlled trials (RCTs) have already been conducted to evaluate procalcitonin-based versus standard protocols to guide the decision to initiate or discontinue the administration of antibiotics in patients presenting with AECOPD (206, 207). The aim of our study was to identify all available RCTs and yield overall effect estimates of the clinical effectiveness of procalcitonin-based protocols to guide the administration of antibiotics in patients with AECOPD.

Our meta-analysis (208) was based on a protocol which was prospectively registered in PROSPERO register for systematic reviews and is available in the following URL: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016036938 (209). The present report follows the PRISMA statement for reporting of systematic reviews and meta-analyses (210).

Eligible studies comprised randomized or quasi-randomized controlled trials comparing procalcitonin-based versus standard protocols to guide the initiation or discontinuation of antibiotics in patients presenting with AECOPD. We also evaluated trials focusing on patients with lower respiratory tract infections or respiratory tract infections in general and we included their subgroups of the recruited patients with AECOPD, provided that they included at least 30 patients and we were able to acquire adequate data regarding the baseline characteristics and outcomes of these subgroups. We only accepted procalcitonin-based protocols if they included a recommendation to initiate or continue antibiotics for serum procalcitonin levels above a pre-specified cut point and to discontinue or not to initiate for lower levels. Any other protocol used in clinical practice was acceptable as a comparator, provided that

the clinicians were unaware of the participants' procalcitonin levels. A previous clinical diagnosis of COPD was considered adequate; AECOPD was defined as a deterioration of the patients' respiratory symptoms that is beyond the normal day-to-day variations and leads to a change in medications. Only patients seeking medical advice in a primary care facility or hospital emergency, respiratory or internal medicine department were accepted. Studies focusing on hospital acquired infections or studies performed in the intensive care unit were excluded. Patients with immunodeficiencies or receiving immune-suppressants (apart from corticosteroids administered for the management of COPD), patients with chronic infections requiring chronic antibiotic therapy and patients with medullary thyroid carcinoma were also excluded.

Outcome measures

The primary outcomes of this meta-analysis included (i) treatment failure for the index exacerbation, defined as symptoms deterioration, non-improvement or death (short term, within one to four weeks) and (ii) length of hospitalization for the index exacerbation. The secondary outcomes included (i) antibiotic exposure for the index exacerbation (including the proportion of patients who were prescribed antibiotics and the duration of the course of antibiotics) and at longest follow-up, (ii) antibiotic prescription after an opposite initial decision, (iii) re-exacerbation rate at longest follow-up, (iv) re-admission rate at longest follow-up and (v) mortality at longest follow up.

Search Strategy and Study Selection

We systematically reviewed the electronic databases of Medline, EMBASE and Cochrane Central Register, using appropriate controlled vocabulary and free search terms to identify studies assessing procalcitonin in patients with COPD. The World Health Organization International Clinical Trials Platform Search Portal (ICTRP), as well as the online abstract proceeding registries of European Respiratory Society and the American Thoracic Society and the reference lists of all included trials and all previous systematic reviews that we identified were also screened for additional ongoing or completed trials. All databases and online registries were searched from inception to May 13, 2016. Two authors independently screened the titles, abstracts and full text (when appropriate) of all identified articles. Disagreement was resolved through discussion or adjudication by a third investigator when that was necessary.

Data abstraction

Two authors independently extracted the following information from each eligible article: Full reference and study identifiers, study design, eligibility criteria, predefined outcomes, number and characteristics of the participants and the details on the results of interest. Missing data were requested from the authors of the primary studies via e-mail.

Risk of bias and Quality of Evidence

Risk of bias of each included study was assessed according to Cochrane's guidance, by two authors independently and discrepancies were resolved through discussion. A domain-based evaluation was used, that included the following domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, attrition, selective reporting bias and other source of bias. Explicit judgments were made about the overall risk of bias according to Cochrane's guidance (211). Risk of bias was assessed separately for different outcomes of interest when that was considered appropriate by the investigators. We were not able to assess the risk of publication bias, due to the small number of included trials (<10).

Quality of evidence for each outcome was assessed using the GRADE (grading of recommendations assessment, development and evaluation) methodology, which incorporates risk of bias as well as imprecision, inconsistency, indirectness and publication bias of the body of evidence, using the outcomes as units of analysis (212). All decisions to downgrade or upgrade the quality of evidence were justified and presented in evidence profile and summary of evidence tables, in accordance with GRADE's guidance. GRADEPro Software (GRADEPro 2014) was used in the development of these tables.

According to the GRADE working group evaluation, high quality evidence suggests that further research is very unlikely to change the confidence in the estimate of effect; moderate quality that further research is likely to have an important impact on the confidence in the estimate effect and may change the estimate; low quality evidence suggests that further research is very likely to have an important impact on the confidence in the estimate effect and it is likely to change the estimate; very low quality that we are very uncertain of the estimate.

Heterogeneity

I^2 statistic will be used to assess statistical heterogeneity within the trials included in each analysis. Substantial heterogeneity was explored by pre-specified subgroup analyses.

Data Synthesis

The data were pooled using the fixed or random effect models in cases where heterogeneity, assessed with the I^2 statistic, was found to be less than 50% or between 50-75% respectively. Meta-analyses were not performed in cases of significant unresolved heterogeneity (I^2 statistic >75%). Results are presented in the form of relative risks (RR) with their 95% confidence intervals (CI) for dichotomous data and in the form of mean differences (MD) with the corresponding 95% CI for continuous data. Meta-analyses were performed using Review Manager 5 (RevMan 2014) Software.

Sensitivity and Subgroup analyses

In different pre-specified sensitivity and subgroup analyses of all outcomes we included (i) only studies with low risk of bias, (ii) only studies with high adherence to the procalcitonin-guided protocols, (iii) only studies using procalcitonin to guide the initiation of antibiotics and (iv) only studies using procalcitonin to guide the discontinuation of antibiotics. Furthermore, for outcomes measured at longest follow up, we grouped studies with duration of up to three months versus more than three months. Finally, in an additional sensitivity analysis, we repeated the meta-analyses which were performed using the fixed effects model using the random effects model and vice versa.

Characteristics of the included trials

Characteristics of the included trials are presented in the Online Appendix 3. Briefly, eight completed trials, evaluating 1,062 patients with AECOPD, met the inclusion criteria. All were conducted in a hospital setting and recruited patients who had an emergency visit or admission. Five trials recruited only patients attending with an AECOPD (206, 213-216), while the rest recruited patients with lower respiratory tract infections in general, but included well-characterized and presented subsets of patients who were recruited with an AECOPD (217-219). Four trials had a follow up duration of 6 months (206, 214, 216, 217), one only followed the patients during the period of their

hospital admission (218) and the rest between four and six weeks. No significant differences in the baseline characteristics of the patients included in each study arm were reported.

The procalcitonin-based protocols used in all included trials were similar. Antibiotics were recommended for procalcitonin levels >0.25μg/L and discouraged for levels <0.25μg/L. In addition, in some of the studies antibiotics were strongly discouraged for levels <0.01μg/L and/or strongly recommended for levels >0.5μg/L. All studies were open labeled or single blinded and the final decision to administer or withhold antibiotics was left to the clinicians, who could deviate from the protocol. In most of the included trials, procalcitonin levels were used to guide the initiation (or not) of antibiotic treatment; in two of the trials, procalcitonin levels guided the early discontinuation of antibiotics (216, 218) and in another two both initiation and discontinuation(214, 219). Adherence to the procalcitonin based protocols was reported in four trials and it varied significantly, between 61.3% and 98.1% (213, 214, 218, 219).

The strategies used in the controlled group were similar in all trials but one. Verduri and colleagues (216) administered a 10-days course of antibiotics in all participants who were randomized to the control group, while in all other studies the responsible physician, who was unaware of the procalcitonin levels of the participants had to decide on the administration (or not) of antibiotics, based on the severity of the presentation, clinical signs and symptoms and biochemical and radiological results.

Risk of bias assessment

Detailed assessment of the risk of bias is depicted in *Figure 1*. In brief, overall risk of bias was considered high for all included studies mainly due to performance and detection bias. None of the included studies was double blinded and the outcomes assessment was only blinded in two studies (206, 219). Moreover, three of the included trials were quasi-randomized and consequently, at high risk of selection bias (213, 214, 217). Finally, target study population was not reached in one of the trials due to slow recruitment rate (216), while power studies were not reported in two others (214, 215). Publication bias was not assessed, because of the small number of studies that contributed to each of the preselected outcomes.

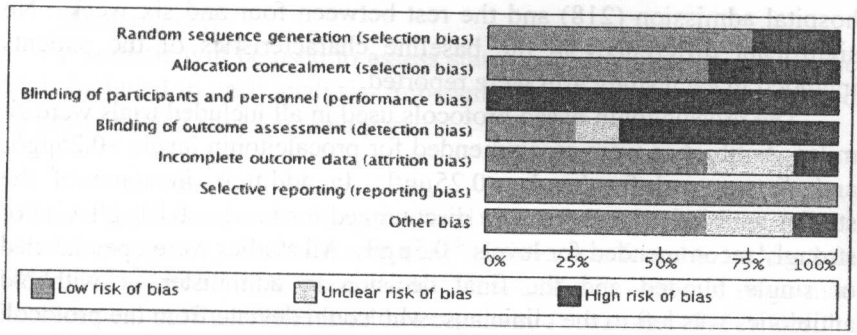


Figure 1. Risk of bias graph – authors' judgements about each risk of bias domain, presented as percentages across all included studies. Attrition bias is low for all short-term outcomes of all included trials.

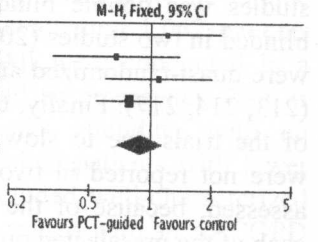
Data synthesis and quality assessment

Overall effect estimates for each outcome are presented in *Figure 2 A-H*. Summary of findings is presented in *Table 16*. Four studies assessed the rate of treatment failure for the index exacerbation, which was defined as symptoms deterioration, non-improvement, ICU admission or death within one to four weeks from recruitment (206, 213, 216, 219). Treatment failure was observed in 159 out of 698 included patients and no difference was found between the treatment groups (RR 0.89 [0.68, 1.16], I^2= 0%, low quality). Only one study, based on a very small number of observations, assessed the proportion of patients who required antibiotic prescription after an initial opposite decision and it did not detect any between group difference (RR 0.92 [0.21, 4.12]) (206).

A.

Study or Subgroup	Procalcitonin-guided Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fally 2015	14	38	14	46	15.1%	1.21 [0.66, 2.21]
Schuetz 2009	11	115	16	113	19.2%	0.68 [0.33, 1.39]
Stolz 2007	18	102	17	106	19.8%	1.10 [0.60, 2.01]
Verduri 2015	30	88	39	90	45.9%	0.79 [0.54, 1.14]
Total (95% CI)		**343**		**355**	**100.0%**	**0.89 [0.68, 1.16]**
Total events	73		86			

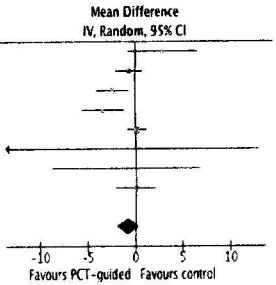
Heterogeneity: Chi^2 = 2.45, df = 3 (P = 0.48); I^2 = 0%
Test for overall effect: Z = 0.85 (P = 0.39)



B.

Study or Subgroup	Procalcitonin-guided Mean	SD	Total	Standard care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Christ Crain 2004	13.7	7.3	29	10.8	7	31	7.7%	2.90 [-0.72, 6.52]
Fally 2015	4.5	2.96	62	5.1	4.44	58	19.9%	-0.60 [-1.96, 0.76]
Kristoffersen 2009	4.8	2.8368	28	7.1	3.6057	32	17.8%	-2.30 [-3.93, -0.67]
Liu 2015	16.06	4.73	52	19.41	6.74	56	14.1%	-3.35 [-5.53, -1.17]
Nangia 2012	7.5	2.5	50	7.3	2.3	50	22.9%	0.20 [-0.74, 1.14]
Schuetz 2009	8.8	51.23	115	9.2	51.23	113	0.8%	-0.40 [-13.70, 12.90]
Stolz 2007	9	30.547	102	10	25.9622	106	2.2%	-1.00 [-8.72, 6.72]
Verduri 2015	5	7.0795	88	5	7.1618	90	14.7%	0.00 [-2.09, 2.09]
Total (95% CI)			**526**			**536**	**100.0%**	**-0.76 [-1.95, 0.43]**

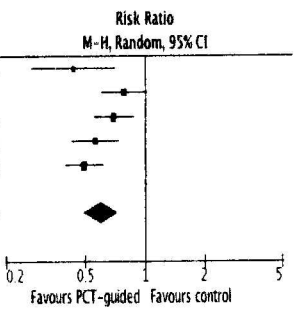
Heterogeneity: Tau² = 1.37; Chi² = 16.93, df = 7 (P = 0.02); I² = 59%
Test for overall effect: Z = 1.25 (P = 0.21)



C.

Study or Subgroup	Procalcitonin-guided Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Christ Crain 2004	11	29	27	31	11.2%	0.44 [0.27, 0.71]
Fally 2015	36	62	43	58	21.0%	0.78 [0.60, 1.02]
Schuetz 2009	56	115	79	113	23.2%	0.70 [0.56, 0.87]
Stolz 2007	41	102	76	106	20.7%	0.56 [0.43, 0.73]
Verduri 2015	43	88	90	90	23.8%	0.49 [0.40, 0.61]
Total (95% CI)		**396**		**398**	**100.0%**	**0.60 [0.49, 0.73]**
Total events	187		315			

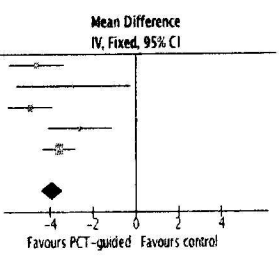
Heterogeneity: Tau² = 0.03; Chi² = 11.05, df = 4 (P = 0.03); I² = 64%
Test for overall effect: Z = 5.08 (P < 0.00001)



D.

Study or Subgroup	Procalcitonin-guided Mean	SD	Total	Standard care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Christ Crain 2004	3.3	2.1	29	7.92	2.8	31	15.9%	-4.62 [-5.87, -3.37]
Fally 2015	6.1	7.41	62	9	7.4	58	3.5%	-2.90 [-5.55, -0.25]
Nangia 2012	2.1	2.62	50	7.02	2.6	50	23.6%	-4.92 [-5.94, -3.90]
Schuetz 2009	2.5	5.6622	115	5.1	5.6622	113	11.4%	-2.60 [-4.07, -1.13]
Verduri 2015	6.42	3.519	88	10	0.1	90	45.6%	-3.58 [-4.32, -2.84]
Total (95% CI)			**344**			**342**	**100.0%**	**-3.93 [-4.42, -3.43]**

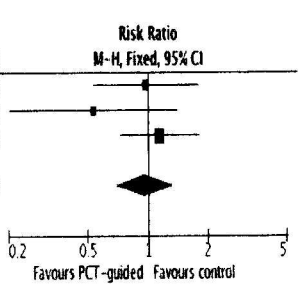
Heterogeneity: Chi² = 9.37, df = 4 (P = 0.05); I² = 57%
Test for overall effect: Z = 15.49 (P < 0.00001)



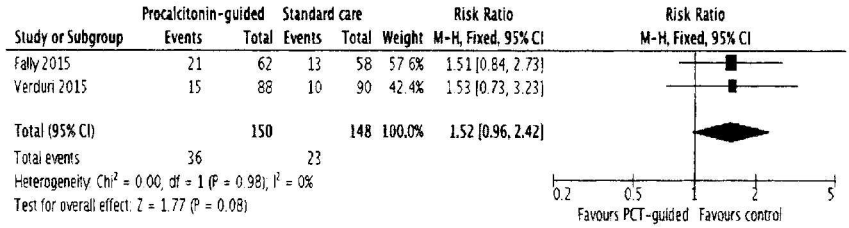
E.

Study or Subgroup	Procalcitonin-guided Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Liu 2015	14	44	15	46	29.1%	0.98 [0.54, 1.78]
Schuetz 2009	6	115	11	113	22.0%	0.54 [0.21, 1.40]
Verduri 2015	28	88	25	90	49.0%	1.15 [0.73, 1.80]
Total (95% CI)		**247**		**249**	**100.0%**	**0.96 [0.69, 1.35]**
Total events	48		51			

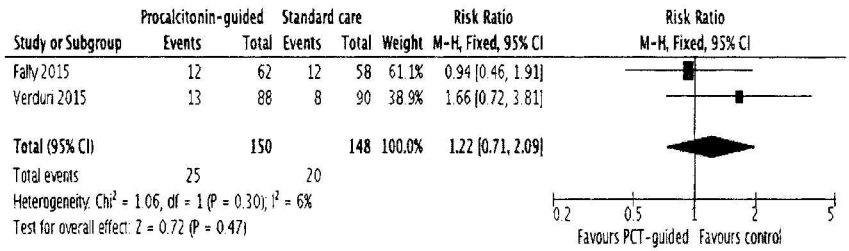
Heterogeneity: Chi² = 2.00, df = 2 (P = 0.37); I² = 0%
Test for overall effect: Z = 0.22 (P = 0.82)



F.



G.



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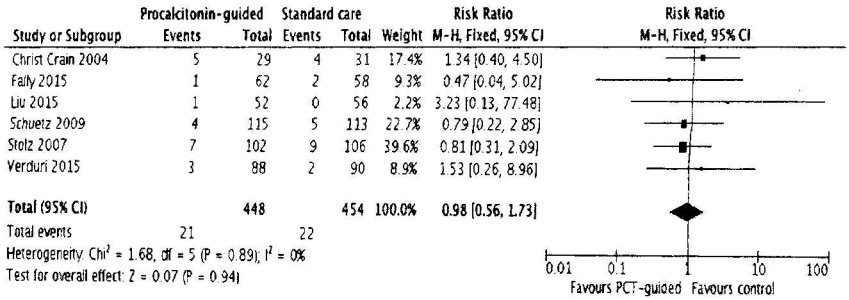

Figure 2. Forest plots depicting the overall effect estimates for each outcome.

A. Treatment failure for the index exacerbation, defined as symptoms deterioration, non-improvement, ICU admission or death within one to four weeks from recruitment. *B. Antibiotic exposure for the index exacerbation:* Proportion of patients who were prescribed antibiotics on admission. *C.* Antibiotic exposure for the index exacerbation: Proportion of patients who were prescribed antibiotics on admission. *D.* Antibiotic exposure for the index exacerbation: Mean duration of the antibiotic courses. *E.* Re-exacerbation rate at longest follow up. *F.* Re-hospitalization rate at longest follow up *G.* Rate of re-hospitalization due to an exacerbation at longest follow up *H.* Overall mortality at longest follow up.

Table 16

Clinical effectiveness of procalcitonin-based protocols to initiate or discontinue antibiotics in patients presenting with acute exacerbations of COPD

				Anticipated absolute effects	
				Risk with standard care	**Risk difference with Procalcitonin-guided protocols**
Treatment failure for the index exacerbation.	698 (4 RCTs)	⊕⊕◯◯ LOW [1,2]	**RR 0.89** (0.68 to 1.16)	242 per 1,000	**27 fewer per 1,000** (78 fewer to 39 more)
Length of hospital stay for the index exacerbation	1062 (8 RCTs)	⊕⊕⊕◯ MODERATE [1]	-	The mean length of hospital stay for the index exacerbation was **9.07** days	MD **0.76 days lower** (1.95 lower to 0.43 higher)
Proportion of patients who were prescribed antibiotics on admission	794 (5 RCTs)	⊕⊕⊕◯ MODERATE [1]	**RR 0.60** (0.49 to 0.73)	791 per 1,000	**317 fewer per 1,000** (404 fewer to 214 fewer)
Duration of the course of antibiotics	686 (5 RCTs)	⊕⊕◯◯ LOW [1,2]	-	The mean duration of the course of antibiotics was 7.59 days	MD **3.93 days lower** (4.42 lower to 3.43 lower)
Re-exacerbation rate at longest follow-up	496 (3 RCTs)	⊕⊕◯◯ LOW [1,2]	**RR 0.96** (0.69 to 1.35)	205 per 1,000	**8 fewer per 1,000** (63 fewer to 72 more)
Re-hospitalization rate at longest follow-up	298 (2 RCTs)	⊕⊕◯◯ LOW [1,2]	**RR 1.52** (0.96 to 2.42)	155 per 1,000	**81 more per 1,000** (6 fewer to 221 more)
Rate of re-hospitalization due to an exacerbation at longest follow up	298 (2 RCTs)	⊕⊕◯◯ LOW [1,2]	**RR 1.22** (0.71 to 2.09)	135 per 1,000	**30 more per 1,000** (39 fewer to 147 more)
Overall mortality at longest follow up	902 (6 RCTs)	⊕⊕◯◯ LOW [1,2]	**RR 0.98** (0.56 to 1.73)	48 per 1,000	**1 fewer per 1,000** (21 fewer to 35 more)

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference
GRADE Working Group grades of evidence **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

The mean length of hospital stay for the index exacerbation was reported in all included trials (1,062 participants). The mean length varied between 4.5 and 16.06 days in the procalcitonin-guided groups and between 5 and 19.41 days in the control groups. Overall, we noted a trend towards decrease in the length of hospitalization in the procalcitonin-guided groups (MD -0.76 [-1.95, 0.43], I^2= 59%, moderate quality).

Antibiotic exposure for the index exacerbation was assessed by the proportion of patients who were prescribed antibiotics on admission and the mean duration of the antibiotic courses. The proportion of patients who received full courses of antibiotics, including patients who were prescribed antibiotics on admission or patients who were not discontinued early, in accordance with each study protocol, was reported in five of the included trials (206, 213, 216, 217, 219), which evaluated 794 patients in total and suggested a 40% decrease in the antibiotic prescription rate with procalcitonin-guided protocols (RR 0.6 [0.49,0.73], I^2= 64%, moderate quality). The mean antibiotic exposure for the index exacerbation, in days was also assessed by five studies (213, 215-217, 219) with a total study population of 686 participants. A significant decrease of about 4 days in the mean antibiotic exposure in the intervention group, compared to standard care was highlighted (MD -3.93 [-4.42, -3.43], I^2= 57%, low quality). Only one trial (206) assessed the total antibiotic exposure at longest follow up and found that the reduction in the exposure was sustained (RR 0.76 [0.64, 0.92]).

The re-exacerbation and re-hospitalization rates at the longest follow up did not significantly differ between the treatment arms. Three studies, including 496 patients, presented the proportion of the participants who had at least one exacerbation during follow up (RR 0.96 [0.69, 1.35], I^2= 0%, low quality) (214, 216, 219). Two trials, with 298 participants assessed the re-hospitalization rate at longest follow-up and suggested a trend towards increased rate in the intervention group (RR 1.52 [0.96, 2.42], I^2= 0%, low quality) (213, 216). However, the same trials also assessed the rate of re-hospitalization due to an exacerbation at longest follow up and this was similar between groups (RR 1.22 [0.71, 2.09], I^2= 0%, low quality).

Finally, mortality at longest follow up was presented by six trials, with a total population of 902 participants (206, 213, 214, 216, 217, 219). No significant difference was found between study arms (RR 0.98 [0.56, 1.73], I^2= 0%, low quality).

Sensitivity Analyses

All included studies were deemed to be of high risk of bias and as such we were not able to perform a sensitivity analysis using studies with low risk of bias. Our results proved robust to each of the remaining sensitivity analyses.

The use of procalcitonin-based protocols to guide the decision to administer antibiotics has been previously evaluated in infections of different origins and in different settings (201-203). A recent well-conducted systematic review supported the effectiveness of procalcitonin-guided protocols in lower respiratory tract infections, based on evidence of moderate quality, according to GRADE assessment (204). However, these results do not necessary imply that such protocols would also be effective in patients presenting with AECOPD, since the chronically elevated baseline inflammatory status and the chronic bacterial colonization of the airways of patients with COPD (205) could possibly affect the serum procalcitonin levels. We are not aware of any previous systematic reviews assessing similar interventions in patients with AECOPD, so we conducted a systematic review and meta-analysis to evaluate the clinical effectiveness of procalcitonin-based protocols it these patients. Our findings suggest that procalcitonin-based protocols may be superior to standard care in patients with AECOPD. More specifically, we showed that procalcitonin guidance significantly limits

and targets the antibiotic exposure, without any obvious impact of the clinical outcomes (such as treatment success, re-exacerbation, re-hospitalization or mortality). However, additional, appropriately powered, confirmatory trials with rigorous methodology are required before considering introducing such strategies in daily clinical practice.

If successful, such an intervention could make a significant difference in the management of patients with AECOPD. Currently, owing to the challenges of distinguishing bacterially induced versus other AECOPD in the acute phase, both antibiotics and oral corticosteroids are administered to most patients presenting with moderate or severe AECOPD. Nevertheless, the aetiology of AECOPD varies and bacterial infections, where antibiotics are indicated, appear to account for approximately half of them (220). These suggest that antibiotics are significantly overused in AECOPD posing significant risks to individual patients and the society (221). Importantly, COPD patients are more prone to the risks associated with antibiotics overuse, because of the chronic airway colonization with bacterial strains which may progressively become less sensitive to antibiotics; also, some of these patients may be more prone to infections, due to defects in their immune system (222), and this leads them to frequent administration of antibiotics anyway.

On the other hand, the majority of patients with moderate or severe AECOPD also receive courses of oral corticosteroids. Previous studies have shown that oral corticosteroids confer mild or moderate advantage over placebo when administered in unselected patients with AECOPD (223, 224). Also they are associated with numerous well-known adverse events such as the risk of pneumonia. It has been hypothesized that oral steroids may be efficient in patients with inflammatory, non-infective exacerbations and not in AECOPD induced by bacteria (225). However, this has not been evaluated in a RCT as of now, likely due to the challenges of the identification of the type of exacerbation in the acute phase. All in all, it appears that procalcitonin-based protocols could contribute to the personalization of the management of COPD exacerbations, decrease the use of both antibiotics and oral corticosteroids and may also enable the design and conduction of new clinical studies that will provide new insights into the mechanisms and management of AECOPD.

A recent meta-analysis assessed the cost effectiveness of the use of serum procalcitonin to guide antibiotic therapy in other infections and estimated the cost of procalcitonin is approximately 11£ per measurement in UK (223). The authors consider this an acceptable cost given the expected net benefits in the management of these patients.

Recent cross-sectional studies noted significant discrepancies between procalcitonin levels and sputum culture results and raised concerns regarding the effectiveness of procalcitonin protocols to guide antibiotic administration in patients with COPD (226, 227). However, this study design is not appropriate to assess procalcitonin protocols and, more importantly, the sensitivity and specificity of sputum cultures to recognize AECOPD induced by bacteria is far from ideal. Firstly, the airways of COPD patients are frequently colonized with bacteria, which may result in false positive results (228). Secondly, the sensitivity of sputum cultures is also limited in patients with COPD (229).

Our meta-analysis has some limitations. Firstly, a high risk of bias is introduced by the fact that none of the included trials was double blinded. Secondly, our results are imprecise, due to the low overall study population and event rates. Consequently, our results are of low-to-moderate quality, according to GRADE, suggesting that additional, well-designed and conducted trials are required to confirm our findings.

On the other hand, all outcomes support the intervention and also, all included studies presented consistent results. These observations can reassure that procalcitonin protocols are very unlikely to be associated with significant risks and highlight the need for further, more rigorous research, with the aim to introduce this intervention to clinical practice in the near future.

Conclusion

Our findings suggest that procalcitonin-based protocols to guide the initiation (or discontinuation) of antibiotics in patients presenting with acute exacerbations of COPD appear effective and safe (208). The quality of the available evidence is low to moderate because of the methodological limitations and small study populations of the available trials. Given the potential impact on the management of these patients, the need for additional, appropriately designed and powered confirmatory randomized controlled trials cannot be stressed enough.

Radiological markers

Emphysema is one of the earliest COPD phenotypes described. Evidence of emphysema on the Chest X-ray (CXR) and/or computed tomography (CT) of the chest is positively correlated with cachexia and negatively correlated with BMI, exacerbation frequency and probability of type 2 respiratory failure (230, 231). Bullous emphysematic disease is treatable with lung volume reduction surgery or with endobronchial valve placement (232). On the other hand, thickened bronchi corresponds to the bronchitic element. A recent study suggests three radiographic phenotypes: emphysema without bronchial thickening, bronchial thickening without emphysema and the combination, which correspond to predominant emphysema, predominant bronchitis and mixed disease (233).

Sleep

Patients with COPD frequently suffer from nocturnal changes of ventilation and gas exchange, which are unrelated to the narrowing of the upper airways or to alterations of airway resistance (234, 235).

Significant decrease in nocturnal oxygen saturation can occur in COPD patients because of alveolar hypoventilation, worsening of ventilation-perfusion mismatching, decrease of functional residual capacity and increased upper airway resistance (236, 237). Severe reductions in PaO_2 to levels as low as 20 mmHg during REM sleep have been reported in COPD (238).

Prolonged low frequency (sustained) hypoxemia is major pattern of hypoxemia characteristic for COPD which was been described (239). Low frequency (sustained) hypoxemia is characterized by oxygen saturation ranging between 80% and 85% that lasts from a few minutes to hours. The cycles of hypoxemia with reoxygenation can be compared with ischemia-reperfusion injury and generate increased production of reactive oxygen species (ROS) and oxidative stress (239). Sustained low frequency hypoxemia can promote both adaptive and maladaptive responses leading to stimulation of erythropoiesis and pulmonary hypertension (240).

Sleep quality is impaired in COPD and is characterized by reduced REM sleep, which protects against sleep apnea because it is more pronounced in OSAS during REM sleep (241). Nocturnal desaturation in COPD patients is associated with more arousals and sleep fragmentation, most notably during REM sleep (242).

Short intermittent high-frequency hypoxemia is major pattern of hypoxemia characteristic for OSAS (243). Short intermittent high-frequency hypoxemia with cyclical pattern of oxygen desaturation lasting 15-60 seconds followed by reoxygenation, occurs during sleep and lasts for weeks to months or longer (239). Intermittent hypoxemia causes maladaptive responses by differential modulation of hypoxia-inducible factors (HIF) 1 and 2 (240). It has been shown that intermittent hypoxemia can contribute to development of multiple comorbidities by complex pathophysiological mechanisms: increased oxidative stress, systemic and vascular inflammation with endothelial dysfunction, increased sympathetic activation and increased blood pressure (244).

Multiple pathophysiological mechanisms can link the relationship between COPD and OSAS (245). COPD patients have an increased risk to pharyngeal obstruction because of increased pharyngeal resistance determined by fluid accumulation around the pharynx due to rostral shift of peripheral oedema when patient is in supine position (246, 247). Another possible common risk factor is neck obesity which can contribute to narrowing of upper airways (248).

Cigarette smoking can predispose COPD patient to OSAS by several well known mechanisms: changes in sleep architecture, relaxation of the upper airway muscles and neural reflexes, increased arousal threshold from sleep caused by nicotine and increased upper airway inflammation and oedema due to smoke inhalation (249, 250). In the Wisconsin Sleep Cohort, an apnea-hypopnea index (AHI) more than 5 events/hour was three times more likely in current smokers than in never-smokers (251). In this study, heavy smokers (> 40 cigarettes per day) had an odds ratio of 6.74 for an AHI of > 5 events/hour (251).

The body-mass index (BMI), also affect pathophysiological relationships (252). Obesity in COPD patients is a key contributor to sleep disordered breathing, accelerated pulmonary hypertension and obesity hypoventilation syndrome, independent to severity of airflow obstruction (236, 245, 253). These patients particularly resemble the bronchitic clinical COPD phenotype or classical "blue bloater" (236). COPD patients with high BMI are predisposed to OSAS, and the detecting of a higher AHI in overweight patients with airflow obstruction supports this possibility (236). Truncal obesity causes ventilatory disturbances by decreasing of chest wall compliance and respiratory muscle weakness (254). In plus, obesity can be associated with

reduced functional residual capacity, which contributes to ventilation perfusion mismatching. However, many patients with severe COPD have a low BMI, which protects against upper airway obstruction (245).

The drugs used for therapy of COPD may impact the interaction between COPD and OSAS (252). Inhaled anti-cholinergic drugs (13), inhaled long-acting β-agonists (255) and theophyllines (256) ameliorate nocturnal oxygen desaturation, probably due to decrease of air trapping and lower airway obstruction. In contrast, corticosteroids may cause upper airway obstruction due to central obesity and fluid retention with associated upper airway narrowing, in addition to myopathy and metabolic alkalosis (245).

The term "overlap syndrome"' is commonly used to describe the coexistence of COPD and OSAS (257). Several epidemiological studies demonstrated a prevalence of approximately 1% for the overlap syndrome (236, 258), but the association of asymptomatic airway obstruction with sleep-disordered breathing is considerably higher. Chaouat et al. demonstrated that approximately 11% of patients with OSAS have airflow limitation on spirometry (259).

OLDOSA syndrome is incorporating OLD and OSAS into a more general entity (260). OLDOSA syndrome is well described (260), but unfortunately there are no exact criteria for diagnosis of this new integrated overlap syndrome. Asthma and COPD often coexist and sometimes are difficult to be differentiated based on current clinical and functional criteria (261). Recently, asthma-COPD overlap syndrome was recognized by Global Initiative for Chronic Obstructive Lung Disease (GOLD) and Global Initiative for Asthma (GINA) scientific committees (262, 263). OLD and OSAS have common risk factors such as age, obesity, smoking, sex, etc.

OSAS seems to be more frequent in COPD and asthma patients and in addition, it can influence the disease control and mortality of both asthma and COPD patients, which can be improved when OSAS is treated.

Patients with overlap syndrome develop more pronounced nocturnal oxygen desaturation than COPD or OSAS alone, which predisposes to pulmonary hypertension (259). Despite the high prevalence of overlap syndrome in general population, long-term follow-up studies are lacking on the pathophysiological and clinical consequences of overlap syndrome, although some clinical outcome studies in this area have been designed (264, 265). Co-existent OSAS represents a risk factor for death after adjusting for COPD severity (266).

It is very important to review the clinical history for symptoms suggestive of sleep disordered breathing in COPD patients, especially in patients, who have hypercapnia during wakefulness, moderate to severe daytime hypoxemia, pulmonary and systemic hypertension and signs of heart failure, despite stable spirometry (238).

Patients with overlap syndrome, in comparison with COPD or OSAS alone with similar ages, tend to be more obese and have more comorbidities (266). Overlap syndrome patients have more daytime sleepiness (236) and worse quality of life measured with the St George's Respiratory Questionnaire than COPD alone (267, 268).

More severe nocturnal hypoxaemia is one of the most important sleep abnormalities in overlap syndrome (245). Polysomnographs in overlap syndrome demonstrate reduced total sleep time, sleep efficiency and higher sleep fragmentation than those in COPD or OSAS patients (4). Patients with OSAS alone return to normal oxygen saturation baseline between obstructive events. In COPD patients nocturnal oxygen saturation decreases more evenly throughout the night and at the end of an apnea, oxygen saturation does not tend to return to the initial baseline level (269). A typical overlap syndrome patient has a reduced baseline oxygen saturation, reduced mean oxygen saturation and longer hypoxaemia than OSAS or COPD patients (270).

Hypoxaemia is associated with increased systemic and pulmonary blood pressure and arrhythmias and in plus can facilitate the development of cor pulmonale (14).

In overlap syndrome patients, surrogates of OSAS severity such AHI, seem to play a minor role for developing pulmonary hypertension compared with parameters that reflect the severity of COPD. Daytime hypoxaemia, hypercapnia and reduced FEV1 were detected to be predictors of right-heart failure (15).

The COPD and Asthma Sleep Impact Scale (CASIS) is only one disease-specific patient-reported outcome measure for use in COPD and asthma patients which have been developed and validated for these diseases (16). At the moment, in majority of cases non-COPD-specific sleep outcome measures are used in COPD patients (i.e. Pittsburgh Sleep Quality Index or the Epworth Sleep Scale), although neither has been tested for reliability or validity in COPD patients (17).

In the appropriate clinical context, polysomnography and a spirometry test are essential and should be performed to confirm the

existence of the overlap syndrome and to establish its severity (4).

The American Thoracic Society and European Respiratory Society recommend a screening polysomnography in patients with mild to moderate airflow obstruction and evidence of pulmonary hypertension or unexplained dyspnea in mild COPD (60).

Comparative patient characteristics of patients with COPD, OSA and overlap syndrome are presented in *Table 17*.

Table 17

Comparative Patient Characteristics

COPD	Overlap syndrome	OSAS
Risk factors		
Smoking, indoor and outdoor air pollution, occupational dusts and chemicals, frequent lower respiratory infections during childhood	rostral shift of peripheral oedema, neck obesity, smoking, high BMI, Use of corticosteroids **Protective factors:** Reduced REM sleep, Low BMI, Use of Inhaled anti-cholinergic drugs, inhaled long-acting b-agonists and theophyllines	obesity, sex, ageing, craniofacial abnormalities, smoking
Symptoms		
Cough Sputum production Dyspnea	Poor sleep quality Insomnia Nocturnal cough/gasp Persistent fatigue Mood changes	Snoring Respiratory pauses Daytime sleepiness
Disease-specific health-related quality of life assessment		
The *COPD Assessment Test* (CAT), Clinical COPD Questionaire (CCQ)	COPD and Asthma Sleep Impact Scale (CASIS)	Epworth Sleepiness Scale (ESS), Berlin OSA Questionnaire
Diagnostic tests		
Spirometry	Spirometry, PG, PSG	PG, PSG
Cardiovascular morbidity		
+	++	+
Mortality		
+	++	+
Treatment		
+/- nocturnal oxygen	nocturnal CPAP +/- oxygen	nocturnal CPAP

PG - polygraphy, PSG - polysomnography, CPAP - continuous positive airway pressure

Actually, there are no specific guidelines for the management and treatment of overlap syndrome (4). The management of overlap syndrome patients must be based on optimising treatment for COPD and OSAS following the actual clinical guidelines (262, 271). The goals of treatment are improvement in patient-related outcomes: sleep fragmentation, sleep quality and daytime sleepiness, daytime activity, rate of COPD exacerbations, hospitalization frequency and mortality (4, 250). Reduction of cardiovascular consequences and extension of survival can be achieved by the correction of hypoxaemia and hypercapnia during sleep (245, 257).

The most severe consequence of hypoventilation, particularly during sleep, is hypoxaemia, and adequate oxygen therapy represents important therapeutic option for any disorder associated with respiratory failure during sleep (245). The risk of carbon dioxide retention with supplemental oxygen therapy in COPD patients may have been overestimated in the past, and there is evidence that carbon dioxide retention with oxygen therapy during sleep is frequently modest and usually non-progressive (20). The 2017 GOLD guidelines recommend that supplemental oxygen therapy be provided to patients whose oxygen saturation fall below 88% or who have a PaO_2 less than 55 mm Hg during wakefulness or PO2 between 55 and 60 mm Hg with evidence of pulmonary hypertension, congestive heart failure or polycythemia (1, 262).

The base of treatment for patients with overlap syndrome is positive airway pressure using either continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) (250, 272). CPAP or BiPAP act as a pneumatic stent to overcome upper airway closure during sleep and effectively decrease the AHI. Sleep quality, diurnal PaO_2 and $PaCO_2$ levels and reduction of AHI are better with noninvasive ventilation supplemented by oxygen therapy than with supplemental oxygen alone (21). Also, CPAP therapy has shown important beneficial effects on secondary cardiovascular conditions including systemic hypertension, pulmonary arterial hypertension and arrhythmias (19).

In a long-term cohort study, patients with overlap syndrome who were not used CPAP therapy demonstrated an increased any cause mortality and hospitalisation caused by COPD exacerbations, compared with overlap patients which used CPAP (266). Also was demonstrated that the use of CPAP and oxygen therapy can reduce the additional mortality risk in overlap syndrome patients with chronic respiratory

failure (22). Stanchina et al. have shown that more time on CPAP in patients with the overlap syndrome was associated with a reduced risk of death, after controlling for common risk factors (23).

Patients with overlap syndrome should get the adequate pharmacological treatment according to current guidelines (53, 262). Long-acting anticholinergics and long-acting β-agonists, have been shown to improve nocturnal SaO_2, but without a clear improvement on the quality of sleep (13, 255). Theophylline may be useful in patients with COPD and sleep disordered breathing; it stimulates the respiratory centre and enhances the activity of the respiratory muscles (24). Benzodiazepines must be avoided in patients with overlap syndrome because they reduce arousal response to hypercapnia, induce hypoventilation and decrease muscular tone (4, 25).

Overlap syndrome of COPD and OSAS is highly prevalent but frequently underestimated and underdiagnosed in general population due to the failure to consider possible coexisting sleep disordered breathing among individual patients with COPD and vice versa, in clinical practice. Overlap syndrome is associated with greater hypoxaemia and hypercapnia in comparison with COPD or OSAS alone. Early diagnosis and appropriate therapy with CPAP will reduce morbidity and mortality of overlap syndrome.

Systemic effects and comorbidities of COPD

There are two different theories relating the observed associations between COPD and systemic manifestations and comorbidities (273). First theory consider that COPD is the result of a systemic "spill-over" of the inflammatory and reparatory events occurring in the lungs of patients with COPD, with the disease remaining primarily in the lungs (274). Second theory states that pulmonary manifestations of COPD are one more form of expression of a "systemic" inflammatory state with multiple manifestations (275).

The best studied risk factor for COPD is cigarette smoking, it is also one of the major risk factors of all chronic diseases (276). Well known that the cigarette smoking induces not only local inflammation (airways and lungs), but also systemic inflammation (cellular and humoral), systemic oxidative stress, marked changes of vasomotor and endothelial function, and enhanced circulating concentrations of several procoagulant factors (277).

A number of patients with COPD have evidence of systemic inflammation (273, 278), measured either as increased circulating cytokines (leukotriene B_4, interleukins-1, 6 and 8 and tumour necrosis factor alpha), chemokines and acute phase proteins (C-reactive protein, fibrinogen, serum amyloid A, surfactant D), and abnormalities in circulating cells (neutrophils, macrophages and T lymphocytes).

One-half of all people aged $\geq$ 65 years have at least three chronic medical conditions, and one-fifth have five or more (252). It can be explain by the concept of inflammaging, in fact, process of aging is associated with a chronic low-grade inflammatory status as a consequence of lifelong antigenic exposure leading to some genetic modifications.

These systemic effects of cigarette smoking or age or some another unknown factors or sum of them could contribute substantially to the development not only of the COPD, but also of comorbidities. Thus systemic inflammation is potentially the common pathway leading to multiple chronic diseases and might explain the high prevalence of comorbidities in the same patient.

The most common comorbidities (279, 280) described in association with COPD are skeletal muscle dysfunction (281), cachexia (282), cardiovascular disease (hypertension, coronary artery disease, heart failure, pulmonary vascular disease) (283), pulmonary infections (284), osteoporosis (285), lung cancer (286) and diabetes (287). Comorbidities widely affect health outcomes in COPD: mortality of COPD patients caused by nonrespiratory diseases, such as cardiovascular diseases and cancer (288). Any COPD patient should be carefully evaluated for comorbidities and the systemic effects of COPD since they not only influence the prognosis, but also have an impact on disease management (275).

It is estimated that 80% of COPD patients are likely to have at least one comorbidity (249, 289). Dal Negro and coworkers reported that one comorbidity of clinical relevance was detected in 78.6% of patients with COPD, at least two in 68.8%, and three or more were found in 47.9% of subjects (237). Besides that, the incidence of diabetes, hypertension, and hyperlipidemia increases with the severity of COPD. For instance, diabetes was found in 4% of patients in GOLD Group A, in 16% of those in GOLD B, and in 29% of those in GOLD D. Similarly, hypertension was found in 38% of patients in GOLD A, in 55% of those in GOLD B, and in 65% of those in GOLD D; hyperlipidemia was found

in 13% of patients in GOLD A, in 30% of those in GOLD B and in 37% of those in GOLD D (290).

It is very important for clinician to know prevalence and disease burden of the comorbidities that are often associated with COPD, as well as their interaction with, and impact on, COPD exacerbations (291).

COPD and cardiovascular diseases

COPD is characterized by low-grade systemic inflammation, probably resulting from spillover of multiple pro-inflammatory markers into the circulation, and thus has a role in the development or acceleration of cardiovascular disease (CVD). Indeed, COPD patients have a two to five times higher risk of coronary artery disease, cardiac dysrhythmia, heart failure, pulmonary vascular disease, and peripheral vascular disease (292).

COPDCoRi (Chronic Obstructive Pulmonary Disease Coronaropathy Risk) is an algorithm for predicting the risk of coronary artery disease (CAD) in COPD patients via a rapid, inexpensive, and non-invasive approach. This predictive algorithm has shown a high diagnostic accuracy of 81.5% (27).

Acute coronary syndrome (ACS) in COPD patients is associated with higher risk of heart failure and major bleeding complications, without increased risk of in-hospital mortality (28). Furthermore, elderly patients with COPD who received influenza vaccine had a lower risk of hospitalization for ACS (29).

In patients with COPD, the coronary artery calcification score (CACS) is correlated with age, pack-years, 6-minute walk distance, modified Medical Research Council (mMRC) dyspnea score, and circulating levels of interleukin (IL)-6, IL-8, Clara cell protein 16, surfactant protein D and peripheral blood neutrophil count, but not with emphysema, rate of exacerbations, predicted forced expiratory volume in one second (FEV1) or decline in FEV1 (31, 249).

Moderate or severe COPD affects the short- and long-term survival of patients who undergo coronary artery bypass grafting (CABG) (32). The postoperative mortality among patients after CABG procedures is also affected by COPD and is 1.4% for mild, 2.9% for moderate and 5.7% for severe stage COPD (33).

Interestingly, Gaisl et al. found, in a large cohort of 1906 patients, who had a median follow-up of 42.6 months, a higher incidence of major adverse cardiovascular events among COPD patients compared to controls with similar coronary artery calcification and epicardial fat burden, but no COPD (34). This reveals a complex interaction and highlights the need to focus on primary and secondary prevention.

Moreover, the prevalence of hypertension among COPD patients is estimated to be between 28.5-64.7% (36, 37, 43). Similarly, arrhythmias are reported in 16.6-23.3% of COPD patients (37, 38). Atrial fibrillation (AF) is more prevalent among patients with severe airflow limitation than among those with mild or moderate airflow limitation (39). In addition, patients on anticoagulants, with AF and COPD, are at a higher risk of death than patients with AF alone (40). In addition, COPD is an independent predictor of major adverse cardiac events in patients with AF (40).

Acute and chronic heart failure (HF) are also frequent in COPD. The prevalence of HF among COPD patients is between 12.3-28.3% (37, 41, 42). Several studies have shown that a low left ventricular ejection fraction is an independent risk factor for mortality in COPD (43, 293).

Another cardiovascular comorbidity that is frequently encountered, but not always diagnosed, is cardiac autonomic neuropathy, which can occur in approximately 40-50% of patients with mild COPD (45, 46). The characteristic intraneural hypoxaemia that is recognized among COPD patients has a pathogenic mechanism similar to that of diabetic neuropathy (47).

Finally, patients with COPD and CVD have a greater risk of hospitalization due to exacerbation, higher BODE (BMI, obstruction, dyspnea, exercise capacity) index, and impaired health-related quality of life; they also tend to have a shorter 6-minute walk distance.

COPD and endocrine diseases

Current data indicate that the metabolic syndrome (MS) affects 21-53% of COPD patients, with a higher prevalence in the early stages of disease (49, 294). MS may also influence natural history of COPD, rate of COPD exacerbations, quality of life and lung function (49). Screening for type 2 diabetes mellitus (T2DM) and hypertriglyceridemia shows a prevalence between 16.8-28.5% and 19.7%, respec-

tively, among patients with COPD: that underlines the importance of a thorough screening program (37, 43, 50). Metabolic disease, unlike cardiovascular disease, tends to be more frequent in females than in males (237).

Patients with COPD have an increased risk of T2DM, independent of sex, age, smoking status, and BMI (51). Other studies show that non-emphysematous COPD (airflow obstruction with a paucity of emphysema on chest computerized tomography (CT) scan) is associated with an increased risk of diabetes (52). Moreover, the presence of diabetes has been suggested as an independent risk factor for readmission after a COPD-related hospitalization (54).

Glycated hemoglobin (HbA1c) levels, either less than 6% or more than 10%, in patients with T2DM, are independently associated with COPD (54). These findings suggest that patients with T2DM should be monitored carefully for COPD (295). However, other authors have failed to find any relationship between COPD and HbA1c in patients with T2DM. Nonetheless, coexistence of diabetes and COPD increases the likelihood of developing heart failure (56).

The pharmaceutical management of patients with T2DM and COPD may be challenging. Steroids may cause acute derangement of the blood glucose levels, and, although they rarely lead to a significant change in HbA1c levels, a higher cumulative dose is a predictor for an increase in HbA1c levels (57). On the other hand, metformin therapy may be associated with a survival benefit for COPD patients, although it could cause a minor and clinically insignificant rise in lactate (58).

An unusual result was shown in a retrospective cohort study that consisted of 20,730 subjects newly diagnosed with COPD and an equal number of matched controls. Among these patients, 5,820 patients had T2DM and 14,910 patients did not have T2DM. The results confirmed that patients with COPD had a significantly higher risk of developing lung cancer than healthy people, but also suggested that there is a protective effect of T2DM against lung cancer among patients with COPD (59).

Associations of COPD with other endocrinopathies have also been investigated. For instance, a low free triiodothyronine (T_3) level is prevalent among patients with chronic diseases and indeed with COPD. T_3 is known to have a role in modulating antioxidant systems and there is evidence of increased oxidative stress in COPD patients with a low T_3

level. This may possibly suggest a lower threshold for prescribing T_3 replacement in patients with COPD (296). Another study indicated that COPD patients with thyroid dysfunction have a greater impairment of maximal inspiratory pressure and maximal expiratory pressure (54). In addition, a negative correlation was observed between hypoxemia and TSH (thyroid stimulating hormone) (297).

It is also well known that the hypothalamic-pituitary-adrenal axis (HPA) may also be affected, either by COPD or by steroid administration during exacerbations. Cortisol levels are inversely associated with re-exacerbation risk (298). It is accepted that immediate and prolonged suppression of the HPA axis is a common finding after an acute exacerbation of COPD (299). Finally, men with COPD have a significantly lower level of testosterone and frequently have erectile dysfunction (300, 301).

COPD and osteoporosis

Osteoporosis is very prevalent among patients with COPD (up to 94% of COPD patients) (302). It is more pronounced among predominantly emphysematic patients and patients with low body mass index and low fat-free mass. Although long-term corticosteroid use is an additional risk factor for osteoporosis, steroid-naive patients are also at significantly higher risk. Even in patients requiring chronic administration of systemic corticosteroids, their use alone cannot explain the rate of the decrease of bone density (303). The severity of COPD correlates positively with the degree of osteoporosis and the risk of fractures (304). Interestingly, inhaled steroids do not appear to increase the risk of osteoporosis. On the contrary, they may have a prophylactic effect in predominantly bronchitic patients, due to their anti-inflammatory effects and their limited systemic exposure (305).

Bone mineral density is an essential measurement that should be determined in those with moderate-to-severe airflow obstruction, for the detection and prevention of osteoporosis-related morbidity (306). In COPD patients, a low BMI in GOLD stage IV strongly suggests loss of bone mineral density and warrants further examination. Patients in GOLD stage IV have a 7.6 times greater risk of abnormal bone mineral density than patients in GOLD stage II (307). Other studies show that sarcopenia is also a risk factor for osteoporosis in COPD patients (266).

Calcium and vitamin D supplementation are of limited efficacy in COPD patients (308). A fragility fracture is quite often the first presentation of osteoporosis or osteopenia. Ribs are the most frequently affected bones, usually fractured after severe coughing, and are followed by vertebral fractures, which pose a risk for the patient's life and health (309). The need for effective screening, prevention, and treatment of osteoporosis among COPD patients cannot be emphasized enough, nor can the need for urgent development of guidelines.

COPD and gastrointestinal diseases

Several links have been found between COPD and gastrointestinal (GI) pathophysiology over recent years. Inflammatory molecules spillover and common embryologic origins of respiratory and GI tracts are considered to be the main causes of these links.

Recent meta-analyses suggested a potential relationship between chronic systemic infections, such as those with *H. pylori*, and the development and progression of COPD (310). In another study, *H. pylori* immunoglobulin G (IgG) antibody titers were measured in serum samples from 4765 patients with mild-to-moderate COPD. Approximately 18% of the patients were seropositive for *H. pylori* and these individuals demonstrated consistently lower FEV_1 values than individuals who were seronegative for *H. pylori*. Moreover, *H. pylori*-seropositive individuals had greater circulating C reactive protein levels than seronegative individuals, and had an increased risk of cardiovascular mortality (311). It has been hypothesized that direct injury and chronic inflammation, via inhalation and aspiration, resulting in *H. pylori* bronchial tree colonization, may contribute to the pathophysiology of COPD (312).

COPD patients with co-existing gastroesophageal reflux disease (GERD) have more severe chronic bronchitis, increased breathlessness and a higher incidence of respiratory infections than individuals with COPD but without GERD (54). Among individuals with COPD and GERD, those who do not use acid inhibitory treatment regularly have an increased risk of COPD exacerbations during follow-up (313).

Gallbladder and pancreatic, but not hepatic, pathologies tend to be more frequent among COPD patients (314).

COPD exacerbations and comorbidities

Acute exacerbations of COPD are episodes of increased breathlessness and productive cough that require more intensive treatment. It is well known that COPD patients with comorbidities tend to have more frequent exacerbations (290). These comorbidities include cardiovascular disease, asthma, cancer, osteoporosis, and neuro-psychiatric complications (315, 316).

Although cardiovascular diseases are associated with increased rates of COPD exacerbations, several studies have reported that β-blockers, whether cardioselective or not, are associated with a significantly lower rate of exacerbations (317). This reduction is more predominant in GOLD Group B patients. This may be explained either by the decrease in airway inflammation and mucus production, or by the increase in the pulmonary β-adrenoceptor density after long-term administration of β-blockers. Data regarding their impact on COPD mortality is still controversial (318, 319).

It has been suggested that statins, another frequently prescribed group of drugs in patients with CAD, are associated with decreased risk of COPD exacerbations and decreased frequency of intubation (320, 321). Interestingly, statins appear to reduce the risk of COPD exacerbations only in patients with coexisting CAD (313). This suggests that the protective action may be secondary to the reduction in vascular inflammation and further supports the inflammatory spillover theory.

The data that links T2DM and COPD exacerbations is very limited and controversial, since some studies linked both hyperglycemia and hypoglycemia to poorer clinical outcomes, including length of hospitalization, risk of adverse effects, readmission, or death, while others did not find any correlation between glucose levels and COPD exacerbations (294, 322-325). Hyperglycemia may be triggered either by the patient's metabolic predisposition or by steroid therapy (326). Characteristically, steroids did not affect the HbA1c of diabetic patients who were treated with steroids for an AECOPD (acute exacerbation of chronic obstructive pulmonary disease), although the total dose of steroids administered is a predictor for an increase in HbA1c level (57). Thus, the role of T2DM in COPD exacerbations is not completely understood but, nevertheless, there is one.

A large real-life study revealed that thiazolidinediones may significantly reduce the risk of AECOPD among diabetic patients with COPD; this highlights the need to review T2DM treatment in patients with COPD (327).

The need for thyroid hormonal treatment is debatable. In one of the studies, non-thyroidal illness syndrome was associated with prolonged weaning in intubated COPD patients admitted to the intensive care unit. They also had a significantly higher APACHE (acute physiology and chronic health evaluation) II score and frequent pulmonary infections (328). Another study showed that the exacerbation frequency in COPD patients with hypothyroidism was significantly higher than in COPD patients with normal thyroid function. Moreover, TSH values and exacerbation frequency had positive correlations (329).

Cortisol levels were inversely associated with re-exacerbation risk among COPD patients in a prospective study (298). Besides that, cortisol is not the only hormone that may play a role in COPD exacerbation, since patients often have other underdiagnosed endocrine dysfunctions (330). During exacerbation there is an increase in circulating leptin and decreased insulin-like growth factor I levels (331).

GERD is considered to be an independent risk factor for COPD exacerbation. Acute exacerbations were diagnosed at incidences of 4.08 and 2.79 per 100 person-years, respectively, in individuals with, versus individuals without, GERD, in a nationwide study in USA (43). Other extensive cohort studies showed similar results (332, 333). GERD is highly prevalent among COPD patients; thus, it is important to diagnose properly GERD symptoms in patients with COPD (334).

Assessment of comorbidities in COPD

There are several approaches for the assessment of comorbidities in COPD patients: Charlson comorbidity index, COPD specific comorbidity test (COTE) index, CODEx (comorbidity, obstruction, dyspnea and previous exacerbation) index, comorbidities in chronic obstructive lung disease (COMCOLD) index, dyspnea score, eosinopenia, consolidation, academia and atrial fibrillation (DECAF) score, COPDCoRi and comorbidome (*Table 18*).

Table 18

The assessment of comorbidities in COPD

Mode of assessment	Description	The spectrum of comorbidities
Charlson comorbidity index	A standard scale with 15 chronic diseases graded for severity of disease	Myocardial infarction, HF, peripheral artery disease, cerebrovascular disease, dementia, diabetes, liver disease, peptic ulcer disease etc.
COTE index	A quantitative risk stratification comorbidity tool which is based on 12 comorbidities that influence survival in COPD	Oncologic (lung, pancreatic, esophageal, and breast cancers) Pulmonary (pulmonary fibrosis) Cardiac (atrial fibrillation/flutter, congestive heart failure, and coronary artery disease) Gastrointestinal (gastric/duodenal ulcer, liver cirrhosis) Endocrine (diabetes with neuropathy) Psychiatric (anxiety)
Comorbidity, airway Obstruction, Dyspnea, and previous Exacerbation (CODEx) index	A prognostic tool to assess mortality, hospital readmission and their composite impact for 3–12 months after hospital discharge in patients hospitalized for exacerbation of COPD	Comorbidity is measured using the age-adjusted Charlson index. Dyspnea, obstruction, and severe exacerbations are calculated according to BODEX (BMI, airflow obstruction, dyspnea, and previous severe exacerbations) thresholds
Comorbidities in Chronic Obstructive Lung Disease (COMCOLD) index	Five comorbidities with greatest impact on patient-reported health status	Depression, anxiety, peripheral artery disease, cerebrovascular disease and symptomatic heart disease
DECAF score	The five strongest predictors of mortality in patients with COPD exacerbation and pneumonia	Extended MRC Dyspnoea Score, eosinopenia, consolidation, acidaemia, and atrial fibrillation
COPDCoRi	An algorithm for predicting the risk of CAD in COPD patients	CAD
Comorbidome	A graphical expression of the comorbidity prevalence and risk of death in the form of an orbital bubble chart	The same as for COTE index

The Charlson comorbidity index

The Charlson comorbidity index is a general index, not specific for COPD. It is a standard scale of 15 chronic diseases graded for severity – including myocardial infarction, chronic heart failure, COPD, peripheral vascular disease, cerebrovascular disease, dementia, diabetes, systemic hypertension, liver disease, renal disease, cancer, connective tissue disease, HIV, skin ulcers, peptic ulcer disease, depression, and use of warfarin. The Charlson comorbidity index was proposed for the first time in 1987 and is used as an important tool for the prediction of patients' survival (335). The high value of Charlson index is associated with reduced survival: multivariate analysis, that adjusted for a variety of different factors including FEV_1, revealed that patients who had a Charlson score of 3 or more (equivalent to two chronic diseases, or one severe disease, apart from COPD) were more than twice as likely to die as individuals with a lower burden of comorbidities.

The COTE index

COTE, a COPD-specific index, is based on 12 comorbidities that influence the survival of COPD patients - cancers of the lung, pancreas, esophagus, and breast, pulmonary fibrosis, atrial fibrillation/flutter, congestive heart failure, coronary artery disease, gastric/duodenal ulcers, liver cirrhosis, diabetes with neuropathy, and anxiety - and is based on a study by Divo and coworkers, who followed up 1,664 patients with COPD for a median of 51 months. During this period 79 comorbidities were recorded, and, of those, 15 differed in prevalence between survivors and non-survivors (336).

Increases in the COTE index are associated with a higher risk of death from COPD-related and non-COPD-related causes. In very severe COPD, the combination of lung function (mainly resting hyperinflation) and comorbidities provides the major prognostic information.

Increases in the BODE and COTE are independently associated with increased risk of death. A COTE score greater than or equal to 4 points causes a 2.2-fold increase in the risk of death (336). The BODE index has a better survival prediction than the ABCD GOLD categories system. Adding the COTE to the BODE index significantly improved outcome prediction (54). COTE-index predictive efficiency was similar to that of the Charlson index and even greater when including age (337).

The CODEx index

For prognosis, both short- and medium-term, after hospital discharge of patients with COPD, Almagro and coworkers proposed the CODEx index. The index was developed to predict mortality, hospital readmission, and their combination, for the period from 3 months to 1 year after discharge of patients hospitalized for COPD. The CODEx index was associated with mortality at 3 months ($p < 0.0001$; hazard ratio (HR), 1.5; 95% confidence interval CI, 1.2-1.8) and 1 year ($p < 0.0001$; HR, 1.3; 95% CI, 1.2-1.5), hospital readmissions in the same periods, and their combination (all $p < 0.0001$) (338).

The COMCOLD index

The COMCOLD index reflects the combined impact of five important comorbidities from patients' perspective and may help clinicians focus on comorbidities affecting patients' health status the most. The conditions that are included in the index are depression, anxiety, peripheral artery disease, cerebrovascular disease, and symptomatic heart disease. The COMCOLD index reflects this impact and complements other comorbidity indices predicting death (339).

The DECAF index

In patients with acute exacerbation of COPD and pneumonia, an alternative to the CURB-65 score, the DECAF score, can be used to predict mortality. The DECAF score includes the five strongest predictors of mortality: extended MRC (Medical Research Council) dyspnea score, eosinopenia, consolidation, acidemia, and atrial fibrillation. The DECAF score showed excellent discrimination for mortality (area under the receiver operator characteristic curve = 0.86, 95% CI, 0.82-0.89) (340).

It is accepted that it can identify low-risk patients (DECAF 0-1) who are potentially suitable for Hospital at Home or early supported discharge services, and high-risk patients (DECAF 3-6) who require escalation planning or appropriate early palliation (341).

GOLD 2011 assessment

COPD comorbidities may also be evaluated by the GOLD combined risk assessment score. For instance, significant associations were found between GOLD score and both emphysema grade and decreased lung function, in patients with more than one comorbidity (342).

Comorbidome

Divo and colleagues developed a graphical representation of the relationship between comorbidities and COPD, the so-called "comorbidome" (343). This was a novel method to express the prevalence of comorbidities and the strength of their association with risk of death in patients with COPD (336). The study was based on stable COPD patients, enrolled in pulmonary services with a lower comorbidity for inclusion and a longer follow-up, which differentiates it from the ESMI (EPOC en Servicios de medicina interna) study of comorbidome (344). In the ESMI study, comorbidity data were collected using the Charlson index, with other disorders identified using a specific questionnaire that included several relevant chronic diseases not included in the Charlson index – depression, arterial hypertension, anemia, arrhythmias, dyslipidemia. Additionally, data on dyspnea, assessed on the mMRC scale, functional status, and previous hospitalizations for COPD or other causes, were collected. Finally, the vital status and the cause of death up to 3 months after discharge were assessed. The final model included cardiovascular disease (arterial hypertension, ischemic heart disease, atrial fibrillation, cardiac failure, peripheral artery disease), cerebrovascular disease, metabolic disorders (abdominal obesity, diabetes mellitus, dyslipidemia), anemia, chronic kidney failure, osteoporosis, mental disorders (depression, dementia, anxiety), respiratory disease (obstructive sleep apnea), and neoplasm. The goal of the ESMI study was to explore, prospectively, comorbidities in COPD patients hospitalized for acute exacerbation in internal medicine services and to examine their effects on short-term mortality (344).

Conclusion

COPD severity is greatly influenced by the presence of comorbidities and, in many cases, COPD is a multi-system disorder. Therefore, it is of great importance, that, in the future, severity systems (scales) of COPD should take into consideration existing comorbidities. Respiratory function and symptom evaluation, noninvasive methods for assessing cardiovascular and metabolic function, along with measurement of inflammatory markers, may prove useful in the management of COPD. At the same time, more holistic screening strategies, and prophylactic and therapeutic interventions should be implemented in order to perfect the management of these patients.

CHAPTER III. NEW WAYS OF ASSESSMENT OF COPD

Actual COPD Assessments: Severity versus Clinical Phenotypes versus Multilateral assessment

There are three well-known and wide accepted approaches to the assessment of COPD: GOLD assessment of severity proposed in 2011 and revised in 2017 by scientific committee, multilateral evaluation and phenotyping (6). The comparative characteristics of these four approaches is presented in *Table 19*.

In the GOLD 2011 report, the scientific committee proposed a new combined staging system with evaluation of (1) the symptomatic status (dyspnoea) as assessed by Medical Research Council (MRC) scale, (2) the physiologic status with the assessment of airflow limitation severity by FEV_1 and (3) the health status assessing the impact of disease on patients daily lives by the COPD Assessment Test (CAT), (4) exacerbation frequency via evaluation of the risk of exacerbations.

In last ten years more than 15 multilateral indices were proposed for the assessment of COPD. The most useful is BODE index, which was proposed by Celli and Cote in 2004 (8). In BODE were included 3 variables which are better predictors of mortality than FEV_1 (BMI, dyspnea assessed by Medical Research Council scale and exercise capacity evaluated by 6 minute walking test). The BODE index may be used to assess the risk of death or hospitalization among patients with COPD (8). Also, the BODE index can predict the exacerbation frequency (92). Given the correlation between the severity of disease and mortality of COPD patients, the BODE index is now suggested as the mainstay of the classification and management of COPD (345).

Multiple studies demonstrated that COPD patients with similar airflow limitation had diverging clinical characteristics, including symptoms, comorbidities and predicted mortality (346). Phenotyping of COPD patients may rely on clinical and physiological manifestations, imaging, assessment of patient-related outcomes (health related quality of life), COPD

comorbidities, exacerbations and systemic inflammation (347, 348).

Recently, it was demonstrated that roflumilast improves lung function and reduces the frequency of exacerbations in patients with predominantly bronchitic symptoms and severe airflow limitation, a specific clinical COPD phenotype (349). This is the first proven personalised treatment based on phenotypic characteristics of COPD. It suggests that multiple phenotypic subgroups of patients exist within the broad range of COPD and specific personalised therapies might improve the disease management (1).

One of the first attempts to implement phenotyping in everyday clinical practice was made in Spanish Guidelines for COPD (350). There were proposed four phenotypes that determine differential treatment: (1) non-exacerbator, with emphysema or chronic bronchitis; (2) mixed COPD-asthma; (3) exacerbator with emphysema; (4) exacerbator with chronic bronchitis (236). BODE multilateral index for the assessment of COPD severity was also included in the classification.

Table 19

Markers used in different approaches for COPD assessment

MARKERS	GOLD 2011	MULTILATERAL INDICES (BODE)	PHENOTYPING	GOLD 2017
Symptomatic	dyspnea assessed by Medical Research Council scale	dyspnea assessed by Medical Research Council scale	symptoms	dyspnea assessed by Medical Research Council scale
Physiologic	FEV1	FEV1 BMI, exercise capacity evaluated by 6 minute walking test	FEV1	-
Health status	the COPD Assessment Test (CAT)	-	-	the COPD Assessment Test (CAT)
Exacerbations	evaluation of the risk of exacerbations	-	evaluation of the risk of exacerbations	evaluation of the risk of exacerbations
Imaging	-	-	X-Ray, HRCT	-

New GOLD COPD Classification: the A, B, C, D system

In the GOLD 2011 report (11), the scientific committee suggested new combined approach with assessment of symptoms, airflow limitation severity, health related quality of life and risk of exacerbations.

Functional domain: well known that dyspnea is a cardinal symptom of COPD. For assessment of dyspnea, new GOLD proposes to use the five-point Medical Research Council (MRC) scale developed by Fletcher and colleagues. The MRC dyspnea scale is a set of five statements about dyspnea. The subject is asked to select the statement that most closely applies. The MRC dyspnea scale considers a single dimension and has proven to be an excellent discriminative instrument for categorizing patients according to the severity of their breathlessness (351). Also, have been shown that the MRC dyspnea scale can predict survival in patients with COPD (84).

Physiologic domain: spirometry is the most reproducible, discriminatory and objective measurement of airflow limitation available (11, 352). The FEV1 remains essential for the diagnosis and quantification of the respiratory impairment resulting from COPD (2, 3, 11). In addition, the rate of decline in FEV_1 is a good marker of disease progression and mortality.

Exacerbation domain: an exacerbation of COPD is defined as an acute event characterized by a worsening of the patients respiratory symptoms that is beyond normal day to day variations and leads to a change in medication (11). Acute exacerbations can be measured in many ways: time to first exacerbation, number of exacerbations, number of unscheduled and emergency department visits for COPD, number of hospitalizations for COPD, and number of intensive care unit admissions for COPD (353). Due to seasonal variation, an evaluation of exacerbation frequency requires a period of $\geq$ 1 year (306). The rate of exacerbations varies greatly between COPD patients (354). The best predictor of having frequent exacerbations is a history of previous treated events (355). In addition, it has been proven that worsening airflow limitation is linked with an increasing prevalence of exacerbations, risk of hospitalizations and risk of death (355-357).

Health status domain: health status measurement provides a standardised method of assessing the impact of disease on patients daily lives, activity and well-being (358). The COPD Assessment Test (CAT) is a short, simple patient-completed questionnaire for COPD with very

good measurement properties (359). The CAT covers a broad range of effects of COPD on patients health, despite the small number of component items (359). The CAT is a easy-to-use questionnaire that distinguishes between patients of different degrees of COPD severity and appears to behave the same way across countries (360).

New approach for COPD finally becomes more complex, but simultaneously can be used easy by respiratory doctors at the global level. This new approach potentially will facilitate a more accurate risk stratification of COPD patients and a better understanding of disease pathophysiology, and eventually develop more targeted therapy and improved management of patients with COPD.

Following the development of the current GOLD classification, the next step for COPD researchers must be performing of the impact studies. These studies should establish both the applicability and the impact on healthcare of implementation of this new approach in daily clinical practice.

Complex assessment of COPD

It was discussed that a complex approach with the assessment of 4 domains: functional (symptoms), physiologic (airflow limitation severity), health status (health related quality of life) and exacerbation (risk of exacerbations) comes to facilitate deeper understanding of the impact of COPD on an individual patient. A new A, B, C, D system is more comprehensive than the old GOLD classification (*Figure 3*).

In everyday practice this approach can be applied very easy. There are two simple steps in complex COPD evaluation: assessment of symptoms and risk evaluation. For assessing of symptoms can be used MRC scale or CAT test: LOW level of symptoms is indicated by MRC grade ≤ 1 or a CAT score < 10 points, HIGH level of symptoms can be characterized by MRC grade ≥ 2 or a CAT score ≥ 10 points (11). For the next step risk evaluation can be applied two methods. Spirometric assessment of the grade of airflow limitation – LOW risk will have patients with GOLD 1 and 2 stage and HIGH risk will have patients with GOLD 3 and 4 stage.

Another option that can be used is the assessment of the the history of COPD exacerbations in the preceding year: 0 or 1 exacerbation indicates LOW risk, while ≥ 2 exacerbations indicates HIGH risk. In case of different level of risk by these two systems, the risk should be determined by the method indicating highest risk (11).

For example: we have a patient with a MRC score of 2 points and CAT test score of 9 points, FEV1 of 55 % predicted and a history of 2 exacerbations per year. The assessment of symptoms by MRC and CAT score demonstrates that the patient has LOW level of symptoms. The assessment of risk by spirometry shows LOW risk because the patient is GOLD 2 (moderate severity of obstruction), but the patient had 2 COPD exacerbations per year this indicates HIGH risk. In this situation the risk must be determined by the method indicating the highest risk, thus our patient will be included in group C.

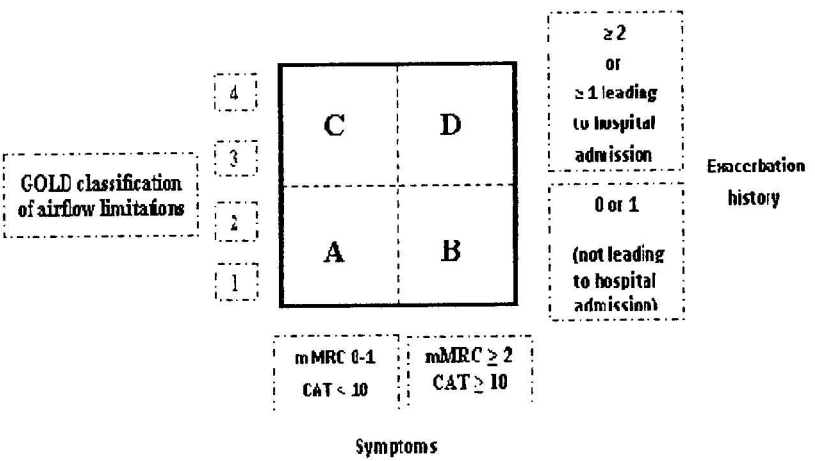

Figure 3. GOLD Classification 2011

In the current 2017 update, the ABCD categories are derived exclusively from symptoms and history of exacerbations (*Figura 4*). The exclusion of airflow obstruction from clinical parameters was made to clarify what was being evaluated and ranked by severity. Spirometry remains golden standard for the diagnosis of COPD, but it will be used more for the confirmation of the diagnosis and for follow up of the decline of lung function.

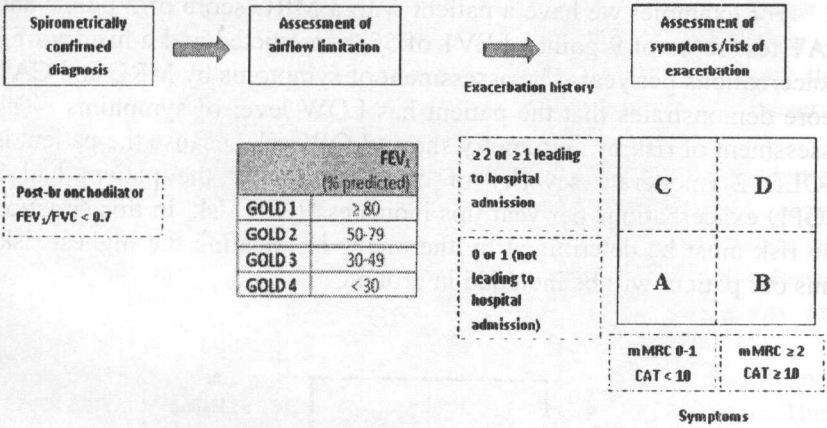

Figure 4. GOLD Classification 2017

COPD exacerbations assessment

Exacerbations of COPD are the most important adverse events in the progression of COPD. It is a common cause of mortality, hospital admission, increased healthcare costs, diminished lung function and worsening of health-related quality of life in COPD patients. The assessment of COPD exacerbations remains a provocation for physicians at the global level, because little systemic research has been done. The most popular stage system for COPD exacerbations is clinical staging based exclusively on clinical symptoms: increase in sputum volume, increase in sputum purulence and increase of dyspnea (150). Aaron et al described recently two distinct patterns of exacerbation onset: sudden and gradual (361). Sudden onset COPD exacerbation is associated with increased respiratory symptoms but shorter recovery times, it can be useful for better clinical management of COPD exacerbations.

Unfortunately, there are currently no known biomarkers of COPD exacerbations with wide acceptance (362), but some biomarkers can provide clinically relevant information (C-reactive protein for the detection of a COPD exacerbation and procalcitonin for antibiotic guidance).

Recently Hurst et al demonstrated that the major determinant of frequent exacerbations in all stages of COPD severity may be a history of COPD exacerbations (355). COPD frequent exacerbator represents

distinct phenotype in moderate and severe stage of COPD and the incidence of frequent exacerbations increases with increasing of severity of obstruction, that is can be easy used for targeting of the exacerbation prevention and treatment strategies.

Multidimensional indices

In patients with COPD, there is an important heterogeneity of clinical presentation, severity of disease and the rate of disease progression (363). In the absence of accepted and validated markers, the measurement of lung function and especially FEV1 was used as a global marker for assessing pathophysiological changes in COPD (63, 122). However, measurement of lung function correlates poorly with the severity of breathlessness and other extrapulmonary symptoms. Only the measurement of lung function cannot be suitably used for assessing the impact of COPD on the human body or for appreciating the efficacy of treatment (122). This led to the development of composite scores for predicting the vital prognosis (60, 364). Some researchers have studied the predictive role of composite scores, which also include non-pulmonary factors to assess whether they better determine the risk of death than only the FEV1 (60, 75, 365).

First attempts in facilitation of risk assessment were made by the development and validation of new staging systems which permit categorization of the heterogeneous population with COPD. There were developed a lot of multidimensional indices, in which widely was used different clinical, functional or quality of life variables. There were proposed more than 15 multilateral indices: BODE index (*Table 20*) which included body mass index (BMI), FEV1, dyspnea and exercise capacity (8), the ADO index which included age, dyspnea, FEV1 (366), the DOSE index which included dyspnea, FEV 1, smoking status, and exacerbation frequency (367), the HADO which included health related quality of life, activity, dyspnea and degree of airflow obstruction (368) (*Table 21*), etc.

The most cited in literature is BODE index, which was proposed by Celli and Cote in 2004. In BODE were incorporated 3 variables which are better predictors of mortality than FEV1 (BMI, dyspnea assessed by Medical Research Council scale and exercise capacity evaluated by 6 minute walking test). The BODE index was shown to be better than FEV1 in predicting the risk of death among patients with

COPD (8). Also, the BODE index is responsive to exacerbations (369), and more importantly acts as a surrogate marker of future outcome after interventions such as lung volume reduction surgery or pulmonary rehabilitation (370). The BODE index as adequate expression of comprehensive severity of disease was proposed for new approach in the management and treatment of COPD patients (345).

Among the COPD evaluation markers, there is also the body mass index (BMI), which was included in the BODE index (371). Both smoking and the evolution of disease determine the decrease of body mass, especially the lean body mass (83, 372). Numerous data indicate that BMI is an independent risk factor for all-cause mortality, including respiratory, in COPD patients, the association being stronger in patients with severe COPD (69, 109, 373, 374). It has been suggested that BMI has a protective effect on the survival rate, compared to a low BMI.

The BODE ranges on a scale from 0 to 10. High values (8-10) indicate a risk of death of 80% in the next 28 months, low values (0-3) indicate a better prognosis of the disease (*Table 20*) (60).

In a study by Celli B., 625 patients with COPD were included, who were evaluated prospectively for 52 weeks for all-cause mortality and mortality caused by respiratory diseases (60, 63). Patients with high BODE index had a greater risk of death. The odds ratio for all-cause mortality for the increase by 1 BODE index point was 1.34 (95% confidence interval, 1.26 -1.42; P <0.001), and the odds ratio for mortality from respiratory causes was 1.62 (95% confidence interval, 1.48-1.77; P <0.001). The ability to predict the risk of death was higher in the case of BODE index than in the case of FEV1 (0.74 versus 0.65).

In more recent studies, it has been shown that the BODE index is a good predictor of hospitalization and mortality in patients with severe emphysema, also it is a sensitive index for the assessment of patients with COPD over (157, 375-377). For example, in a group of 127 patients with COPD, the BODE index was compared with FEV1 to predict hospitalization for 16.2 months (375). During the study, 47% of patients were hospitalized and 17% died. Using the BODE index, one can forecast the risk of hospitalization more accurately than using FEV1 (BODE – relative risk 1.20; 95% confidence interval, 1.15-1.25 p <0.001 versus FEV - relative risk - 0 08; 95% confidence interval, 0.04 to 0.16; p <0.001).

In the study *National Emphysema Treatment Trial*, Martinez and colleagues evaluated the risk factors for mortality in 609 patients with severe emphysema (376). In the multivariate analysis, older age ($p = 0.04$), low exercise tolerance ($p = 0.002$), decreased total lung capacity and residual volume ($p = 0.05$) and increased BODE index ($p = 0.02$) were predictive of mortality.

Cote and Celli (378) reported the BODE index decreasing by 19% in 246 patients with COPD who performed pulmonary rehabilitation, which was associated with reduced mortality and prolonged hospital stays.

In 2006, Esteban and his colleagues published a study on 604 consecutive patients with BPCO (364), in which they appreciated the degree of dyspnea, FEV1, the activity level, the health status. As a result, the HADO score was established (*Health-Activity-Dyspnoea-Obstruction*), which is a very simple and easy-to-calculate score in outpatients and can be used for assessing the severity of COPD and for predicting the survival rate in the following 3 years.

In comparison to the BODE index, the HADO score is much simpler and does not require the 6-minute-walk test. However, the BODE index is more accurate in predicting the risk of death compared to the HADO index and FEV1 (364). The HADO index closely correlated with the quality of life assessed by SGRQ, especially with SGRQ total score, as this aspect of the BODE index remains less studied.

The SAFE index (SGRQ, *Air-Flow limitation and Exercise tolerance*) appeared in 2007 and includes appreciation of the quality of life with SGRQ, the degree of bronchial obstruction and exercise tolerance (365). SAFE index can be used to stratify the severity of COPD and moderately correlates with the number of COPD exacerbations ($r = 0.497$, $p < 0.001$).

Multidimensional indices, such as BODE, HADO and SAFE, have several advantages in assessing disease severity and treatment effects, because they include non-pulmonary markers, that reflect the impact of systemic factors. Moreover, BODE index includes the assessment of dyspnea as a cardinal symptom of the disease. But on the other hand, it is not known which variables are still the most important and which need to be introduced in multidimensional indices, such as markers that may reflect disease pathogenesis (63).

Table 20

Body-Mass Index, Degree of Airflow Obstruction and Dyspnea, and Exercise Capacity (BODE) Index (60)

Variable	Points on BODE Index			
	0	1	2	3
FEV1 (% of predicted)	≥ 65	50-64	36-49	≤ 35
Distance walked in 6 min (m)	≥ 350	250-349	150-249	≤ 149
MMRC dyspnea scale	0-1	2	3	4-5
Body-mass index (kg/m^2)	> 21	≤ 21	-	-

Majority of multidimensional indices was developed for clinical use, but unfortunately they all lack sufficient evidence for implementation. Impact studies are required to establish if the use of prognostic indices improves or not COPD disease management and patients outcome (379).

Table 21

Comparison of the main multidimensional indexes

	Indices for assessment of COPD					
Risk factors for mortality	**BODE**	**e-BODE**	**BODEx**	**ADO**	**DOSE**	**CODEX**
FEV1	+	+	+	+	+	+
Dyspnea	+	+	+	+	+	+
BMI	+	+	+			
Exersise tolerance	+	+				
Exacerbaions rate		+	+		+	+
Smoking					+	
Age				+		
comorbidity						+

COPD phenotypes

The following definitions are needed in order to facilitate the understanding of the pathogenesis of diseases and their management in general (348).

Genotype: The genetic constitution of an individual organism, the inherited map that carries the genetic code (DNA). However, not all organisms with same genotype look or act the same way, because of epigenetic influences such as, environmental factors. The final, end result

of both genetic and environmental factors is called phenotype (348).

Thus, the definition of phenotype could be: The set of observable characteristics of an individual resulting from the interaction of its genotype with the environment (380).

Finally, the terms such as subgroup, endotype or subtype have been used to define distinct patho-physiological mechanism. Thus, endotype differs from phenotype (the observable characteristics) since it is referring to a subgroup with a distinct pathobiological mechanism. It is a common phenomenon the presentation of COPD with a number of phenotypes that could be subdivided into a number of endotypes. Finally, the above terms are used by many researchers indistinguishably and this causes a great confusing in the medical literature (381-383).

Phenotype(s) is (are) primarily applied in diseases with a strong epigenetic pathobiological mechanism(s) such as, COPD. It is obvious from the definition that this disease is the result of an environmental insult(s) (cigarette smoke, biomass fuels) that interact with the genotype of a "susceptible" individual (384-386).

GENETIC FACTORS IN COPD: A BRIEF SUMMARY

If the genome is genetically severely altered, as in α1-antithrypsin deficiency, then the disease appears without a significant involvement of the environment. However, it is well known that environmental insults such as smoking and biofuel smoke exposure can promote the earlier development of the disease in this condition (387). In addition, an interaction between genetics and the environment is supposed to enhance the development of the disease in susceptible individuals (388).

Proposed pathogenetic mechanisms in COPD include the protease-antiprotease imbalance, response to oxidative stress, cell death and inflammation (389-391). Family-based and single-gene studies have discovered genes and loci that are associated with COPD susceptibility, while recent genome-wide association studies (GWASs) have discovered novel candidate genetic pathways. The phenotype of a1-antithrypsin deficiency, caused by mutations in SERPINA1, accounts only for the 1-2% of the total COPD population; however, it is the only established genetically driven cause of COPD that has a potential intervention so far (392). Inducible heme oxygenase (HO-1) is a cyto-protective enzyme that plays a critical role in lung defense against in-flammatory and oxidant-induced cellular and tissue injury in COPD

(393). Polymorphisms of the HO-1 promoter associated with reduced HO-1 expression have been linked with increased susceptibility to smoking-induced emphysema (394, 395). Other candidate genes for COPD recently identified by GWASs include CHRNA3/5 (cholinergic nicotine receptor alpha 3/5), IREB2 (iron regulatory binding protein 2), HHIP (hedgehog-interacting protein), FAM13A (family with sequence similarity 13, member A), and AGER (advanced glycosylation end product–specific receptor), (396-399). Although their pathological roles are still largely unknown, potential liaisons with COPD susceptibility and associations with emphysema severity (400), the chronic bronchitis sub-type (401), lung function (402), COPD exacerbations (403) and pathogenesis of pulmonary hypertension (404) have been proposed and replicated in multiple populations.

Thus, the most common pathway to develop COPD is the epigenetic one, when environmental factors affect the genome of susceptible individuals (404-407).

The basic epigenetic mechanisms are DNA methylation, which suppresses gene transcription, and various post-translational modifications of core histones (histone acetylation, methylation, ubiquitination and phosphorylation), that may result in either activation or repression of genes (405-407). Several studies have proposed that oxidative damage related to smoking is associated with epigenetic modifications that may mediate COPD development and progression by modulating gene expression of proinflammatory cytokines and inflammatory signaling pathways (408, 409), as well as inducing cell apoptosis (410). Moreover, evidence show that oxidative damage contributes in genetic instability of specific non-coding DNA sites (microsatellite sequences, telomeres, promoters and sites of methylation) adjacent to or included in genes implicated in the pathogenesis of COPD or supposed to be associated with certain phenotypic expressions of the disease (411, 412).

However, in some cases there is a protective role of the environment that can prevent the development of the disease, such as nutrition. This may explain, the fact that not all smokers develop COPD (388).

Since the insults of the environment could hit different loci of the genome of a susceptible individual, a number of phenotypes of COPD could be identified. This may be the answer to such heterogeneity seen in COPD. This also could explain the fact that clinical phenotypes can overlap in the same patient (several pathogenetic pathways) (413).

In addition, since the interaction between the environment and the genome has a long-life duration, it raises the question if a certain phenotype is constant overtime.

Phenotyping COPD

A phenotype of a heterogeneous disease defines a subgroup of patients with similar observable characteristics. In such complex disease as COPD that lasts the whole life, this exercise is quite difficult. It is obvious, that clustering patients with clinical or epidemiological criteria is quite different than clustering by pathophysiological or pathobiological criteria and it is extremely complex if we use a large number of criteria. Thus, due to these limitations the medical literature is lacking sufficient number of valid studies on the issue of the phenotypes of COPD! (381-383, 414, 415).

Historically, two classical phenotypes of COPD had been described: the Chronic Bronchitic and the Emphysematous one. Using pathophysiological criteria these phenotypes were named also as "blue bloaters" and "pink puffers" (416). Recently, a number of distinct phenotypes had been described such as, the frequent exacerbator, the fast decliner (fast drop of FEV1 over the years), the phenotype with systemic inflammation, the one with a number of severe co-morbidities such as cardiovascular or metabolic ones (417), the one of significant hyperinflation.

To complicate even further the issue of phenotyping COPD patients, we acknowledge that any one individual may manifest multiple phenotypes, etiologically different. Although, there are significant difficulties and confusions in this area of research, the current scientific efforts are focusing to identify biomarkers that can describe a similar underlying mechanism(s) and thus, define better a COPD phenotype or endotype. Therefore, the efforts are to describe disease attributes deferent between COPD patients that are related to meaningful clinical outcomes, such as, symptoms, exacerbations response to treatment disease progression or death (415, 417-420).

The major goal of defining phenotypes in COPD is to identify the individuals that could respond to specific mode of treatment, because it is well known, that not all patients are affected by all available medications. This would lead to personalized treatment with consequence the better manager of the disease, better quality of life for the patient, and reduction in the cost of therapy.

Finally, the overlap syndrome between COPD and asthma (ACOS) has been considered as specific phenotype of COPD or asthma. As we believe that this syndrome is very rare and could be relevant only to the smoking asthmatic (421, 422).

Another important step in reflection of heterogeneity of clinical presentation and progression of COPD was introduction of phenotyping. Was proposed specific definition of COPD phenotype (423): a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression or death).

Clinical COPD phenotype must have predictive value, needs validation in prospective studies for each of the outcomes to which they may relate and must be able to classify patients into distinct subgroups that allow physicians to better determine the most appropriate therapy to improve clinically meaningful outcomes (423).

Phenotypic characterisation of COPD subjects may rely on clinical and physiological manifestations, imaging, assessment of patient-related outcomes (health related quality of life), COPD comorbidities, COPD exacerbations and systemic inflammation (347).

In recent years, it has been proposed that cluster analysis can be applied for examining COPD phenotypic heterogeneity. Multiple studies demonstrated that COPD patients with similar airflow limitation had very different clinical characteristics, including symptoms, comorbidities and predicted mortality (346).

In recent studies (424, 425) it was shown that roflumilast improved lung function and reduced the frequency of exacerbations in patients with specific clinical COPD phenotype (bronchitic symptoms and severe airflow limitation). This is the first proven personalized treatment based on phenotypic characteristics of COPD (425). Its suggest that multiple phenotypic subgroups of patients exist within the broad range of COPD, and that specific therapies might improve disease management.

Thus, the exact clinical, functional, imaging, and molecular characterization of clinical COPD phenotypes presents great clinical value because it would allow its early identification, with eventual using of more targeted therapy and as a result improved management of COPD patients.

GOLD scientific committee has updated the classification of COPD patients to include apart from spirometric measures, the level of symptoms and previous history of exacerbations, while the Spanish guidelines took a further step, differentiating predominantly emphysematic/bronchitic patients and also including a COPD-asthma overlap phenotype (350). Many different molecular, radiologic and clinical biomarkers have been suggested as potential bases for the formation of phenotypes and supported by different levels of evidence (5).

The ultimate aim of phenotypes exceeds even the determination of predictive factors. Further studies in groups with similar characteristics may uncover a variant pathophysiological or immunological background or a different clinical entity.

Alpha-1 antitrypsin deficiency (α1-AT) consists an ideal example of the aim of clinical phenotypes. Initially identified as a subgroup of COPD patients with familial predisposition for early emphysema, it was then recognised as a separate genetic syndrome, characterised by a deficiency of the serine protease inhibitor α1-AT, associated with different clinical features and prognosis and requiring a different management (392).

Biomarkers are naturally occurring molecules, genes or characteristics by which a particular pathological or physiological process, disease or phenotype can be identified. Current COPD research emphasises in the detection of accurate but also simple and cheap biomarkers to determine different clinical phenotypes.

Spanish COPD guidelines (GesEPOC) apart from the exacerbation frequency and the COPD-asthma overlap, also encompass predominantly bronchitic versus predominantly emphysematic classification, defining four clinical phenotypes:

a) Asthma-COPD overlap,

b) Infrequent exacerbators, regardless of the bronchitic/emphysematic elements,

c) Frequent exacerbators with predominant emphysema,

d) Frequent exacerbators with predominant bronchitis.

The clinical significance of bronchitis/emphysema phenotype has been challenged over time. Being among the oldest classification, initially suggested by Dornhost in 1955 (426), its clinical use has been limited until recently. It is now recognized that COPD patients with chronic bronchitis phenotypes, defined as the presence of productive

cough for more than three months per year for at least two consecutive years, are characterized by bronchial hypersecretion and increased airway inflammation that may predispose them to airway colonisation and recurrent infections-exacerbations (427). For this reason, the bronchitic phenotype is more frequently associated with frequent exacerbations.

Classical COPD phenotypes

Old classical division of COPD patients in blue bloaters and pink puffers as well as the clinical definition of chronic bronchitis or the histological one of emphysema had been described in many textbooks. Chronic bronchitis is characterized by cough and sputum production for at least 3 months in each of two consecutive years (clinical definition). Emphysema is characterized by the destruction of the gas-exchanging surfaces of the lung (alveoli), beyond the terminal bronchioles (morphopathological definition).

Since both characteristics can coexist in many patients the term COPD had been introduced. To describe the pathogenetic mechanisms the first attempt of phenotyping COPD was to use the terms "pink puffer" (emphysema-hyperinflation phenotype) and "blue bloater" (chronic bronchitis phenotype).

Chronic Bronchitis phenotype

In blue bloaters the primary pathology is chronic bronchitis (mucus-producing glands hypertrophy, goblet cell metaplasia, chronic inflammation of the bronchial tree). The ventilation-perfusion mismatch is increased leading to hypoxemia and hypercapnia occurs due to altered pattern of breathing. They present cyanosis in the face and lips, thus the "blue".

Chronic bronchitis is a common clinical phenotype in COPD and is classically defined as chronic cough and sputum production for 3 months a year for 2 consecutive years, but many studies have used different definitions to define it (428). However it is described, it is clear that chronic bronchitis is associated with multiple clinical consequences, including hastening lung function decline, increasing risk of exacerbations, reducing health related quality of life, and possibly raising all-cause mortality (429).

Despite its clinical consequences, the literature regarding its pathophysiology, radiologic characteristics, and clinical phenotype has been sparse. Recently, however, there has been a growing body of literature that more carefully describes environmental risk factors, epidemiology, and genetics associated with chronic bronchitis (428, 429). In addition, as computed tomography technology continues to improve, the radiologic phenotype associated with chronic bronchitis is better understood.

Emphysema-hyperinflation phenotype

In brief the pink puffer is a patient with emphysema as primary pathology: destruction of the airways distal to the terminal bronchiole, and gradual damage of the pulmonary capillary bed. This leads to less ventilation - perfusion mismatch than the blue bloaters, and thus, to relatively "normal" blood gases due to hyperventilation (puffers). These persons usually develop muscle wasting and weight loss, although have less hypoxemia than the blue bloaters.

The identification of the emphysema-hyperinflation phenotype was a probable oversimplification in that it integrates the simultaneous damage to the parenchyma and airways, especially the small airways (430). The relative contributions of emphysema and airway remodeling to airflow limitation remain unclear, although the degrees of emphysema and air trapping may contribute to the different response patterns to bronchodilator (431).

Using quantitative computed tomography (CT), Subramanian et al identified four imaging-derived phenotypes reflecting "emphysema-dominant", "airway disease-dominant", "mixed" disease and "mild" disease (432). The ''emphysema-dominant'' phenotype presents a lower rate of exacerbations compared with ''airway disease-dominant'' and ''mixed'' disease phenotypes (433).

The "emphysema-dominant" group had significantly higher lung volumes, lower gas transfer coefficient, lower oxygen (PaO_2) and carbon dioxide ($PaCO_2$) tensions, higher level of haemoglobin and higher blood leukocyte numbers than the "airway disease-dominant" group (432).

The "airway disease-dominant" phenotype is characterized by airway wall thickening that is a feature of chronic bronchitis.

The *"mixed"* phenotype is defined as the presence of both airway wall thickening and emphysema on quantitative CT (434). Furthermore,

patients with COPD with the "mixed" phenotype are associated with more severe dyspnea and more frequent hospitalizations than those with each of the remaining CT based phenotypes (434).

Patients with *"mild"* disease had better spirometric measures than the other phenotypes. They demonstrated relative preservation of FEV_1 and gas transfer with QCT indices consistent with minimal emphysematous change and airway wall thickening, despite comparable age and smoking history to the other groups. It is uncertain whether this phenotypic group represents a truly mild form of COPD or consists of a sub-group of subjects on the cusp of abnormality, who have been "misclassified" as a consequence of the current, commonly employed definition of COPD (432).

The current morphopathologic classification of emphysema, based on its acinar distribution, which was proposed by Reid (435), is divided emphysema into four major groups: centroacinar, paraseptal or periacinar, panacinar, and irregular. However, the distribution of these findings in the lung parenchyma and their relationship with the diagnosis, severity, treatment, and prognosis of COPD are still poorly understood (430). It has been documented that lower lung predominant pulmonary emphysema is associated with more severe disease than is upper lung predominant pulmonary emphysema (436). In addition, patients with homogeneous-emphysema tend to have greater hyperinflation. The distribution of emphysema could have a major impact on functional parameters and should be considered in the assessment of COPD patients (436).

Early-onset/basal panlobular emphysema that is classically considered to be associated with alpha-1 antitrypsin deficiency (AATD) should be also included in this phenotype (437). However, there is solid evidence that AATD presents with multiple physiological phenotypes with differing clinical impact and progression, possibly due to genetic modifiers, as in 'common' COPD. Patients may present with bronchiectasis and no emphysema, upper zone and centrilobular emphysema, as well as the classic lower zone panacinar emphysema (438). Furthermore, many patients with AATD have a degree of reversibility and recurrent exacerbations (438). More than 120 genetic variants (also known as Pi types) of AAT exist, confirming the highly polymorphic nature of this gene (430). The predominant wildtype phenotype is MM (PiMM), while the most common deficiency alleles are PiZ and PiS.

Severely deficient amounts of AAT are produced by phenotypes PiZZ, PiSZ and some other rare genes. Many PiSZ patients exhibit no emphysema or upper-zone-dominant disease (439). All these findings clearly indicate that even the traditional distinction between panlobular emphysema (typically distributed in the basal regions and characteristic of AATD) and centrilobular emphysema (located towards the apical region and characteristic of subjects with 'common' COPD) is likely an oversimplification (439) and, in any case, there is an overlap between the "emphysema-dominant" and "frequent exacerbator" phenotypes (430).

New COPD Phenotypes

Frequent Exacerbator Phenotype

Frequent exacerbator phenotype is defined if the patient has two or more exacerbations per year and implies worse prognosis. This phenotype detected from clinical records or during history taken from the patient. According to Hurst et al. this is a quite stable phenotype over the years (420).

It is important to mention that in the frequent exacerbator phenotype, exacerbations are not homogenous, but differ in etiology, severity and biological substrate (430). Causes of COPD exacerbations are multiple and various: 5-70 % of exacerbations of COPD are due to respiratory infections (including bacteria, atypical organisms and respiratory viruses), 10% are due to environmental pollution (depending on season and geographical placement) and up to 30% are of unknown etiology (440). Severity classification includes three categories: mild exacerbation, which is characterised by increasing of respiratory symptoms that can be controlled by the patient with an increase in the usual medication; moderate exacerbation, which requires treatment with systemic glucocorticosteroids and/or antibiotics; and severe exacerbation, which describes exacerbations of COPD that require hospitalization or a visit to the emergency department (441).

Exacerbations of COPD are heterogeneous also according to inflammatory pattern. In fact, four distinct biological exacerbation clusters have been identified: bacterial -, viral -, and eosinophil-predominant, and a fourth associated with limited changes in the inflammatory profile termed "pauci-inflammatory" (442).

Fast decliner phenotype

The fast decliner phenotype is defined if the patient shows greater than the average fall in Forced Expiratory Volume in 1s (FEV1). This needs at least 3 years measurements of FEV1 to conclude the fast declining and this is a significant limitation, in detecting this phenotype (443, 444).

Tantucci et al have demonstrated that information provided in recent years about the rate of FEV1 decline in COPD patients strongly supports the concept that the faster progression of functional impairment in COPD occurs early and it particularly occurs in GOLD stage II (11). It seems more logical to make efforts for an early spirometric detection of COPD, based on risk factors rather than symptoms, and to plan randomized clinical trials to show the efficacy of an early strategy of intervention on the natural history of such a disorder (11).

Inflammatory phenotype

Inflammatory phenotype is described in patients with persistent elevation of serum inflammatory markers, such as CRP or other proinflammatory cytokines (178, 278, 445, 446).

In his study Agusti demonstrated three extremely important points (278): first, it characterizes inflammome (the systemic inflammatory network pattern) in patients with COPD and distinguishes it from that of smokers with normal lung function and non-smokers. Secondly, it shows that systemic inflammation is not a constant feature in all COPD patients, since about a third of persons from this study did not have any abnormal biomarker at baseline and about the same proportion remained 'non-inflamed' after one year of follow up. Finally, it identifies a subgroup of COPD patients with persistently elevated inflammatory biomarker levels that, despite relatively similar lung function impairment, had significantly increased all-cause mortality and exacerbation frequency. These inflamed patients may therefore constitute a novel distinct phenotype within the larger group of patients with COPD and could be the target of novel therapeutic strategies.

Current smoker phenotype

Some researchers consider the current smoking COPD patients as a district phenotype with specific psychosomatic behavior, worse prognosis and poor adherence and response to treatment (447).

The systemic or co-morbidities phenotype

The systemic or co-morbidities phenotype is the COPD patient with multiple cardiovascular, metabolic or other comorbidities. However, no specific criteria had been reported, as far the number or the severity of those comorbidities is concerned. Epidemiological studies had shown that COPD patients commonly are suffering from other chronic diseases such as the metabolic syndrome, arterial hypertension, ischemic heart diseases, diabetes, osteoporosis and psychological disorders (anxiety/depression) (291). The theory of "spill over" had been proposed as the possible pathobiological mechanism(s). According to the "spill over" the prime site of the "burning" and the inflammation is the lungs but the products of this inflammation are spilled over via the circulation to various sensitive organs such as the brain, the liver, the muscles, the kidneys etc. (448-451). It is obvious that this patho-genetic mechanism is present only in a specific phenotype or subgroup of COPD and it is not the case in all COPD patients. Finally a number of other phenotypes had been proposed such as the "eosinophilic" one. However, eosinophilia had been seen mainly during the exacerbations in some patients (452-455).

Phenotypes in European guidelines for COPD

A recent review showed that the identification of patient subtypes had been included in various European guidelines for COPD (456). In addition it was noticed that there was a great variability between those guidelines as far as the criteria used to identify the phenotypes. However, the classical ones emphysema, chronic bronchitis, pink puffer, blue bloater, those with dyspnea, the frequent exacerbators and the overlap syndrome ACOS were presented in most of the guidelines (456).

COPD-asthma overlap phenotype

Chronic obstructive pulmonary disease (COPD) and asthma are frequent chronic diseases, which pose a significant burden to health status, quality of life and –in the case of COPD- survival of the patients (457, 458). The reported prevalence of COPD ranged from 0.2% in Japan to 37% in the USA, but this varied widely across countries and populations, by diagnostic criteria, and by age group analyzed (459). COPD is one of the leading causes of death (460); it is estimated that in 2020 it will be the third leading cause of death worldwide and fifth

leading cause of years lost through early mortality or handicap (disability-adjusted life years). COPD, a disease of the elderly, is usually associated with a number of significant comorbidities (461).

Asthma also is a serious global health problem affecting all age groups, with global prevalence ranging from 1% to 21% in adults (462). Thus, asthma is also a common condition, responsible for considerable morbidity, healthcare utilization and costs, which include those costs caused by the days off work and decrease productivity of patients with uncontrolled asthma (463, 464). Asthma is also characterized by the presence of comorbidities which substantially affect the quality of life and the number of exacerbations (465).

In 1961, during the first Bronchitis symposium held in Groningen, the Netherlands, Orie and colleagues hypothesized that the various forms of airway obstruction, such as asthma, chronic bronchitis, and emphysema, should be considered not as separate diseases but as different expressions of one disease entity, which they named chronic nonspecific lung disease (163). Later on in 1969 this hypothesis was termed the Dutch hypothesis (466). The Dutch hypothesis is in contrast to the "British hypothesis", where asthma and chronic obstructive pulmonary disease (COPD) are seen as distinct entities generated by different mechanisms (467).

In recent years, it became clear that some patients share clinical characteristics of both asthma and COPD. This presentation could be another phenotype of airway disease called asthma-COPD overlap syndrome (ACOS). The frequency of emergency room visits and intensive care unit admissions are higher among those patients with overlap syndrome compared to those with COPD but not asthma (468). In addition, overall healthcare expenditure for patients with co-existent asthma and COPD is almost twice the expenditure for patients with asthma but not COPD (469).

Unfortunately, distinguishing asthma from COPD is challenging, especially in elderly patients (470, 471). Quite often the diagnosis can change during life and more authors report about cases of unclassified airflow limitation (472). Moreover, it has been suggested that ACOS may include not one but several heterogeneous phenotypes with different underlying mechanisms and since these patients were previously excluded from clinical trials we have limited data of this

condition (473, 474). Thus, a significant phenotype of COPD could be the smoking Asthmatic (475).

Definitions

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation according to the 2016 Global Initiative for Asthma (GINA) guidelines (378).

In the 2017 Global Strategy for Diagnosis, Management, and Prevention of COPD (GOLD) guidelines, defined COPD as a common, preventable and treatable disease, that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases (1).

ACOS is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACOS is therefore identified by the features that it shares with both asthma and COPD (377). The prevalence of this syndrome among patients with obstructive pulmonary disease varies depending on the diagnostic criteria and country from 2.1% to 55% (377, 476, 477). Several specialists in obstructive lung disease state that since there is limited data to this subject a more specific definition of ACOS till now cannot be developed and others challenge its existence. Therefore ACOS is a new clinical syndrome that recently appeared in respiratory medicine and till now is poorly defined and poorly understood.

Another theory is that asthma, COPD, and ACOS do not represent separate diseases but a continuum, consisting of several endotypes and phenotypes. ACOS allows a more simple approach to therapy which on the other hand hinders progression towards the concept of personalized medicine (264, 478). It is also accurately stated that ACOS term may lead to clinical confusion and potential inappropriate use of resources (479).

The terms asthma and COPD are based on "Oslerian paradigm" which was introduced by Sir William Osler more than 100 years ago on the basis of the principal organ system in which symptoms and signs are attributed (480). However, classical Oslerian approach is not taking in

consideration new genetic, molecular and imagistic data, it can be sometimes efficient in "stereotypical" cases and not so good in patients with combination of asthma and COPD (264). In the post-genomic era it has been recognized that both terms represent "umbrella" terms that include distinct groups of patients. In recent years, we have identified several phenotypes, which are subgroups of patients defined by different clinical characteristics, which have different prognosis or respond differently to treatments. More importantly, we have managed to divide some of these phenotypes to endotypes by identifying the underlying molecular pathways (typical example – a1 antitrypsin deficiency) (481, 482). Recently Agusti et al proposed a new holistic approach to the assessment and management of chronic airway disease, which is based exclusively on treatable traits in each patient (264). Treatable traits are classified in multiple domains, which can coexist: airflow limitation, eosinophilic airway inflammation, chronic bronchitis, airway bacterial colonisation, bronchiectasis, cough reflex hypersensitivity, pre-capillary pulmonary hypertension, chronic respiratory failure, deconditioning, etc. Patients with airway disease could present with any combination of the above mentioned traits and their management should be guided accordingly.

All in all, there is still a significant ongoing disagreement on the use of the term ACOS and characterization of these patients with intermediate clinical characteristics. While treatable traits and personalized medicine lead to a more overall management of all patients with chronic airway disease, the concept of ACOS also serve in the understanding of the underlying mechanisms and simplification of the management of these patients by non-specialists (483).

Pathogenesis and pathophysiology

Pathophysiology and underlying immunological pathways of asthma and COPD differ significantly. Similarly the clinical presentation, pathophysiology of ACOS receives several characteristics from both asthma and COPD.

The inflammation in asthma patients is usually caused by eosinophils which release pro-inflammatory mediators and basic proteins that may damage epithelial cells and cause airway remodeling (484). Mast cells are also considered to play an important role in asthma and contribute to inflammation with bronchoconstriction mediators

(485, 486). Furthermore, other cells such as lymphocytes, dendritic cells, macrophages are abundantly present and contribute to inflammation (487). On the other hand, in non-eosinophilic asthma, neutrophils appear to be the predominant inflammatory cells (488, 489). Neutrophilic inflammation can be present in severe or late-onset asthma, chronic infections or in smokers (490). Particularly bronchial infiltrate of CD8(+) T cells and CD68(+) macrophages, and epithelial remodeling resembling COPD-like features can be present in smokers with asthma (491).

COPD is characterized by a specific pattern of inflammation involving increased numbers of CD8+ (cytotoxic) Tc1 lymphocytes present only in smokers that develop the disease (492). The inflamed airways of COPD patients contain also macrophages, T lymphocytes, and dendritic cells (493). Still there are reports of eosinophilic airway inflammation in patients with severe COPD exacerbations which further complicates the pathogenesis and pathophysiology of an already complicated disease (494). The Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) cohort also demonstrated that 37.4% of patients with stable COPD had eosinophil counts persistently $\geq$ 2% at all visits, 13.6% had eosinophil counts persistently < 2% at all visits, and an intermittent group of 49% subjects had variable eosinophil counts that oscillated above and below 2% (495).

Oxidative stress plays an important role in the pathogenesis and pathophysiology of COPD but not asthma. Shortage of antioxidant nutrients, especially of ascorbic acid and lycopene, as well as reduced glutathione can be found in some of COPD patients but not those with bronchial asthma (496). It had been shown that there were significant differences in the CD83(+) dendritic and B cells in smoking asthmatics render those patients less responsive to corticosteroids and more susceptible to infections (483).

In addition asthma cytotoxic immune response is represented by granzyme A and B, whereas in smoking asthmatic perforin and 8-OHdG are additionally involved, resembling the immune response of COPD (497). Those markers could be used to identify ACOS patients in the future.

Mitochondrial dysfunction due to oxidative stress -normally a characteristic of COPD- also contributes to the pathogenesis of ACOS (498).

Finally, genetic factors can also play an important role and there are genetic variants associated with ACOS reported in the literature such as single nucleotide polymorphisms in the genes CSMD1 and GPR65 (499).

Risks factors

Ageing is associated with a marked decrease in the prevalence of diagnosed asthma and with a marked increase in the prevalence of COPD. The prevalence of the overlap of asthma and COPD is also increased with ageing (500, 501). Kiljander and colleagues suggested that age more than 60 years and smoking for more than 20 pack-years are the best predictors of ACOS. COPD is six times more prevalent among patients who meet these two criteria, compared to patients who do not fulfill any of them (odds ratio 6.08 [2.11, 17.49]) (502).

Moreover, patients with ACOS have lower cumulative smoking, suffer more from obesity and atopic diseases and used more asthma treatments compared to COPD patients. The authors stated that the dyspnea, quality of life, exacerbations, comorbidities and mortality are not different from COPD patients (503). Data on sex predominance of ACOS is conflicting (477, 504).

Finally, ACOS shares risk factors with asthma (505). Subjects who developed asthma before the age of 40 years may be at higher risk for ACOS (477).

Diagnosis

Spanish Respiratory Society proposed diagnostic criteria for ACOS in 2012. Diagnosis is confirmed when 2 major and 2 minor criteria are met (*Table 22*) (506).

Table 22

Criteria proposed by Spanish Respiratory Society for ACOS diagnosis

Major criteria	Minor criteria
Increase in FEV(1) ≥ 15% and ≥ 400ml	High total IgE >100 UI/ml
Eosinophilia in sputum > 5%	Personal history of atopy
Personal history of asthma	Increase in FEV(1) ≥ 12% and ≥ 200 ml on 2 or more occasions

However, globally consensus is still lacking on the existence of ACOS as a separate syndrome, and on its diagnostic criteria (507).

According to GOLD/GINA recommendations normal FEV1/FVC pre- or post bronchodilatator test is not compatible with ACOS unless there is other evidence of chronic airflow limitation. FEV1 more or equal to 80% predicted is compatible with diagnosis of mild form of ACOS. FEV1 less than 80% is an indicator of severity and possible complications in the future. Post bronchodilatator increase in FEV1 more or equal to 12% and 200 ml from baseline is common in ACOS if FEV1 is low. Moreover an increase in FEV1 more than 15% and 400 ml is also compatible with ACOS diagnosis (377).

Other methods such as the assessment of fractional exhaled nitric oxide (FENO) and immunoglobulin E (IgE) in COPD patients were also used in the diagnosis of ACOS. When the cutoff value of FENO was 35 ppb the prevalence rate of ACOS was 16.3% in COPD group. But if both FENO and IgE were assessed, the high-FENO/high-IgE group was 7.8% among patients with COPD. This indicates both asthma-like airway inflammation and the presence of atopy in COPD patients (508).

Future studies may demonstrate other markers and criteria for diagnosing ACOS. A recent study demonstrates that inflammatory cytokines IL-4, IL-8, IL-10, and TNF-α are different among control, asthma, COPD with exacerbation and ACOS groups and might be useful in assessing the development of these diseases (509).

Radiology investigations

It has been suggested that ACOS has radiological features similar to those of COPD. However, recent studies suggested patients with ACOS have less emphysema, that is differently distributed; they also have greater post-bronchodilatation variations in air trapping, compared to patients with COPD, suggesting a different CT densitometry between the two clinical entities (510). Interstitial changes in ACOS patients are associated with age and smoking history and can be found in up to 23.3%. ACOS with interstitial changes tend to have a higher rate of fungal sensitization. (511).

The percentage of total cross-sectional area of pulmonary vessels less than 5 mm^2 is also higher in ACOS rather than COPD patients (262). On the other hand nearly half of the patients with asthma and

fixed airflow limitations in elderly asthma patients show coexisting COPD components (512).

Nevertheless current data is too limited to confirm the possibility of characteristic or pathognomonic radiological features in ACOS.

Assessment

It is still debatable whether ACOS represents a more severe disease than asthma or COPD. Several studies concluded that COPD patients have a more pronounced rate of decline in FEV1, SGRQ and 6MWD compared to asthma and ACOS patients (263). However, others found that ACOS is more likely to be associated with low lung function, low socioeconomic status, short education duration, lower self-rated health, and past diagnosis of pulmonary tuberculosis or bronchiectasis. Multiple logistic regression analysis revealed that both overlap syndrome and asthma groups were independently associated with lower self-rated health after adjustment for age, sex, socioeconomic status, education level, smoking status, comorbidities, and lung function(513). ACOS appears to be associated with the poorest health-related quality of life (HRQL) (514).

Compared to the COPD cohort, ACOS patients had a 1.13-fold adjusted incidence rate ratio of pneumonia and a 2.58-fold adjusted incidence rate ratio of acute exacerbation (515). Past medical history of tuberculosis was more frequent among patients with ACOS. Within the ACOS cohort, the adjusted hazard ratio for tuberculosis was higher among patients receiving short acting beta agonists and short acting muscarinic antagonists (3.06), long acting beta agonists and long acting muscarinic antagonists (3.68), and inhaled corticosteroids (2.79, all $p<0.05$). Also, patients with more than 15 outpatient visits and hospitalizations per year demonstrated the highest adjusted hazard ratio for tuberculosis (8.09; 95% CI, 6.85-9.56) (516). Pulmonary embolism appears to be more frequent among patients with ACOS, compared to COPD alone. The risk of pulmonary embolism also increases with the number of outpatient visits and hospitalizations (517). On the other hand ACOS patients appear to have less emphysema (499).

In general subjects with ACOS were more likely to have respiratory symptoms, physical impairment, and to report hospital admissions compared to asthma or COPD alone (477, 500, 518, 519). On the other hand, ACOS patients have a better one-year prognosis than

clinically similar COPD patients with no ACOS criteria (504). Finally, 15-year mortality rate showed that long-term prognosis of ACOS is similar to COPD, and worse than asthma and healthy controls (520).

In adjusted analyses, allergic rhinitis, anxiety, gastroesophageal reflux disease, and osteoporosis were more frequent in ACOS than COPD. Chronic kidney disease and ischemic heart disease were less frequent. Still, in patients with ACOS, cardiovascular diseases showed the strongest prognosis for hospitalization (521). The ACOS group was more likely to have at least one comorbidity than the COPD group (522).

Vitamin D deficiency is present in ACOS patients and circulating 25(OH)D level may be of prognostic significance, since a positive correlation was found between 25(OH)D level and FEV1, forced vital capacity, forced expiratory flow between 25% and 75% of FVC, and peak expiratory flow (523).

Management

Until now only limited data exist on the management of ACOS, mainly because ACOS patients were excluded by most COPD or asthma trials. The management should include smoking cessation, oxygen supplementation, pulmonary rehabilitation, vaccines and management of comorbidities since all of these are well justified clinically (458, 524).

There is consensus that first-line treatment for ACOS is the combination of a long-acting β2-agonist and inhaled steroid, and this combination can be used with a long-acting antimuscarinic agent (triple therapy) for severe ACOS (507).

As mentioned, very limited data are available from randomised controlled trials. A 12-week, randomized, open-label cross-over study was conducted in 16 patients with ACOS compared the effectiveness of once-daily fluticasone furoate/vilanterol versus twice-daily fluticasone propionate/salmeterol. Furoate/vilanterol was found to provide substantial improvement in lung function, indicating that this combination should be considered for the treatment of ACOS (525). Another study which included 40 stable ACOS patients and 100 stable COPD patients with no differences between groups for sex, age, smoking history, body mass index, FEV_1%predicted, vital capacity results and their ratios of residual volume to total lung capacity demonstrated that compared to baseline, budesonide/formoterol treatment significantly increased the

FEV1 and decreased the degree of airway wall thickness as well as pulmonary microvascular density (% cross-sectional area < 5) in ACOS patients (262).

While inhaled corticosteroids are recommended in the management of patients with ACOS, its effectiveness is controversial. In a observational 12-year retrospective cohort study involving 125 patients by Lim and coworkers, ICS treatment was not associated with significant improvements in the annual rate of decrease in FEV1, the incidence of severe exacerbations or the overall mortality compared with the non-ICS treatment group (526). Thus individualized management is probably the best option at present. Among the predictors for ICS response may be high sputum eosinophil counts and bronchial wall thickening on chest high-resolution computed tomography (527).

Montelukast administration showed good results in asthma patients who smoke suggesting that leukotrienes may play an important role in this particular case. More studies are required to determine whether leukotriene modifiers can be recommended for the manageent of ACOS patients (528).

Multiple studies suggested that phospodiasteraze 4 inhibitors (PDEI) such as roflumilast can significantly improve pre-bronchodilator FEV1 and reduce the rate of moderate to severe exacerbations (529, 530). Evidence show that asthma patient can also benefit from treatment with roflumilast since it decreases airway inflammation, remodeling and hyperresponsiveness (531, 532). The results are better when combined with montelukast or ICS (531, 533). It also enhances efficacy of the concomitant ICS/LABA/LAMA therapy (534). Therefore, it is logical to presume that roflumilast may be helpful in the treatment of ACOS. However, it should be used cautiously and only in severe cases, not controlled with other medications, given its frequent and significant adverse events.

Recently, several reports demonstrated that anti-IgE therapy (omalizumab) may be an effective and safe therapy for patients with ACOS (535). The efficacy was demonstrated in a 12 months study, in a small group (10 patients) treated with omalizumab. After the treatment patients had a decreased IgE, FENO, eosinophil, neutrophils, macrophages, eosinophil cationic peptide and serum IL-4 levels. They also had decreased dyspnea, wheezing, bronchial hyper-responsiveness) and migraine attacks (536).

Table 23

Pharmacological therapy for ACOS

Drugs	Current data	References
SABA	Widely used bronchodilators in the management of COPD and asthma	(378, 537, 538)
LABA/ICS	Several studies showed positive results in ACOS patients when LABA are combined with ICS	(262, 525)
ICS	Controversial and depends on the patient. High sputum eosinophil counts and bronchial wall thickening on chest high-resolution computed tomography may be used as predictors in ACOS patients	(262, 525-527)
LRA	Showed positive results in asthma patients who smoke	(528)
MCS	Are used in the management of allergic asthma and recent data indicate that mast cells may also play an important role in COPD	(539, 540)
Xanthines	Theophylline can modulates corticosteroid activity and the efficacy of ICS	(541)
LAMA	Significantly improves lung function and quality of life in COPD. Improves lung function in patients with inadequately controlled asthma	(524, 542)
PDEI	Positive results in the management of COPD and asthma. Combination with ICS and montelukast shows beneficial positive effect. Enhanced efficacy of the concomitant ICS/LABA/LAMA therapy	(529-534)
anti-IgE	Several studies demonstrated the effectiveness of omalizumab in ACOS patients particularly decreased IL-4, allergic and pulmonary symptoms and migraine attacks	(535, 536)

Conclusion

ACOS is a relatively new syndrome in the literature of pulmonary medicine and its definition, etiology, pathophysiology, management and treatment are not clear yet (543). Therefore, there are still very limited recommendations and guidelines.

There is a critical need to better define the management of this syndrome that we believe it refers primarily to the smoking asthmatic (543). Large, well conducted trials are urgently required to inform

the diagnosis and management of ACOS. Unfortunately, clinicians have to manage this syndrome empirically at present.

Assessment of health related quality of life in different COPD phenotypes

The multidimensional approach of chronic respiratory disorders required quantification of health-related quality of life (HRQL) in conditions when strictly functional evaluation does not correlate strongly with the degree of dyspnea and the quality of daily life of patients (270).

Several questionnaires are used in respiratory medicine for the assessment of HRQL. Some of the most widely used questionnaires are: St. George's Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT) and Clinical COPD questionnaire (CCQ) (544).

SGRQ is currently the most widely used questionnaire in assessing the HRQL in chronic respiratory disorders. Managing the SGRQ questionnaire can detect changes in quality of life without significant changes to FEV1. Studies have shown that this instrument is reproducible, valid and sensitive. The downside of this method is that SGRQ is time consuming compared to CAT and CCQ. CAT is a quick and easy test for patients to complete since it consists of 8 questions each can be graded from 0 to 5 that determine the patient's overall QOL. CCQ is also a simple questionnaire which has 10 questions, graded from 0 to 6 and the results are presented by a total CCQ score, symptom score, mental score and functional state. Thus CCQ have a total score that has a prognostic value for COPD outomes and is divided into 3 major domains that can separately indicate distinct HRQL changes.

There is currently an ongoing interest towards COPD phenotypes as well as their impact on HRQL, lung function and pharmacological management (348, 545, 546).

Taking into consideration all mentioned above, the aim of our study was to evaluate and to analyze the HRQL in COPD patients classified into different phenotypes.

The patients were divided into four groups according to phenotypes: non-exacerbators, frequent exacerbators with chronic bronchitis (CB), frequent exacerbators without CB, and patients with asthma-COPD overlap syndrome (ACOS). The criteria of diagnosis were based on the recommendation from the Spanish and Czech COPD guidelines

(547, 548). Patients with COPD-bronchiectasis overlap, pulmonary cachexia phenotype were not included into the study.

Chronic bronchitis was defined as a cough that occurred every day with sputum production and lasted for ≥3 months, 2 years in a row. Asthma diagnosis before the age of 40 years or a positive bronchodilator test in the previous 12 months with a history of atopy and/or allergy was defined as ACOS. Non-exacerbators had a maximum of one self reported acute exacerbation within the past 12 months. Frequent exacerbators were required to have ≥2 exacerbations per year.

Pulmonary function data were obtained using standard equipment according to the American Thoracic Society/European Respiratory Society consensus guidelines (352, 549). The HRQL was assessed with SGRQ, CAT and CCQ.

The cohort consisted of 395 COPD patients with mean age 62.7 ± 9.4 years, 79 % were males.

Table 24

Distribution of COPD patients according to the disease phenotype

Phenotype	Number of patients	%
Non-exacerbators	175	44
Asthma-COPD overlap syndrome	33	8
Frequent exacerbators with chronic bronchitis	138	35
Frequent exacerbators without chronic bronchitis	49	12

The patients were divided into four groups according to phenotypes (*Table 24*): 44% of the patients were non-exacerbators, 35% frequent exacerbators with CB, 12% frequent exacerbators without CB, and 8% were patients with ACOS.

Patients with frequent exacerbations with CB (FEV1 37.1 ± 12.1%) and without CB (FEV1 38.6 ± 13.9%) had a lower pulmonary function (*Table 25*) compared to patients with rare exacerbations (FEV1 45.7 ± 17.2%) and patients with ACOS (FEV1 54.2 ± 14.2%).

Table 25

Assessment of pulmonary function in different COPD phenotypes (ANOVA test)

Variable	Phenotypes			
	non-exacerbators	asthma-COPD overlap syndrome	frequent exacerbators with chronic bronchitis	frequent exacerbators without chronic bronchitis
FEV1, %	45.7±17.2	54.2±14.2	37.1±12.1	38.6±13.9
FVC, %	59.5±17.1	68.3±13.3	51.2±17.2	51.7±13.8
FEV1/FVC, %	58.6±13	61.8±9.6	55.4±11.9	57.2±10.5

Note: The differences were statistically significant p <0.01

Table 26

Life quality assessment using CAT, SGRQ, CCQ questionnaires in different COPD phenotypes (ANOVA test)

Variable	Phenotypes			
	non-exacerbators	asthma-COPD overlap syndrome	frequent exacerbators with chronic bronchitis	frequent exacerbators without chronic bronchitis
CAT	24.1±7.21	24.2±7	27.3±6.96	29.9±5.36
SGRQ SYM%	69.4±14.6	68.6±16.7	83.2±11.7	84.9±10.9
SGRQ ACT%	65±18.5	66.4±16.2	72.5±17.8	73.7±19.7
SGRQ IMP%	54.5±17.8	54.7±19.5	68.6±13.8	62.5±11
SGRQ TOTAL%	60.2±15	62.1±16.6	72.2±13	73.1±10.9
CCQ SYM	3.4±0.98	3.58±1.3	3.91±0.89	3.82±0.88
CCQ FUN	2.69±0.9	2.76±1.22	3.1±0.95	3.74±0.98
CCQ MEN	3.83±1.29	3.37±1.17	4.39±1.02	4.6±1.27
CCQ Total	3.2±0.87	3.23±1.14	3.67±0.86	3.72±0.89

Note: The differences were statistically significant p <0.01

The HRQL assessed with the CAT, SGRQ, CCQ questionnaires was significantly affected in frequent exacerbators (*Table 26*). Thus, the overall CAT score in those with frequent exacerbators with CB was 27.3 ± 6.96 points, in those with exacerbators without CB was

29.9 ± 5.36 points, and in patients with non-exacerbators in patients with ACOS the quality of life was less affected. Analyzing the data obtained after processing the SGRQ, we pointed out that the HRQL is severely affected by the disease in the groups of patients with COPD with frequent exacerbations. This severe deterioration was demonstrated by affecting all areas of the SGRQ questionnaire in patients with frequent exacerbators with CB (total SGRQ score 72.2 ± 13%) and without CB (73.1 ± 10.9%) compared to patients with non-exacerbations (60.2 ± 15%) and patients with ACOS (62.1 ± 16.6%). The manifest damage to the quality of life at frequent exacerbators is also demonstrated by increasing all areas of the CCQ questionnaire.

The statistical analysis shows a moderate correlation between the COPD and MRC phenotype ($r = 0.34$, $p < 0.01$), between the phenotype and the BODE index ($r = 0.38$, $p < 0.01$). A negative correlation was found between the COPD phenotype and the distance traveled during the 6-minute walk test: the Spearman correlation coefficient was -0.32, $p < 0.05$.

A phenotype of a heterogeneous disease defines a subgroup of patients with similar observable characteristics (348). In such complex disease as COPD that lasts the whole life, this exercise is quite difficult. It is obvious that clustering patients with clinical or epidemiological criteria is quite different than clustering by pathophysiological or *pathobiological criteria and it is extremely complex if we use a large* number of criteria. Thus, due to these limitations the medical literature is lacking sufficient number of valid studies on the issue of the phenotypes of COPD (381-383, 414, 415).

The aim of the study was to evaluate and to analyze the HRQL in COPD patients classified into different phenotypes. Phenotypes represent a step towards personalized medicine but the classification is still an ongoing process. The introduction of phenotypes is tightly linked with the results of many studies, which demonstrated that FEV1 alone cannot predict the response to treatment and the long-term evolution of COPD patients, and many other patient-specific parameters that are often so different should be taken into consideration (546, 550, 551). The list of the proposed markers is extensive: nutritional status, tolerance physical exercise, bronchial hyperreactivity, exacerbation rate, genetic factors, age and others.

Historically two classical phenotypes of COPD have been described: the Chronic Bronchitic and the Emphysematous, which are also known as "Blue Bloaters" and "Pink Puffers" (552). The number of phenotypes has increased since as well as the opinions how to diagnose them. Recent studies demonstrate that there is significant variability between guidelines as far as the criteria used to diagnose phenotypes (553).

Several studies have recently been published which, by analyzing the clinical characteristics of large populations of COPD patients and their statistical grouping, led to the identification of several COPD phenotypes (544-546).

A study by Burgel et al, brings a new perspective in COPD phenotypes. In the study based on Initiatives BPCO study group, they analyzed 322 patients with COPD through statistical grouping and managed to identify 4 COPD phenotypes (554). Phenotype 1 were young subjects with predominant severe to very severe respiratory disease. Phenotype 2 were older subjects with mild airflow limitation, mild symptoms and mild age-related comorbidities. Phenotype 3: young subjects with moderate to severe airflow limitation, but few comorbidities and mild symptoms. Phenotype 4: older subjects with moderate to severe airflow limitation and severe symptoms ascribed, at least in part, to major comorbidities (554). These results also reflect the differences in HRQL which can be seen between the young and elderly groups of patients with COPD (139).

In our study the results of distribution of COPD patients according to the disease phenotype differ from the medium values of the POPE study (44% vs 63% of patients were considered non-exacerbators; 8% vs 20,4% of patients with ACOS; 35% vs 9,5%, frequent exacerbators with CB; and 12% vs 6,9%, frequent exacerbators without CB) (555). These differences can be partially explained by a difference in the studied population, group size and socio-economical status. For instance in the POPE study countries with higher proportions of exacerbators (Austria, Bulgaria, Croatia, Poland, Russia and Serbia) have a phenotype distribution similar to our study of the Moldavian population (555). These countries were also largely represented by hospital-based outpatient clinics unlike our results where all patients were presenting to pulmonologists' offices (555).

Several studies revealed the impact of another very important phenotype of COPD as a prognosis: the frequent exacerbation (545,

546, 556, 557). The most important prognostic factor for a new exacerbation is a previous exacerbation, these patients having a rapid decline in FEV1 and an increased risk of mortality. These patients also have a poorer HRQL increased mortality, and a greater decline in lung function (545, 546, 556).

Non-exacerbators when compared to exacerbators have a milder COPD (558). We also found similar results that ACOS patients had a better lung function, but slightly more impaired HRQL than non-exacerbators *(558). There are studies, which demonstrated that subjects with ACOS* demonstrated worse HRQL but we did not see that in our analysis.

Frequent exacerbators with CB have a poorer HRQL compared to other phenotypes (559). In our study, patients with frequent exacerbations and without CB had the poorest HRQL.

Finally, phenotypes were proposed for a specific reason. The management of the patients should be different. Our findings highlight the importance of phenotyping the patient before the initiation of the treatment and point up the significance of exacerbation prophylaxis in patients who are frequent exacerbators (348, 544).

One of the purposes of our study was to investigate the impact of COPD phenotypes on HRQL. Our data suggest that COPD is a major cause of severe deterioration in HRQL, physical activity and functional status, and this influence depends on the frequency of exacerbations.

There are several limitations in this study. First, the number of the subjects in the present study is small. Second, we applied clinical COPD phenotypes. Clinical COPD phenotype must have predictive value, needs validation in prospective studies for each of the outcomes to which they may relate and must be able to classify patients into distinct subgroups that allow physicians to better determine the most appropriate therapy to improve clinically meaningful outcomes (348).

Conclusions

Frequent exacerbators with chronic CB and without CB have a more severe deterioration of the HRQL and worse lung function then non-exacerbators and patients with ACOS. These findings point up the importance of exacerbation prophylaxis in patients with frequent exacerbations and should be taken in consideration especially in the management of patients.

Scale-free networks in COPD

The key components of the pathology of COPD are well studied (oxidant-mediated tissue damage, especially the oxidative damage of the cell DNA (385, 412), protease/antiprotease imbalance and leucocyte-driven inflammation). It is immediately apparent that these three central processes are intrinsically linked (560). For describing of network of innate and adaptive immunity and inflammation, which coexist in continual dialogue and as self-modifying systems was proposed term contiguous immunity (561). To better define COPD, Sabroe and colleagues suggest that we should think in terms of complex systems with a scale-free topology.

Consideration of COPD as a chronic network of inflammatory processes may allow new approaches to its modelling in vitro and potential development of new drugs.

Diseasome

Diseasome is a combined set of all known disorder/disease gene associations that results from linking the Human Disease Network (a scale-free network whose nodes are connected if there is at least one gene that has been implicated in both) and the Disease Gene Network (a scale-free network whose nodes are connected if they are involved in the same disease) (562, 563).

This absolutely new concept of "diseasome" may link cellular networks and phenotypic manifestations of the disease and this concept may be applied with success in COPD.

P4 Medicine

The P4 medicine is a proposed new form of medical practice that combines Personalized, Predictive, Preventive, and Participatory elements (563). The P4 medicine is a medicine of the future and will be very useful in the management of COPD patients.

What does the P4 Medicine for COPD means? It will be "personalized" because it will be based on the genome of each person; it will be "predictive" because this personalized information will be able to determine the risk for COPD in each individual; it will be "preventive" because, given the prediction of risk of COPD, prophylactic measures will be able to be taken to decrease risk; and it will be "participative" because many of these prophylactic interventions will require the participation of the COPD patient (563).

The expanding knowledge on human physiology and pathophysiology leads to a different approach to health and disease. Genome studies and the other -omics enable us to accurately signalise people predisposed to diseases and to accurately predict their response to treatments and prognosis. Medicine is evolving to centralise to patient subgroups or even to specific patients, rather than diseases. On the other hand, patients are now more educated and informed regarding their problems. All these are summarised as P4 medicine: predictive, preventive, personalised and participatory medicine.

The complexity of COPD makes it an ideal candidate for P4 medicine. There are clear preventive targets and also a growing need for co-operation between doctor and patients, which extends from patient self-monitoring and tele-monitoring to therapeutic decisions. Most importantly, the expanding amount of the available biomarkers and subpopulations allows a personalised approach to the COPD patients. On the one hand this can ensure that each patient will receive the best treatment with the less side effects and on the other side feedbacks subgroups to the -omics in order to uncover the pathogenetic background of this diversity and develop new targeted treatments. And some studies have already shown connections between biomarkers and genetic loci.

COPD Control Panel

Agusti proposed COPD control panel which includes three disease domains (severity, activity and impact). Each of these domains contains information on a number of elements of the system (COPD) that provide complementary and relevant information for the proper management of the individual patient, either because of its prognostic implications and/or requirement for specific therapeutic intervention. A newer assessment/indexing approach - COPD control panel, has recently been proposed, and includes different components of COPD, such as: *severity* (functional impairment, including airflow limitation, hyperinflation, arterial hypoxemia and reduced exercise capacity), *activity* (exacerbations, FEV_1 decline, and weight loss), and *impact* (individual patient's perception of disease severity and activity).

The severity of COPD is inversely proportional to the functional reserve left in the target organ, which can be assessed very easy by spirometry (FEV1), although other physiological measurements such as the inspiratory to total lung capacity ratio (IC/TLC), arterial blood gases

and exercise capacity provide complementary information that also reflect the severity of COPD, and importantly, may require specific therapeutic interventions (bronchodilator treatment, antiinflamatory therapy, lung volume reduction surgery, oxygen therapy, NIV or rehabilitation). Agusti proposed to include the number and severity of the comorbidities because of their well known prognostic impact and need for specific therapy. The ways of assessment of comorbidities were discussed earlier.

The concept of 'activity of COPD' was depeloped recently. The rate of decline of FEV1 is an obvious one since recent research has shown that the rate of change in FEV_1 among patients with COPD is highly variable. Another potential clinical marker of disease activity may be the rate of exacerbations, although they tend to increase in patients with more severe disease, the frequent exacerbator phenotype can also occur in patients with moderate or mild obstruction. Among potential biological markers which can be used for assessment of disease activity, are number circulating leukocytes, C-reactive protein, interleukin-6 and/or fibrinogen. In addition was demonstrated that unintentional weight loss is also associated with poor prognosis in COPD, thus low BMI can be used as marker of activity of COPD.

The impact of any disease depends on how the patient perceives the disease and modifies his/her activities of daily living. The impact of disease can be assessed by different instruments, like the St George's Respiratory Questionnaire and the COPD Assessment Test (CAT).

The COPD control panel provides a way to visualise the complexity of COPD, and that the combined assessment of the severity, impact and activity can best inform the physician on the most appropriate management strategies for an individual patient.

Treatable traits

Recently Agusti et al proposed a new approach to assessment and management of chronic respiratory diseases, which is based exclusively on treatable traits in each patient (264). Treatable traits are classified in multiple domains, which can coexist: airflow limitation, eosinophilic airway inflammation, chronic bronchitis, airway bacterial colonisation, bronchiectasis, cough reflex hypersensitivity, pre-capillary pulmonary hypertension, chronic respiratory failure, deconditioning, etc (264).

CHAPTER IV. IMPACT OF CLASSIFICATIONS OF COPD ON THE TREATMENT

Non-pharmacologic and pharmacologic treatment should be guided by COPD severity and aim to control symptoms, decrease exacerbations, and improve patient function and quality of life (53). Both non-pharmacologic and pharmacologic interventions are essential to the management of stable COPD. Non-pharmacologic therapy include: smoking cessation, reduction of other risk factors, vaccinations, and pulmonary rehabilitation.

Inhaled bronchodilators (beta agonists and anticholinergics) are currently the mainstay of pharmacologic management of stable COPD (564). Inhaled bronchodilators can be used alone or in combination with inhaled glucocorticoids depending on the severity of COPD and risk of exacerbations. The goals of the treatment in stable COPD include symptomatic relief, improvement of the health status and exercise tolerance, prevention of disease progression and exacerbations, and thus mortality.

Non-pharmacologic treatment

Smoking cessation

Smoking cessation is considered the most important intervention for all COPD patients who smoke regardless of the level of disease severity. Smoking cessation is essential part of the treatment of COPD, because it can reduce the accelerated pulmonary function decline rate of smokers with COPD, as it was clearly shown in the Lung Health Study (565).

Interventions that assist smoking cessation include clinician advice and encouragement, nicotine replacement therapy, bupropion, varenicline and nortriptyline, and counseling. The best cessation rates can be achieved when counseling is combined with medication therapy in comparison with each strategy separately (566).

Vaccinations

Exacerbations of COPD are the most important adverse events in the progression of COPD. The most common cause of COPD exacerbations is infection (150). Vaccinations can prevent some infections and should be offered to patients with stable COPD.

Pneumococcal vaccine and annual influenza vaccine should be offered to all patients with COPD. Pneumococcal vaccine significantly reduces the risk of community acquiring pneumococcal pneumonia in patients with COPD (567). Influenza vaccination significantly reduces the risk of acquiring influenza-related acute respiratory infections in patients with COPD, especially in patients with severe airflow obstruction (567).

Pulmonary rehabilitation

Pulmonary rehabilitation is recognized as a core component of the management of patients with chronic respiratory disease. Pulmonary rehabilitation has been clearly demonstrated to decrease dyspnea and health care utilization, increase exercise capacity and improve quality of life in individuals with COPD (568). Also pulmonary rehabilitation may decrease hospital admissions and mortality (569).

Pulmonary rehabilitation program includes supervised exercise training, self-management education, and psychosocial support (570). In all stages of COPD, exercise training has been demonstrated to be efficient in a number of outcomes of patients with COPD, such as improvement of exercise tolerance, muscle strength, quality of life and decrease of dyspnoea and fatigue (571). Pulmonary rehabilitation is a well-recognised therapy that should be available to all patients with symptomatic COPD, and exercise training represents the cornerstone of a pulmonary rehabilitation programme (571).

Pulmonary rehabilitation represents an ideal opportunity to facilitate chronic disease self-management (572). Chronic disease self-management includes methods designed to: facilitate smoking cessation; optimise pharmacotherapy; assist with early identification and treatment of acute exacerbations; manage acute dyspnoea; increase physical activity; improve body composition; promote mental health; facilitate advance care planning and establish a social support networks (572).

Pharmacologic treatment

Bronchodilators

Bronchodilators have been the mainstay of management of COPD, which is characterised by a substantially irreversible airflow obstruction (2). Bronchodilators include beta agonists, anticholinergics, and theophylline, which is used less often. Inhaled agents are preferred to oral because of the reduction in systemic side effects.

Beta agonists and anticholinergics as well as improving dyspnea through their direct bronchodilatory effects, also appear to work by reducing static and dynamic hyperinflation. This probably explains why long-term improvements in symptoms and exercise capacity may be seen without clear changes in the FEV1 (573).

Short-acting Bronchodilators

Short-acting beta agonists (SABA) are the most widely used bronchodilators in the management of COPD, with salbutamol being the most common among them. Short-acting beta agonists appear to be as effective when used on an as needed basis as when used regularly, on the contrary to other bronchodilators (574). The advantage of short-acting beta agonists is their rapid onset of action.

Short-acting muscarinic antagonists (anticholinergics): Ipratropium has been demonstrated to reduce dyspnea, increase exercise tolerance, and improve gas exchange in patients with COPD.

Short-acting beta agonists and short-acting muscarinic antagonists (SAMA) can be used alone or in combination. The combination of a short-acting beta agonist plus a short-acting anticholinergic is often preferred because combination therapy can achieve a greater bronchodilator response than either one alone (575).

Long-acting Bronchodilators

Two classes of long-acting inhaled bronchodilators are available – long-acting β2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs).

Long-acting β2-agonists, salmeterol and formoterol provide 12 hour bronchodilation. Ultra-LABA provide 24 hour bronchodilation and include indacaterol, olodaterol, vilanterol (recently approved as a component of a combination drug), carmoterol and some new agents (575).

Salmeterol and formoterol

Salmeterol significantly improved lung function (including reduction in lung hyperinflation) and dyspnoea, increased exercise capacity and enhanced health related quality of life (576). In the largest trial of salmeterol, Toward a Revolution in COPD Health (TORCH), salmeterol significantly decreased exacerbation rates, improved lung function, and improved health-related quality of life compared to placebo (577).

Formoterol has been demonstrated to provide a rapid onset bronchodilatation that occurs within minutes after inhalation, which is comparable with the effect of SABA. The rapid onset of action and prolonged, potent bronchodilatory effect of formoterol suggest a drug effective for both quick relief and prolonged effect. In COPD patients, formoterol induces a significant spirometric improvement lasting for 12 hours. Despite these positive characteristics, it appears to be inferior to salmeterol in terms of health related quality of life (HRHRQL) scores and its ability to reduce the rate of COPD exacerbations.

Indacaterol

Indacaterol is the first ultra-long-acting β2-agonist (ultra-LABAs) approved for the treatment of COPD, that allows for once-daily administration. It has a rapid onset and prolonged action, with an onset of action in five minutes and a bronchodilatory effect that lasts for 24 hours. In long-term clinical trials in patients with moderate to severe COPD, indacaterol 150 or 300 μg improved lung function significantly more than placebo, and improvements were also significantly greater than twice daily formoterol 12 μg or salmeterol 50 μg, and noninferior to tiotropium bromide 18 μg. Indacaterol improves dyspnoea and health related quality of life, reduces the use of rescue medications significantly more than placebo, salmeterol or tiotropium bromide, and the degree of improvement in these endpoints is similar to or greater than that achieved with formoterol.

Long-acting and ultra-long-acting β2-agonists induce considerable improvements in FEV1, reduce dynamic hyperinflation, and improve exercise tolerance, determining amelioration in dyspnea and health-related quality of life. Moreover, they reduce the rate of COPD exacerbations.

Long-acting muscarinic antagonists

Long-acting muscarinic agents (or long-acting anticholinergic medications) include tiotropium, aclidinium and glycopyrronium.

Tiotropium

Tiotropium is a once-daily, long-acting muscarinic antagonist. Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT), a four year randomised clinical trial which compared inhaled tiotropium versus placebo, demonstrated an improvement in lung function and quality of life, with a concomitant decrease of the risk of exacerbations. However, it does not decrease the rate of decline of pulmonary function. A recent meta-analysis has shown that tiotropium handihaler may prolong the survival of COPD patients (578).

Aclidinium

Aclidinium bromide is a recently developed LAMA administered twice daily. In a 12-week, double-blind study, 200 and 400 mcg of aclidinium significantly reduced night-time/early morning symptoms and daily rescue medication use in patients with COPD. Besides, it has noticeably improved health related quality of life and decreased dyspnea of patients with moderate to severe COPD (579).

Glycopyrronium

Glycopyrronium is a novel once daily LAMA. A 26-week double-blind treatment with 50 μg of glycopyrronium bromide once daily induced clinically significant bronchodilation with rapid onset and maintained for 24h, throughout the study (580). Moreover, it provided a significant improvement in dyspnea at 26 weeks compared to placebo, which was accompanied by a significant improvement in health-related quality of life and reduced rescue medication use.

LABA versus LAMA

The efficacy of LABAs and LAMAs has been compared in multiple meta-analyses and randomised trials.

The Prevention of Exacerbations with Tiotropium in COPD (POET-COPD) trial was specifically designed to directly compare the effects of tiotropium with those of salmeterol on the risk of moderate and severe exacerbations (581). Tiotropium increased the time to the first severe exacerbation of COPD, reduced the risk of developing an

exacerbation by 17 percent (hazard ratio 0.83, 95% CI 0.77-0.90) and reduced the annual number of severe exacerbations compared to salmeterol (581). It is important to mention that it was not a direct comparison of a long-acting β_2-agonist with a long-acting anticholinergic agent, since concomitant medications were allowed; more than 50% of the patients were receiving, on a regular basis, inhaled glucocorticoids which also reduce exacerbations.

Another study compared indacaterol, a once daily inhaled beta agonist, versus tiotropium, in patients with moderate to severe COPD. Similar outcomes regarding pulmonary function, dyspnea and quality of life were obtained in this trial (582).

Seven clinical studies including a total of 12,223 participants with COPD were included in a meta-analysis, comparing tiotropium with salmeterol, formoterol, or indacaterol (583). Tiotropium was more effective than LABAs in preventing COPD exacerbations and disease-related hospitalisations, although there were no statistical between group differences in overall hospitalisation rates or mortality. No significant difference was found in improvements in quality of life between tiotropium and the LABAs either. Symptom improvement and changes in lung function were similar between the treatment groups.

Until recently, LAMAs were preferred over existing LABAs because of their superiority regarding most of the significant endpoints. However, after the development of novel once daily LABAs and twice daily LAMAs, the initial selection of a long acting bronchodilator is often based on clinical response of each patient, co-morbidities, and side effects.

Dual (Double) Bronchodilator Therapy

A recent trial demonstrated that the combination of LABA and LAMA is potentially effective in symptoms control of patients with stable moderate COPD sub-optimally controlled by tiotropium monotherapy(584). Multiple studies showed a superior bronchodilation effect of a LABA and LAMA combination compared to individual agents alone, in patients with moderate to severe COPD (575). Moreover dual bronchodilator approach induce greater improvements in patient-centred outcomes such as dyspnoea, symptoms, rescue medication use and health-related quality of life than individual drugs (585). LABAs and LAMAs directly act on airway smooth muscle working through different pathways(575). The combination of bronchodilators of different

classes seems a convenient way of delivering treatment and obtaining better results for patients with inadequate symptoms control by maintenance monotherapy.

A new "dual" bronchodilator, with both antimuscarinic and beta2-adrenergic activity combined in a single molecure, was recently launched. It was shown to have a rapid onset of action and a potent bronchodilatory effect in moderate and severe COPD, while it appears to be safe and well-tolerated [50].

This approach can potentially offer several advantages over combination therapy of two separate drugs: the benefit of delivering a fixed ratio into every region of the lung reducing the complexity of combination inhalers, a single pharmacokinetic profile, a uniform ratio of activities at the cellular level and a simplified clinical development programme (575).

Xanthines

A meta-analysis of 20 randomized controlled trials demonstrated that theophylline has a modest effect on FEV1 and forced vital capacity (FVC) and slightly improves arterial blood gas tensionscompared to placebo, in moderate to severe COPD (586). Improvement in exercise performance depended on testing method. The use of xanthines is limited by the risk of toxicity and multiple adverse reactions (central stimulation, gastric secretion, diuresis and arrhythmias) (575).

The development of newer xanthines, such as bamiphylline, acebrophylline, and doxofylline, for the treatment of COPD, was carried out in anticipation that such drugs would have a greater efficacy than theophylline but with an improved side-effect profile (575). Doxofylline has been shown to have a better efficacy (combining bronchodilator and anti-inflammatory properties) and fewer side effects than theophylline.

Inhaled Corticosteroids

Beclomethasone, budesonide and fluticasone are the commercially available inhaled corticosteroids (ICS) for treatment of COPD. In COPD, inhaled glucocorticoids are used as part of a combined regimen, but should not be used as monotherapy for COPD. ICS therapy decreases exacerbations and modestly slows the progression of respiratory symptoms, meanwhile it has a minimal or no impact on lung function and mortality.

Numerous studies have proved that ICS therapy decreased the risk of exacerbation compared to placebo. Furthermore, it was demonstrated that ICS therapy slowed the progression of respiratory symptoms modestly (577) and slowed the rate of decline of health-related quality of life (587).

Soriano et al. reported that ICS therapy did not modify the FEV1 decline rate(588). A Cochrane analysis (587), which examined 55 primary studies with 16,154 participants, also demonstrated that long-term use of ICSs (> 6 months) did not consistently decrease the rate of decline in FEV1 in COPD patients. Moreover, no significant difference was found in mortality rate with the use of ICS as a mono-component compared to placebo. New studies reassure regarding the possibility of osteoporosis secondary to ICS (305).

Bronchodilators plus inhaled glucocorticoids

Combined inhalers include the twice-daily fluticasone-salmeterol, budesonide-formoterol and mometasone-formoterol combinations and a once daily dry powder inhaler, containing fluticasone furoate and vilanterol. Inhaled glucocorticoids are traditionally used in combination with a long-acting bronchodilator for patients, who have significant symptoms or frequent exacerbations, despite an optimal bronchodilator regimen (589).

The efficacy of LABA/ICS combinations in COPD has been well supported by some large trials. LABA/ICS combinations have been shown to improve lung function and health related quality of life and to reduce exacerbations in COPD patients.

Treatment with ICS/LABA is associated with a significant increase of the pre- and post-bronchodilator FEV1 difference, the mean change in health related quality of life and with a significant decrease in the dyspnea score compared to treatment with LABAs alone (577).

Several randomized clinical trials have demonstrated that LABA/ICS combinations reduce the risk of exacerbation by 10-20% beyond that achieved by inhaled LABA alone. A meta-analysis of 18 randomized controlled trials demonstrated a beneficial effect of the LABA/ICS combination over LABA alone, on the frequency of moderate, but not severe COPD exacerbations. It was recently suggested that ICSs in combination with LABAs might also reduce cardiovascular disease and all-cause mortality (589).

Triple therapy

The triple inhaler therapy with a long-acting beta agonist plus an inhaled glucocorticoid plus a long-acting anticholinergic is often used in patients with severe COPD.

The benefits of triple therapy are confirmed by the UPLIFT study (590). The addition of tiotropium to patients receiving a LABA and an ICS as usual care significantly improved pulmonary function, decreased the rate of exacerbations, and improved health related quality of life. More recently, it was pointed out that triple therapy provides further improvements in post-bronchodilator FEV1 and quality of life from baseline compared to LAMA monotherapy on patients with severe and very severe COPD.

Systemic Corticosteroids

Long-term systemic glucocorticoid therapy is not recommended, even for severe COPD, because of the significant side effects (most frequent are osteoporosis and diabetes) and evidence of increased morbidity and mortality with this treatment (591).

Inhibitors of the Phosphodiesterase 4

Roflumilast, an oral phosphodiesterase 4 inhibitor, significantly improved pre-bronchodilator FEV_1 and reduced the rate of moderate to severe exacerbations (17 percent [95%, CI 8-25]) in a 52 week, randomized trial of 3091 patients with COPD (424).

Roflumilast can be recommended for patients with COPD with severe airflow limitation, symptoms of chronic bronchitis and frequent exacerbations, whose disease is not adequately controlled by long-acting bronchodilators. Roflumilast provides additional benefits when combined with other respiratory medications. Roflumilast is the first-in-class phosphodiesterase 4 inhibitor used as an add-on therapy in patients with moderate to severe COPD and frequent exacerbations who are already receiving a long-acting bronchodilator. The effect of roflumilast when given as additional therapy to COPD patients already taking long-acting bronchodilators and ICS is currently not known.

Mucoactive agents

Thick secretions can be a major problem in patients with COPD, but there is little evidence that thinning or increasing the clearance of

sputum induces clinical improvement. A recent Cochrane review has shown that the treatment with a mucolytic may produce a small reduction in acute exacerbations, but may have little or no effect on the overall quality of life (592). Thus, mucoactive agents are not accepted as routine care for patients with stable COPD.

Chronic antibiotic therapy

Chronic antibiotic therapy is generally not indicated by guidelines for the patients with stable COPD. However, certain antibiotics, macrolides in particular, may have anti-inflammatory and immunomodulatory activity in addition to their antibiotic effect.

Long-term treatment with macrolides was asserted to reduce COPD exacerbations in doses lower than bactericidal doses. However, the risk of microbial resistance associated with the long-term use of azithromycin in patients with COPD must be considered as part of the risk–benefit ratio of this treatment. In addition, the effect on microbial resistance in the community is still unknown (12).

Oxygen therapy

Many patients with stable severe COPD have chronic hypoxemia. Long-term oxygen therapy should be prescribed for all patients with stable COPD, with chronic hypoxemia at rest ($PaO_2 \leq 55$ mmHg or $SpO_2 \leq 88$ percent). The detection of hypoxia is of great importance because long-term oxygen therapy improves survival, severe resting hypoxemia and quality of life in patients with COPD.

Therapeutic strategies in stable COPD

New guidance for the management of COPD becomes more complex, but can be simultaneously used by respiratory doctors at a global level. This up-to-date approach will potentially facilitate a more accurate risk stratification of COPD patients and a better understanding of disease pathophysiology and phenotypes. It may eventually help to develop a more targeted therapy and an improved management of COPD patients.

Table 27 represents a comparison of the main differences between GOLD 2017 guidelines and Spanish Guideline for Treatment of stable COPD (236) (Gula Espanola de la EPOC - GesEPOC), some of which are described below.

Table 27

Comparison of GOLD and Spanish Guideline for Treatment of stable COPD for COPD management

	GOLD staging	GOLD 1st line	Phenotypes	Spanish Guidelines 1st line
NON-EXACERBATOR (1 exacerbation not leading to hospital admission)	A B	SABA or SAMA LAMA or LABA	non-exacerbator, with emphysema or chronic bronchitis	LAMA or LABA SABA or SAMA
EXACERBATOR (≥ 2 exacerbations or ≥ 1 exacerbation leading to hospital admission)	C D	ICS+LABA or LAMA ICS+LABA and/or LAMA	exacerbator with emphysema exacerbator with chronic bronchitis	LAMA or LABA LAMA or LABA
	Asthma COPD overlap syndrome (ACOS)	No recommendations in GOLD 2014	mixed COPD-asthma phenotype	LABA+ICS

The use of bronchodilators is central to the management of COPD. The management of non-exacerbator phenotype, with emphysema or chronic bronchitis is very similar to GOLD A and B stages. Short-acting beta-agonists are used on an as-needed basis or regularly for prevention of symptoms in the early stages or in COPD patients with a low symptom burden. Long-acting bronchodilators should be used as a first therapeutic option in the treatment of all COPD patients with permanent symptoms who regularly require short acting bronchodilators, because they provide better control of the symptoms and improve quality of life as well as pulmonary function and exercise tolerance, while also reduce exacerbations. The choice between LABA and LAMA depends on the availability of medication and the patient's response.

For patients whose symptoms are not controlled by a LABA or LAMA, combination of these is recommended.

The basis of treatment of exacerbator phenotype with emphysema (air traping, dyspnoea, low body mass index) is long-acting bronchodilators and in more severe cases triple therapy (LAMA+LABA+ICS) can be also used.

Exacerbator phenotype with chronic bronchitis (bronchitic symptoms) should be treated with long-acting bronchodilators.The addition of ICS or/and roflumilast is suggested in severe cases.

The updated version of GOLD Strategy reports that regular treatment with ICS improves symptoms, lung function and quality of life and increases the rate of exacerbations in COPD patients with an FEV1 < 60% predicted. Therefore, ICSs are recommended in combination with LABAs or, alternatively, with LAMAs for exacerbators (≥ 2 exacerbations or ≥ 1 exacerbation leading to hospital admission) who have few symptoms (GOLD C stage) and also for exacerbators who have significant symptoms (GOLD D stage). Moreover, for these categories of patients, a triple therapy (ICS + LABA + LAMA) is recommended as an alternative.

Although ICS have limited role in patients with infrequent exacerbations regardless of the bronchitic/emphysematic predominance, their use is suggested for frequent exacerbators, or patients with severe or very severe obstruction according to GOLD classification. The Spanish guidelines suggest that among frequent exacerbators, ICS only benefit predominantly bronchitic patients, by decreasing the frequency and severity of exacerbations. Characterised by a high inflammatory status, this patient group is also associated with more frequent extra-pulmonary inflammatory manifestations secondary to spillover of inflammatory mediators to the systematic circulation (593) and ICS down-escalate inflammatory levels, decreasing both pulmonary and extra-pulmonary manifestations such as cardiovascular disease (594). Furthermore, although steroids is a known cause of osteoporosis, it seems that low dose of ICS may protect especially bronchitic patients - who have a higher inflammatory status- from developing osteoporosis, by decreasing pulmonary as well as extra-pulmonary inflammation (595).

Frequent exacerbators with predominantly bronchitic phenotype need intensive treatment and seem to benefit by different medications such as mucolytics, theophylline or phosphodiesterase-4 inhibitors and

longterm antibiotics. Mucolytics seem to reduce the exacerbation rate and severity in this category (456). Theophylline and roflumilast, a new phosphodiesterase-4 inhibitor, are also suggested to benefit particular this category (and not patients of other categories) (596). Finally, in contrast to GOLD, the Spanish guidelines accept a potential role of longterm treatment with macrolides in reducing the exacerbation rate and improving the quality of life of these patients, due to their immunomodulatory effects (597).

Moreover, GesEPOC, taking into consideration the adverse prognosis of asthma-COPD overlap phenotype and the responsiveness of this category to steroids, suggests early screening and early addition of ICS to their treatment.

It is necessary to mention that the overlap syndrome is considered to be one of the four COPD clinical phenotypes, according to the Spanish Guideline for Treatment of stable COPD (236) (Gula Espanola de la EPOC - GesEPOC). The term Asthma-COPD overlap syndrome (ACOS) was recognized and for the first time included in GOLD in 2014, but without clear definition and therapeutic options.

Patients with overlap syndrome, "asthmatic smokers", present a greater degree of bronchial eosinophilic inflammation. That is why they have a good response to inhaled corticosteroids, even early in the course of disease (mild and moderate COPD). Consequently, patients with overlap syndrome should be started on inhaled corticosteroids together with long-acting bronchodilators irrespective of the severity of the airflow obstruction, in contrast to previous guidance(350). In severe cases a LAMA can be added as well. (350).

COPD is a heterogeneous and complex disease. The management of COPD in every patient should be personalized and guided by the symptoms, exacerbations, pulmonary function and co-morbidities. Unfortunately very few treatments can slow the rate of lung function decline or significantly reduce mortality, therefore prevention of the disease is very important.

Conclusions

COPD is a multilevel disease from clinical, cellular and molecular point of view. This review summarized the evolution of our knowledge from the simplistic classical approach, based on degree of airflow limitation to the new GOLD assessment, which combines the

functional, physiologic, exacerbation and health status domains. New GOLD classification will facilitate understanding of the impact of COPD on an individual patient.

In anticipation of progressive changes of our knowledge about complexity of COPD there were reviewed new tools (phenotypes, scale-free networks, diseasome) which will help all medical community to develop and apply new concept of participatory medicine (P4) in the management
of COPD.

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