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EXPERT OPINION

Treatable Traits in COPD – A Proposed Approach

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Abstract: The well-recognized individual heterogeneity within COPD patients has led to a growing interest in greater personalization in the approach of these patients. Thus, the treatable traits strategy has been proposed as a further step towards precision medicine in the management of chronic airway disease, both in stable phase and acute exacerbations. The aim of this paper is to perform a critical review on the treatable traits strategy and propose a guide to approach COPD patients in the light of this new concept. An innovative stepwise approach is proposed – a multidisciplinary model based on two distinct phases, with the potential to be implemented in both primary care and hospital settings. The first phase is the initial and focused assessment of a selected subset of treatable traits, which should be addressed in all COPD patients in both settings (primary care and hospital). As some patients may present with advanced disease at diagnosis or may progress despite this initial treatment requiring a more specialized assessment, they should progress to a second phase, in which a broader approach is recommended. Beyond stable COPD, we explore how the treatable traits strategy may be applied to reduce the risk of future exacerbations and improve the management of COPD exacerbations. Since many treatable traits have already been related to exacerbation risk, the strategy proposed here represents an opportunity to be proactive. Although it still lacks prospective validation, we believe this is the way forward for the future of the COPD approach.

Keywords: COPD, precision medicine, treatable traits strategy, phased approach, future

Introduction

Over the last 20 years, the management of chronic obstructive pulmonary disease (COPD) has undergone significant changes.[1,2] In the first Global Initiative for Chronic Obstructive Lung Disease (GOLD) document, published in 2001,[3] the classification and management of COPD were based solely on the severity of airflow limitation: this was the so-called FEV1-centric approach.[1] As a result of the intensive research in this area, GOLD moved towards a more patient-centric approach, de-emphasising the importance of FEV1 in favour of symptoms and exacerbation history.[2] In 2019, the need for individualised follow-up was addressed, along with the introduction of new treatment algorithms.[4] This recent trend indicates that we are moving towards a precision medicine approach in COPD. Similarly, other guidelines, such as the Czech guidelines, already advocate a more personalised treatment strategy, with a phenotype-based concept but also incorporates some elements of the treatable traits strategy by recognising that a patient can be characterised by more than in phenotype and by treating all phenotypical labels that apply.[5]

A careful analysis of the evolution of COPD management reveals that the natural history of the disease could only be modified with personalised treatment

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strategies. This was evidenced by the results obtained with: i) smoking cessation in smokers;[6] ii) long-term oxygen therapy in COPD patients with chronic hypoxia;[7] and iii) lung-volume reduction surgery, in a subset of emphysematous COPD patients.[8] In recent years, triple therapy has also been shown to modify the natural history of the disease in exacerbators.[9] Other strategies have shown promising results, such as alpha-1-antitrypsin (AAT) augmentation therapy and lung transplant.[10–12] In all these studies, patients were approached through their individual characteristics and treated accordingly.

There is significant individual heterogeneity within COPD.[13] This reflects different biological and physiological mechanisms underlying different clinical presentations: endotypes and phenotypes respectively.[13–15] In 2010, a variation of the phenotype concept was proposed[16] that encompasses clinically meaningful outcomes. In the last decade, intensive research has been conducted to identify the underlying biological mechanisms that result from the complex interaction between the genetic background and cumulative environmental exposures.[13,17] This research has culminated in the emergence of the Treatable Traits (TT) strategy: a "new strategy where patients are individually assessed for a specified set of treatable problems, and an individualised treatment programme is developed and implemented based on this multidimensional assessment".[18] In this context, a TT can be defined as a "therapeutic target identified by phenotype or endotype, through validated biomarker(s)".[18]

The TT strategy acknowledges that several phenotypes can co-exist in the same patient and that all must be addressed.

The key message of this strategy is that TTs are not mutually exclusive.[18] Indeed, several TTs can be addressed in a COPD patient, and an individualised treatment programme shall be developed in a multidimensional approach.[18]

Many researchers consider this strategy a first step towards deconstructing existing labels such as asthma and COPD. Within this label-free approach, several candidate traits have already been identified for chronic airway diseases.[14,15,18,19] Some authors have also explored this approach to manage asthma and COPD individually.[20–23]

Considering the potential impact of the TT strategy on COPD patients, healthcare professionals would greatly benefit from harmonised recommendations based on the research conducted so far. The aim of this paper is to perform a critical review on the TT strategy and propose a guide to approach COPD patients in the light of this new concept.

Treatable Traits for COPD

Treatable traits should fulfil three characteristics: be clinically relevant and associated with specific outcomes (symptoms, health status, risk of future events), be easily identifiable and measurable, and be treatable.[15,18]

The identification of a TT should be carried out objectively through a biomarker. The classic and best established biomarker in COPD is alpha-1-antitrypsin (AAT) levels. In fact, the quantitative determination of AAT levels in blood is crucial to identify deficiency of AAT – a treatable trait.[10]

However, and because those markers, besides biological, may be functional, imaging or clinical, the term TIM – treat identification marker[18] has been proposed. In the setting of the discussion herein proposed, we consider that this term is more appropriate and will therefore be adopted it in the following sections of this article. It should be ensured that the markers are feasible and easy to measure.

GOLD recognizes two major treatable traits in COPD – dyspnea and exacerbations.[24] Furthermore it recommends that follow-up regarding pharmacological and non-pharmacological treatment should be based on these two traits. However, should they be regarded as treatable traits or as therapeutic goals? A Spanish group published a critical analysis of the treatable traits approach and introduced the concept of therapeutic goal (Figure 1).[19] According to this group, therapeutic goals 'are not therapeutic targets, but rather clinical problems that must be eliminated or improved'.[19] For each therapeutic goal, there is a set of treatable traits. Thus, the treatable traits to address must consider the selected therapeutic goal. For example, in a patient whose therapeutic goal is symptom control, the TTs to address should only be those that have been proven to be related to the symptoms. Likewise, a given treatable trait may be associated with different therapeutic goals.

We have identified some issues regarding the therapeutic goals approach. Firstly, some therapeutic goals such as mortality are common to all COPD patients. Secondly, there is a risk of selecting some therapeutic goals over others, reducing the overall benefit of this approach. Addressing all potential treatable traits, although more complex, allows meeting the individual variability of COPD patients.

In the treatable traits strategy, most authors[14,18] dot not consider dyspnea and exacerbations as treatable traits, since there are several traits that can be related to them. The treatable traits identified in most publications are specific characteristics, measurable through a marker or diagnostic test and with an effective treatment.

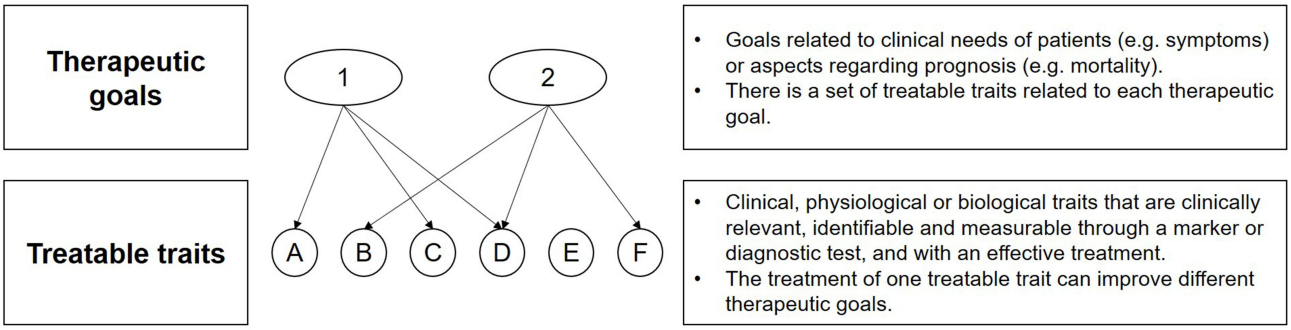

Figure 1 Definition of therapeutic goals and treatable traits. The numbers and letters are for illustrative purposes only.

They were divided into three main groups: pulmonary, extrapulmonary, and behavioral.[14]

An important question arises: how to assess TTs?

The key point of this approach is the importance and priority given to each TT during patient assessment. In this process, attention shall be paid to identifying appropriate TTs, based on their i) clinical impact; ii) prevalence, iii) impact on specific disease outcomes; iv) impact on the patient; and v) availability of measurement methods.[14] With this in mind, two approaches have been proposed:[18]

i) a broad approach, in which the TTs are assessed all at once. This systematic assessment may achieve the greatest benefit by meeting the individual heterogeneity of COPD patients. However, it increases complexity and is more time consuming, limiting its feasibility, especially in primary care.

ii) a focused approach, in which only some treatable traits are assessed. Although easier to implement, it raises some questions about the priority of some TTs over others. The recognized individual variability in COPD limits the potential benefits of such an approach.

The possibility of a phased-approach has already been mentioned,[18] but to our knowledge there is no guide proposed with this type of approach yet.

We, herein, suggest a phased-approach – a multidisciplinary model based on two distinct phased strategies to be adopted independently, in sequence, or with some degree of overlap, with the potential to be implemented in both primary care and hospital settings. By hospital setting, we mean care by respiratory specialists, whether provided in hospital outpatient departments, in outpatient clinics, or even in inpatient settings.

Initially, patients should be assessed using a focused approach, with one subset of TTs being addressed in all patients with COPD. However, some patients may present with advanced disease at diagnosis or may progress despite this initial treatment. These patients require more specialized assessment and should progress to a second phase, in which a broader approach is recommended.

In this paper, we will be using the terms:

- first phase, meaning the initial and focused assessment that shall be performed on each COPD patient, in both settings (primary care and hospital);

- second phase, meaning the extended approach that shall be implemented in severe and progressive cases where a more refined assessment is warranted. This second phase shall ideally be implemented in the hospital setting.

Regarding COPD, the TT approach proposed here considers both stable disease and exacerbations.

Treatable Traits in Stable COPD

The pulmonary, extrapulmonary, and behavioral treatable traits proposed to be addressed in the first and second phases, along with the corresponding TIM and therapeutic approaches, are presented in Tables 1 and 2.

The treatable traits included in the first phase (Table 1) are well known among the medical community and easily measured, by non-respiratory physicians, using widely available biomarkers. In addition, they provide essential information for initial diagnosis and treatment proposal. Like most authors, we are not considering frequent exacerbations as a treatable trait, as several TTs may be related to it. However, the initial assessment regarding the history of exacerbations is extremely important as these patients deserve a more accurate and comprehensive assessment. Patients with frequent exacerbations should have a broad approach right from the start, with assessment of all treatable traits, which allows the identification of different therapeutic pathways. In Figure 2, patients who benefit from a broad approach as an initial assessment are identified.

Table 1 Treatable Traits to Be Addressed in the First Phase

Treatable Trait	Trait Identification Marker	Therapeutic Options
Pulmonary		
Airflow limitation	Post-bronchodilator $FEV_1/FVC < 0.7$ or LLN	Bronchodilators, pulmonary rehabilitation
Exercise intolerance	6MWD (distance <350m), mMRC ≥ 2	Exercise, Pulmonary Rehabilitation
Chronic bronchitis	Cough and sputum for at least 3 months, for 2 years	Smoking cessation, mucolytics
Eosinophilic airway inflammation	Blood eosinophil count	Inhaled corticosteroids
Alpha-1 antitrypsin deficiency	Alpha-1 antitrypsin levels	Proceed to the second phase
Extrapulmonary		
Nutritional state		
Obesity	BMI > 30	Physical activity
Malnutrition	BMI < 20	Supplements
Behavioral		
Low physical activity and sedentary lifestyle	Self-reported	Exercise plan
Smoking and other environmental exposures	Self-reported or exhaled concentration of CO ≥ 10 ppm	Cessation support, nicotine replacement therapy, varenicline, bupropion. Avoid other environmental exposures.
Poor inhalation technique	Direct observation, training devices	Education
Nonadherence to therapeutics	Prescription refill rate, chipped inhalers, self-report	Education, self-management support
Poor family/social support	Self-report, assessment of familial context	Family therapy; self-management support
Inhaler device polypharmacy	Self-report	Therapy re-evaluation

Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; LLN, lower limit of normal; mMRC, modified Medical Research Council dyspnoea scale; 6MWD, 6-minute walking distance.

Some TTs are present in both phases, reflecting different TIMs and/or different treatments. AAT deficiency, for example, should be investigated in every COPD patient using a widely available and inexpensive biomarker – quantitative determination of serum AAT.[25] If low AAT levels are found, patients should progress to the second phase, where this trait will have a more refined assessment through phenotyping and genotyping, and other traits will also be addressed. It is important to acknowledge that AAT levels should be assessed outside of inflammatory and infectious processes, as AAT behaves as an acute phase protein.[26]

Also, chronic bronchitis takes part of both phases. It is easily identified in the first phase and can be addressed initially by smoking cessation and mucolytics. More specific treatments like phosphodiesterase-4 (PDE-4) inhibitors should be reserved for the second phase.

Depending on the patient's response to the proposed treatment, it might be necessary to resort to the second phase to identify the traits that underlie disease progression.

However, an important question remains: when should COPD patients progress to the second phase, and which patients would benefit from the broad approach (concomitant first and second phases) at diagnosis?

According to our proposal, this transition should be based on the level of severity (Figure 2).

Eosinophilic Airway Inflammation

The role of eosinophils in the pathophysiology of COPD is not entirely understood. In contrast to asthma, COPD was traditionally regarded as a mainly neutrophilic inflammatory disease. However, increased numbers of eosinophils have been detected in the airways of COPD patients, from sputum to bronchoalveolar lavage.[27] Indeed, in a subset of COPD patients, eosinophilic airway inflammation may be present both in stable disease and during exacerbations.[28,29]

Why is eosinophilic inflammation a treatable trait? Firstly, it relates to clinically important outcomes: an increased blood eosinophil count (BEC) in stable phase is related to increased risk of exacerbations[30,31] and increased decline in lung function.[32,33] Furthermore, it has been shown to predict therapeutic response. The presence of eosinophilic airway inflammation has been consistently associated with response to inhaled corticosteroids (ICS) treatment in post-hoc[33,34] and pre-specified analyses of

Table 2 Treatable Traits to Be Addressed in the Second Phase

Treatable Trait	Trait Identification Marker	Therapeutic Options
Pulmonary		
Chronic bronchitis	Cough and sputum for at least 3 months, for 2 years	Smoking cessation; mucolytics, macrolides, PDE-4 inhibitors
Chronic respiratory failure		
Arterial hypoxemia	PaO_2< 55 mmHg	Long-term oxygen therapy
Arterial hypercapnia	$PaCO_2$ > 45 mm Hg	Non-invasive ventilation, lung transplant
Chronic bronchial infection	Sputum culture, quantitative PCR	Antibiotics
Bronchiectasis	Chest computed tomography	Drainage, macrolides, nebulized antibiotics, surgery, vaccination
Eosinophilic airway inflammation	Blood eosinophil count, FeNO	Inhaled corticosteroids, biologic therapy
Emphysema	Chest computer tomography, DLCO	Lung volume reduction surgery, Bronchoscopic lung volume reduction, Lung transplant
Lung hyperinflation	Decreased IC/TLC	Bronchodilators, pulmonary rehabilitation, bronchoscopic lung volume reduction, lung volume reduction surgery.
Pulmonary hypertension	BNP, Doppler echocardiography, right heart catheterization	Oxygen/NIV/Lung transplant
Alpha-1 antitrypsin deficiency	Alpha-1-antitrypsin levels, phenotype, genotype	α1-antitrypsin replacement
Exercise-induced oxygen desaturation	Desaturation ≥ 4% on SpO2 and minimum SpO_2 < 90% during 6MWD test	Ambulatory oxygen therapy if demonstrated clinical benefit
Extrapulmonary		
Deconditioning	6 MWD, Cardio-pulmonary exercise testing	Exercise, pulmonary rehabilitation
Comorbidities		
Cardiovascular disease	BNP, Electrocardiogram, Doppler echocardiography	ACE inhibitors, diuretics, β blockers
Anxiety and depression	Questionnaires, psychological or psychiatric assessment	Cognitive behavioral therapy, pharmacotherapy
Obstructive sleep apnea	Questionnaires, polysomnography	Continuous positive airway pressure; weight loss, mandibular advancement splint
Osteoporosis	Low BMD (T-score ≤−2.5)	Smoking cessation, Diet, Exercise, Calcium, Vitamin D, Bisphosphonates
Systemic Inflammation	High sensitivity C-Reactive Protein	Statins
Gastro-esophageal reflux	Gastrointestinal endoscopy, pH monitoring	Proton pump inhibitors, H_2 antagonists; surgery

Abbreviations: ACE, angiotensin-converting enzyme; BMD, bone mineral density; BNP, brain natriuretic peptide; DLCO, diffusing capacity for carbon monoxide; FeNO, fractional exhaled nitric oxide; IC, inspiratory capacity; NIV, non-invasive ventilation; PaO2, partial pressure of oxygen; PaCO2, partial pressure of carbon dioxide; PDE-4, phosphodiesterase type 4; SpO2, peripheral oxygen saturation; TLC, total lung capacity; 6MWD, six-minute walking distance.

randomized controlled trials.[35] The GOLD document already recognizes BEC as a biomarker to guide ICS therapy in patients with COPD.[36] This treatable trait is identifiable and measurable through a TIM – BEC. Previous studies have considered sputum eosinophil counts.[21] However, it raises questions regarding accessibility and reproducibility (as patients do not always provide adequate samples).[24] BEC is widely available, demonstrates a good correlation with sputum eosinophil counts and may be used as a surrogate measure for airway eosinophilia in COPD.[37] Most authors consider that BEC should be regarded as a continuous variable rather than a dichotomous one. In fact, BEC is a dose-dependent variable, so different thresholds represent therapeutic responses of distinct magnitude.[24] Approximate thresholds have been suggested – some COPD studies suggest a relative threshold ≥2% of total white blood cells,[38,39] while others suggest an absolute threshold.[9,40] The GOLD report considers two absolute thresholds: 100 and 300 cells/μL blood. Studies consistently show that BEC below 100 eosinophils/μL is not associated with a clinical benefit of ICS in terms of exacerbation prevention. This benefit occurs in patients with BEC ≥100 eosinophils/μL,

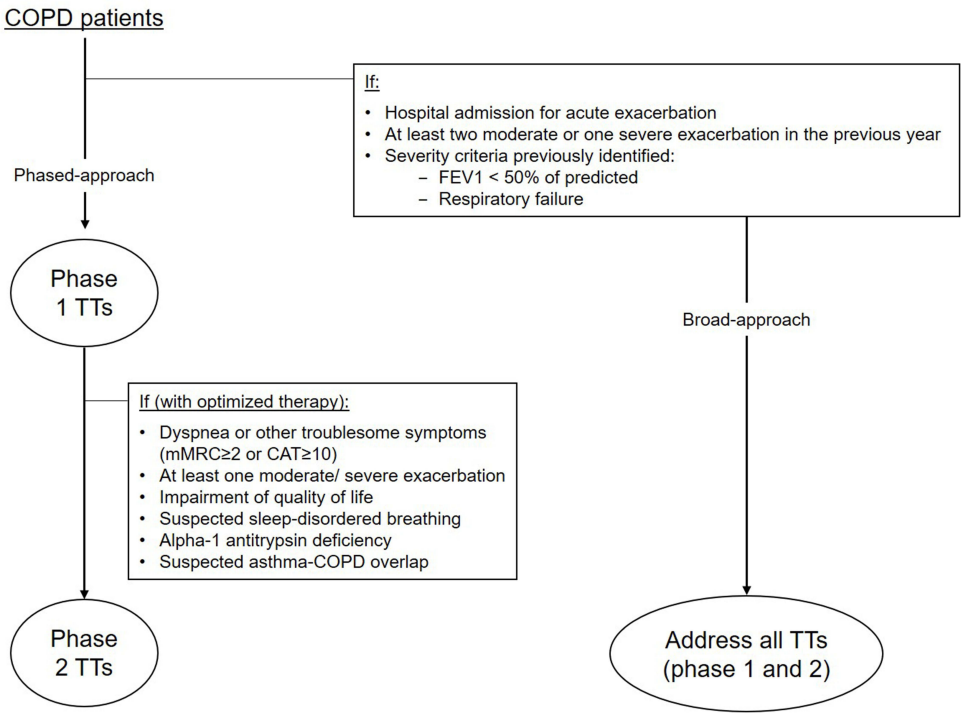

Figure 2 Algorithm for COPD management based on the treatable traits strategy.
Abbreviations: CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume; mMRC, modified Medical Research Council dyspnea scale; TTs, treatable traits.

and a greater magnitude of response is expected when BEC ≥ 300 eosinophils/μL.[24]

Some authors have studied the potential benefit of IL-5 targeted biological therapy in the subset of COPD patients with eosinophil-mediated airway inflammation, with promising results when patients are carefully selected.[41]

What about neutrophilic airway inflammation in COPD? Neutrophils and neutrophil dysfunction are implicated in the inflammatory changes in the airways of COPD patients, causing chronic bronchitis and emphysema.[42] Airway neutrophilia in COPD has been associated with clinical severity,[43] disease progression[44] and exacerbations.[45] However, there are no specific treatments available targeting this trait.[18] Rather, there are specific subsets of COPD patients generally related to neutrophilic airway inflammation that can be addressed in this TT approach, such as chronic bronchitis and chronic bronchial infection.[46,47]

Chronic Bronchial Infection

Over the last decade, several studies, based on culture-independent microbial sequencing, have demonstrated that the lung is not sterile. Instead, a complex microbial ecosystem exists – the lung microbiome.[48,49] The majority of the microbiota plays an essential role in lung epithelial integrity, resistance to colonization, and homeostasis of the respiratory immune system.[50] However, it also contains potentially pathogenic microorganisms.[51]

It has been shown that the composition of the lung microbiota differs in healthy individuals and in COPD patients, both in richness and diversity.[52] The composition of the microbiota varies along the bronchial tree and according to the stages of severity in COPD.[53,54] More severe COPD is associated with reduced microbial diversity. Changes in lung microbiome diversity and abundance have a profound impact on respiratory immune system homeostasis and make the airways of COPD patients susceptible to opportunistic growth of pathogenic microorganisms – dysbiosis.[51] Indeed, studies have shown that in stable COPD, 25–50% of patients have bacterial growth in respiratory samples.[51,55] In the absence of symptoms of acute infection, this isolation has been regarded as bacterial colonization. However, persistence of these bacteria leads to maladaptive immune responses, with deleterious consequences,[56] making the term chronic bronchial infection more adequate.[47]

Chronic bronchial infection is more frequent in patients with concomitant bronchiectasis,[47] and potentially pathogenic microorganisms isolated include *Haemophilus*

influenzae, Moraxella catarrhalis, Streptococcus pneumoniae and *Pseudomonas aeruginosa*.[51,57] Chronic bronchial bacterial infection is an important TT to address – it has clinical relevance (for example, colonization of the airways with *Haemophilus influenzae* appears to be related to a more rapid decline in lung function and higher exacerbation rates), is feasible to identify, and is treatable, although the correct treatment is still under debate.[47]

Although not considered treatable traits, attention should also be paid to fungi and mycobacteria.[17,58,59] The role of fungi in COPD is less well understood. *Aspergillus* species cause most fungal infections in COPD patients, but apart from the increased risk of invasive aspergillosis, the clinical significance of a positive filamentous fungal culture remains uncertain.[60,61] Viruses are detected during half of COPD exacerbations, but the role of chronic viral infection is yet to be determined.[62]

It should be borne in mind that the history of mycobacterial infection limits the ICS use in COPD patients, as an association between ICS use and the risk on nontuberculous mycobacterial pulmonary infection in this population has already been suggested.[63]

Emphysema

Emphysema is a recognized treatable trait with undeniable clinical relevance,[64] identifiable and measurable through chest computed tomography (CT)[65] and treatable. Indeed, lung volume reduction surgery has been shown to increase survival in a subset of emphysematous COPD patients.[8] This evidence provides a solid basis for discussing the importance of imaging in the management of COPD.

Airway disease and pulmonary emphysema are the major determinants of airway obstruction in COPD.[66] It is undeniable that patients with predominantly airway disease and those with predominantly emphysema are distinct patients.[65] Furthermore, these determinants may coexist in the same patient to varying degrees,[66] and the relative contributions of each determinant may be assessed by imaging.[67] Chest CT enables objective quantification of each determinant,[62] more than a visual assessment[68–70] allowing identification of TTs.

Chest CT has other advantages: i) it excludes alternative diagnoses; ii) it establishes the presence of pulmonary comorbidities that are often related to COPD, such as bronchiectasis, diffuse lung disease, and lung cancer; and iii) it assesses the need for both lung surgery and transplantation.[4,71]

More than emphysema itself, it is already recognised that the occurrence of lung hyperinflation (LH) is related to symptoms, decreased exercise capacity, occurrence of exacerbations and is an independent predictor of mortality.[20,72–75] We consider LH as a treatable trait to be addressed by respiratory physicians in Phase II. Conventionally, LH is defined as an increase in total lung capacity (TLC) > 120% of the predicted value. Several authors have suggested that this definition should be avoided, but there is still no consensus on the definition or classification of severity. Definitions based on residual volume (RV), functional residual capacity (FRC), RV/TLC or IC/TLC (IC: inspiratory capacity) have been proposed.[76,77] In this document, we define LH as a reduced ratio IC/TLC. Indeed, this measure, with a cutoff of ≤25%, has already demonstrated a relationship with poor outcomes such as mortality.[72,73,75]

Systemic Inflammation

COPD is increasingly considered a multisystemic disease, with airway and systemic inflammation.[78] High levels of several inflammatory markers have been found in COPD patients, indicating the presence of persistent systemic inflammation.[79] This is also considered a treatable trait by most authors.[14,15,18,21] In fact, systemic inflammation is related to worse outcomes, such as increased exacerbation rates and increased all-cause mortality.[80] A link between systemic inflammation and increased risk of cardiovascular disease, diabetes, lung cancer, and pneumonia has also been detected.[81]

In 2013, a pilot study addressing treatable traits in COPD used an inflammometry algorithm, addressing airway inflammation (eosinophilic and neutrophilic) and systemic inflammation. In fact, inflammatory processes are not mutually exclusive, and a patient may exhibit more than one and require more than one therapeutic approach.[21]

Several inflammatory markers have already been used to identify systemic inflammation in COPD. However, in the TT strategy, availability and feasibility are required, making C-Reactive Protein (CRP) the appropriate TIM.[14,18,21] The proposed cut-off for CRP to detect systemic inflammation is 3 mg/L.[18,21]

Some meta-analyses have found a beneficial effect of statins on clinical outcomes in COPD patients.[82,83] McDonald and colleagues described improvements in health-related quality of life (HRQoL) when targeting systemic inflammation with statins.[21,84]

Comorbidities

COPD often coexists with other diseases. In 2012, the impact of comorbidities on COPD was highlighted with the development of a COPD-specific comorbidity test score (COTE index).[85] A COTE score ≥ 4 points proved to be associated with an increased risk of death in each quartile of the BODE index. Comorbidities that contributed to increased risk of death were displayed graphically in the so-called "COPD comorbidome".[85]

Cardiovascular comorbidities are highly prevalent in COPD patients,[86] and recently complex cardio-respiratory interactions have been identified – many authors refer to a "cardiopulmonary continuum"[87] – with an important link to the systemic inflammation discussed above.

The TT strategy recommends that comorbidities be researched and addressed from an integrative perspective to improve outcomes in COPD patients.

Particular mention should be made regarding osteoporosis. In fact, most published reference articles on the TT strategy do not mention it as a treatable trait. Lately, there has been increasing evidence linking the presence of osteoporosis, especially osteoporotic fractures, with poor outcomes in COPD, making it a potential treatable trait to address.[88,89] Recognising that COPD-associated osteoporosis is underassessed and undertreated, and that osteoporotic fractures have profound impact on the quality of life of patients with COPD, we have included osteoporosis as a treatable trait.

Treatable Traits Applied to COPD Exacerbations

Exacerbations, defined as acute worsening of respiratory symptoms resulting in additional therapy, are major events with a negative impact on COPD patients.[4] Indeed, research has demonstrated their association with worse clinical outcomes, such as accelerated decline in lung function, increased rates of hospital admissions and readmissions, poor quality of life, worsening of underlying comorbidities and increased mortality.[17,58,75,90]

According to GOLD report, moderate exacerbations are defined as an acute worsening of respiratory symptoms that results in additional therapy with antibiotics and/or oral corticosteroids and severe exacerbations those requiring hospitalisation or an emergency department visit. Severe exacerbations should be distinguished from moderate ones, as they pose significantly more risks.[91,92] In fact, following a hospitalization for COPD exacerbation, the 1-year mortality risk is 25%;[93] this figure is higher than that observed following hospital admission for acute myocardial infarction.[94]

Despite advances in the management and treatment of COPD, exacerbation rates remain high, with a considerable burden on healthcare systems.[95] This trend calls for specific action, towards the management of these events, as well as their risk factors.

The TT approach has been traditionally applied to the management of stable COPD. Some authors have looked at its application to exacerbations, particularly for risk assessment and management of these events.[18,22,59]

We, herein, aim to explore how the TT strategy can be applied to reduce the risk of future exacerbations and improve the management of COPD exacerbations.

Risk of Exacerbation

Several factors have been associated with an increased risk of COPD exacerbations.[4] However, the strongest predictor for a future exacerbation remains the history of exacerbations in the previous year,[96] and this is the only risk factor addressed in most COPD guidelines.[4] From the ECLIPSE study, it is known that after a first exacerbation, the risk of having a second event more than doubles. After a second exacerbation, the risk of a future event more than quintuplicates.[96]

A question arises: should we wait for the first exacerbation to occur? Or should we be proactive?

The TT strategy represents an opportunity to be proactive. It allows for addressing TTs already related to exacerbation risk (Table 3):

- In a patient with no previous exacerbations, the first phase in the TT approach proposed here contains some of the TTs related to exacerbation risk.
- After a first moderate/severe exacerbation, the focus should be on the prevention of future events and thus we propose that patients progress to the second phase, in which all these TTs can be addressed.

The effectiveness of this approach in preventing exacerbations remains to be determined.

Finally, we acknowledge hospitalization as a golden opportunity to apply the TT strategy. There is no denying the major impact of hospitalizations on the natural course of COPD – increased risk of future events, delayed recovery, impaired quality of life and mortality.[95–97] This approach, in the hospital setting, is facilitated for readier access to diagnostic tests (to characterize TIMs) and a multidisciplinary team approach. However, this does

Table 3 Treatable Traits Associated with Increased Risk of Exacerbation*

Pulmonary
Eosinophilic airway inflammation[30]
Bronchiectasis[118]
Chronic bronchial infection[80]
Airflow limitation[96,120]
Lung hyperinflation[72,75]
Chronic bronchitis[121,122]
Extrapulmonary
Obstructive sleep apnea[123–125]
Cardiovascular disease[59]
Anxiety/ Depression[126]
Persistent systemic inflammation[80]
Cachexia[127]
Exercise intolerance[128]
Physical inactivity[129,130]
Behavioral
Poor inhalation technique[131,132]
Smoking and other environmental exposures[133]
Non-adherence[134]
Poor family/social support[135]

Note: *Treat identification markers and therapeutic options for each treatable trait are listed in Tables 1 and 2.

not apply to all TTs as many traits need to be assessed in a stable phase. These should be addressed at reassessment ≥ 4 weeks after discharge from hospital.

Exacerbation Management

Research and clinical practice have highlighted that the management of COPD exacerbations depends on a variety of factors. At present, some studies have identified TTs that can guide the management of these events and improve outcomes.[18,98,99]

The GOLD document already mentions the importance of sputum color and biomarkers, such as CRP and procalcitonin, for the management of exacerbations, namely, to guide the use of antibiotics during these events.[4]

As exacerbations are heterogeneous disease states (varying in terms of clinical manifestations, etiology and response to treatment), patients may benefit from a systematic identification of associated traits that would guide their management.[17] Understanding the biological mechanisms underlying exacerbations and grouping them according to their etiology seems to be an effective way to improve intervention strategies. In this context, an approach based on the acronym ABCDEFGX – Airway viral infection, Bacterial infection, Coinfection, Depression/anxiety, pulmonary Embolism, cardiac Failure (or failure of lung integrity-pneumothorax), General environment and X (unknown) – has been proposed.[100–102] This acronym-based approach was evaluated in a pilot study with patients hospitalized due to COPD exacerbations.[101] To identify etiologic phenotypes, patients underwent sputum culture, nasopharyngeal swab (for respiratory viruses), chest X-ray, serum white blood cells, CRP measurement, and application of the Hospital Anxiety and Depression Scale. Changes in patients' environment were addressed and the investigation of pulmonary embolism was left to the decision of the attending physician. This study highlighted the clinical relevance of characterizing exacerbations by using available methods in routine clinical practice.

In a study by Bafadhel and colleagues, four clusters of acute exacerbation were identified: bacterial, viral, eosinophilic predominant and pauci-inflammatory.[17] These clusters were clinically indistinguishable, creating the need to find biomarkers. Randomized controlled trials (RCTs) were then designed to validate a biomarker-driven approach in exacerbation management, with promising results.[103–105] These RCTs showed that this targeted approach has the potential to reduce treatment failure and minimize adverse effects by reducing unnecessary treatment.

Classification of COPD exacerbations according to their causative agent seems to be the most consensual approach: bacterial infection, viral infection, increased eosinophilic inflammation, and others (eg enhanced exposure to noxious agents).[22]

Bacterial Infection

Despite the widespread use of antibiotics, bacteria are responsible for only about 50% of all COPD exacerbations.[106,107] Current approaches to exacerbation management lack a reliable marker of bacterial infection that would guide antibiotic prescribing in a targeted manner. Some markers have been proposed. Clinical markers such as the Anthonisen criteria and sputum color are subjective and lack sensitivity and specificity.[22,108] The most commonly referred biomarkers are CRP and procalcitonin.

The CRP-guided approach in COPD exacerbations has been shown to reduce antibiotic use without affecting clinical outcomes, both in primary care[109] and in hospital admissions[103] with thresholds of 40 $mg.L^{-1}$ and 50 $mg.L^{-1}$ for antibiotic prescribing, respectively.

Procalcitonin has also been regarded as a useful biomarker in guiding antibiotic therapy. However, a recent

meta-analysis contradicted these results[110] and therefore further investigation is warranted.

Viral Infection

Viruses, mainly rhinovirus, influenza, and respiratory syncytial virus, have been detected in 30–50% of COPD exacerbations.[102,111,112]

There is also a subset of COPD exacerbations with bacterial and viral coinfection, which is related to poorer outcomes such as increased length of hospital stay.[21] Concurrent or recent upper respiratory symptoms or coryza may indicate viral etiology, but also coinfection. Some biomarkers have been studied, but a reliable biomarker of viral infection in COPD exacerbations remains to be identified.

Further research is needed to support new therapeutic strategies. In the meantime, prevention through vaccines is recommended to decrease the risk of exacerbation, the frequency of exacerbation and the morbidity associated with COPD.

Increased Eosinophilic Inflammation

As in the stable phase, eosinophilic airway inflammation has been identified as an important TT in the management of COPD exacerbations. Since it is associated with a lower length of hospital stay and reduced mortality, it has prognostic significance.[99] In fact, eosinopenia (BEC<50 cell/μL) correlates with worse clinical outcomes and is therefore being considered a poor prognostic factor.[99] Moreover, there has been evidence of an inverse relationship between blood eosinophil counts and bacterial infection, in COPD exacerbations.[113]

Just as BEC predicts therapeutic response to inhaled corticosteroids in stable COPD, it also predicts therapeutic response to systemic corticosteroids during exacerbation. A post-hoc analysis of 3 RCTs showed that patients with BEC≥2% who did not receive oral corticosteroids had significantly more treatment failure than patients who did.[114] Similarly, treatment with oral corticosteroids in patients with BEC<2% showed no benefit. In severe exacerbations, the Corticosteroid Reduction in COPD trial (CORTICO-COP)[105] applied a BEC-based algorithm to guide oral corticosteroid treatment – prednisolone was prescribed on days with BEC≥300 cell/μL, for a maximum of 5 days, and compared with standard treatment. The eosinophil-guided approach had similar outcomes, while reducing systemic corticosteroid exposure by 60%. This systemic steroid-sparing strategy may minimize harm by reducing unnecessary treatment. Given the variability in blood eosinophil counts during COPD exacerbations, the appropriate threshold for guiding oral corticosteroid treatment is still under debate.

Others

Pulmonary embolism (PE) is one of the other causes of COPD exacerbations and has a prevalence of 20–25% among unexplained COPD exacerbations.[115] However, many of these are subsegmental PEs and may not be clinically relevant.[116] More research is warranted before a systematic assessment of PE can be proposed.

A clinical trial of over 16.000 COPD patients with cardiovascular disease or risk factors for cardiovascular disease demonstrated that acute exacerbations increase the risk of subsequent cardiovascular events, especially in the first 30 days after exacerbation.[117] European experts now recommend cardiovascular risk assessment in all hospitalized patients with an exacerbation of COPD. They recommend that troponin and Brain Natriuretic Peptide (BNP) be assessed, within 4 hours of admission.[118]

Based on the research to date, and the availability and feasibility of trait identification markers and therapeutic options, we propose two major TTs in the management of COPD exacerbations with respect to etiology:

- bacterial infection
- increased eosinophilic inflammation.

Discussion

The high morbidity and mortality associated with COPD require a change regarding the management of this condition. A strategy based on the TT approach may create conditions to improve the quality of life and survival of COPD patients.

Some personalized approaches are already in place in COPD management. In daily practice, physicians choose the right inhaler for the right patient and respiratory rehabilitation is probably one of the best current examples of multidimensional and personalized approaches in COPD.

On the other hand, many patients are still assessed in a one-size-fits-all format. This is evident, for example, during the management of most acute exacerbation events, which are still approached conservatively, with double prescription of antibiotics and systemic corticosteroids, most often disregarding what might have triggered the event.

Recent advances in more personalized approaches have been proposed, but far from the level of personalization already seen in other therapeutic areas.

Our multidisciplinary TT model for addressing COPD, based on a two-phase strategy, considers distinct disease stages and severity as a means of ensuring appropriate assessment and treatment of all patients by primary care physicians (in an early or less severe stage) and respiratory physicians (in non-responders and severe disease). However, the implementation of a TT approach introduces a wide range of additional parameters to the standard routine, increasing the complexity, costs, and length of consultations. In addition, the multidisciplinary nature of this strategy requires extended and reinforced teams comprising specialized healthcare professionals who can intervene and manage identified TTs. All these aspects may create resistance to its widespread implementation. Still, as tailored treatment strategies are generally more effective and allow better risk-benefit ratios, we believe that the benefits will soon outweigh the costs of the initial stage.

Given the complexity, some authors propose that the TTs to be address should be more focused, according to the selected therapeutic goal,[19] as mentioned above. However, the authors also recognize that most patients have multiple therapeutic goals and that some, such as mortality, should be assessed ubiquitously.[119] This calls for a serious investment in the identification of therapeutic markers in the stable stages of the disease.

This strategy cannot translate into reality without adequate validation of the TT approach in the setting of specifically designed clinical trials, which would compare the outcomes of traditional assessment with those of a TT approach. In line with this requirement, McDonald and colleagues[21] designed a pilot study to validate a strategy developed to identify therapeutic targets and implement an individualized treatment program based on inflammometry, multidimensional assessment and case management. The authors proved that this strategy could result in tangible benefits for COPD patients, mainly in terms of quality of life.[21,84]

In conclusion, the treatable traits strategy has been proposed as a step towards precision medicine in the management of chronic airway diseases in both stable phase and acute exacerbation. This article sought to provide a guide for clinical practice in the application of this strategy to COPD. Although its prospective validation is still lacking, we believe that this is the way forward for the future of the COPD approach.

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