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COPD: Providing the right treatment for the right patient at the right time

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PREFACE

Chronic Obstructive Pulmonary Disease (COPD) is a common disease associated with significant morbidity and mortality that is both preventable and treatable. However, a major challenge in recognizing, preventing, and treating COPD is understanding its complexity. While COPD has historically been characterized as a disease defined by airflow limitation, we now understand it as a multi-component disease with many clinical phenotypes, systemic manifestations, and associated co-morbidities. Evidence is rapidly emerging in our understanding of the many factors that contribute to the pathogenesis of COPD and the identification of "early" or "pre-COPD" which should provide exciting opportunities for early treatment and disease modification. In addition to breakthroughs in our understanding of the origins of COPD, we are optimizing treatment strategies and delivery of care that are showing impressive benefits in patient-centered outcomes and healthcare utilization.

This special issue of Respiratory Medicine, "*COPD: Providing the Right Treatment for the Right Patient at the Right Time*" is a summary of the proceedings of a conference held in Stresa, Italy in April 2022 that brought together international experts to discuss emerging evidence in COPD and Pulmonary Rehabilitation in honor of a distinguished friend and colleague, Claudio Ferdinando Donor (1948–2021). Claudio was a true pioneer in the field of pulmonary rehabilitation and the comprehensive care of individuals with COPD. He held numerous leadership roles in in the field, provide editorial stewardship of several respiratory journals, authored numerous papers, statement and guidelines in COPD and Pulmonary Rehabilitation, and provided mentorship to many in our field. Claudio's most impressive talent was his ability to organize spectacular conferences and symposia that highlighted cutting edge science and clinical medicine. It is in this spirit that this conference was conceived and planned.

These proceedings are divided into 4 sections which highlight crucial areas in the field of COPD: (1) New concepts in COPD pathogenesis; (2) Enhancing outcomes in COPD; (3) Non-pharmacologic management of COPD; and (4) Optimizing delivery of care for COPD. These presentations summarize the newest evidence in the field and capture lively discussion on the exciting future of treating this prevalent and impactful disease.

We thank each of the authors for their participation and applaud their efforts toward pushing the envelope in our understanding of COPD and optimizing care for these patients. We believe that this edition is a most fitting tribute to a dear colleague and friend and will prove useful to students, clinicians, and researchers as they continually strive to provide the right treatment for the right patient at the right time. It has been our pleasure and a distinct honor to serve as editors and oversee such wonderful scholarly work.

1. New concepts of COPD

1.1. COPD: definition and natural history: David Mannino, Michele Vitacca

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality globally. COPD has, traditionally, been defined by the presence of airflow limitation on spirometry after the administration of a bronchodilator, although this definition has been challenged in recent years [1].

1.1.1. The changing definitions of COPD

In 2019 COPDGene researchers proposed a new way of defining and thinking about COPD that: 1) recognized the importance of imaging changes and symptomatology in the classification of disease; and 2) expanded the spirometric definition of COPD to include those with restricted spirometry (or preserved ratio impaired spirometry [PRISM]) in addition to obstruction [2]. (Figs. 1 and 2) In a real-world clinical population of patients with a COPD diagnosis many of the patients excluded by the current Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition were included as probable or possible COPD cases by this new COPDGene definition [3]. This expanded definition has the potential to identify patients earlier in their disease process when their disease course could be potentially modified.

More recently, a group of experts in COPD created a new definition of COPD to overcome several deficiencies in current definitions [4]. These limitations include: 1) failure to identify COPD at its early stages; 2) considering it as a single disease entity; 3) focusing on only one major factor (cigarette smoking) in its pathogenesis; and 4) underemphasis of the heterogeneity of processes contributing to its clinical manifestations. This definition is as follows: "*Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, expectoration) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow limitation*".

1.1.2. COPD subtypes

The manifestations of COPD are highly variable, and the degree of airflow limitation does not always capture the heterogeneity of the disease [5]. COPD subtypes can be defined by the following characteristics:

1 Clinical: Symptoms such as dyspnea, cough, and sputum production are an important part of how COPD is diagnosed and how patients present to health care providers. These are also an important part of the classification of COPD patients, using tools such as the Medical Research Council (MRC) dyspnea scale and the COPD Assessment Test (CAT) [1].

Exacerbations, the worsening of COPD symptoms beyond usual day to day fluctuations, e.g., related to infections or other factors, are another important clinical characteristic that defines COPD severity and guides therapy [1,6]. Although acute exacerbations are common, they can vary from year to year, with few people reporting more than 2 per year [7]. Individuals with COPD who are adherent to inhaled medications have fewer hospitalized exacerbations and reduced mortality [8]. Those with frequent exacerbations are more likely to become housebound and need targeting in physical activities and rehabilitation programs [9].

Approximately 25–40% of COPD are underweight and 35% have a severely low fat-free mass index. This negatively affects muscle function and lung function as well as increases exacerbations, mortality risk and cost, and is more common in patients who have emphysematous features [10–12]. Depletion of fat-free mass (FFM) commonly occurs in COPD and is an important contributor to

[1] Editors: Enrico Clini, Jose Jardim, Linda Nici, Jonathan Raskin, Richard ZuWallack.

skeletal muscle weakness and impaired exercise capacity in these patients [13–15].

Systemic inflammation is a feature of COPD, and comorbidities – which may, in part, be due to systemic inflammation - are common and impactful [16,17]. For example, one comorbid condition that is often overlooked is pulmonary hypertension, which reduces 5-year survival in COPD by 40% [18,19]. Section 1.3 discusses systemic inflammation in more detail.

2 Physiologic: COPD is defined by the presence of airflow limitation, although recent data demonstrate that in some people this impairment may start in childhood [20]. While all adults lose lung function over time, accelerated declines are seen in those with emphysema, low diffusion capacity for carbon monoxide (DLCO) and hyperinflation [21]. Another characteristic used in subtyping COPD is the degree of (incomplete) reversibility on pulmonary function testing following the administration of a bronchodilator, which is seen in most patients with COPD, and an even higher percentage of those with asthma/COPD overlap [22]. In addition to flow obstruction, the pathophysiology of COPD may be characterized by static hyperinflation, dynamic hyperinflation, and maldistribution of ventilation to perfusion [21].

3 Radiologic: Computed tomography adds more depth to the classification of COPD, and with the new COPDGene metrics, could become part of the definition. The main classifications are airway predominant, with thickening of the bronchioles and/or bronchiectasis, and parenchymal (emphysema-predominant), with loss of lung tissue [23–25]. These radiologic characteristics put into question the traditional diagnosis of COPD, which relies on the demonstration of airflow limitation, since radiologic emphysema may not be associated with this finding.

4 Activity and Physical Function Limitations: Exercise capacity and physical activity are separate but related constructs, are both are decreased in COPD, and both affect survival [26,27]. Social, motivational, and economic factors, in addition to exercise capacity, contribute to physical inactivity. The relationship between daily physical activity recorded by accelerometer and change in end expiratory lung volume is well known: the reduction in activity is associated with increasing dynamic hyperinflation [28]. While the increased survival is related to higher levels of activity ("do do") [29], recent research indicates that a higher level of exercise capacity ("can do") is a stronger predictor of this important outcome [30].

1.1.3. Natural history

Lung function decline in COPD varies considerably [31,32]. While the traditional view of natural history concerns what happens in people with established COPD, an alternative view is how COPD develops - which then raises two related concepts, "pre-COPD" and "early COPD." Like the COPDGene definition of COPD [2], these look beyond spirometric abnormalities, which occur relatively late in the COPD development process [33].

Pre-COPD [34] refers to those at any age without spirometrically-demonstrated airflow limitation but are likely to progress to COPD (i.e., overt airflow obstruction without further intervention). Factors predicting progression to COPD include: 1) certain respiratory symptoms, including cough with sputum production; 2) physiologic abnormalities, including low-normal FEV1, DLCO, and/or accelerated FEV1 decline; and 3) radiographic abnormalities, including airway abnormalities and emphysema [35].

Early COPD refers to patients under 50 years old with at least 10 pack-years of smoking history with one or more of the following characteristics: 1) airflow limitation (post-bronchodilator FEV_1/FVC less than lower limit of normal); 2) computed tomography (CT) abnormalities (visual emphysema, air trapping or bronchial thickening graded mild or worse); and 3) evidence of rapid FEV_1 decline (greater than 60 mL/year) that is accelerated relative to FVC decline [36,37]. The term, early COPD, is discouraged by Global Initiative for Obstructive Lung Disease (GOLD) because it refers to the initiation of the biologic processes that lead to COPD and this is almost impossible to determine in clinical practice. Instead, the term, COPD in young individuals, is recommended [38].

Two ongoing studies are attempting to evaluate early COPD: the Determinants of Onset and Progression of COPD in Young Adults (ClinicalTrials.gov identifier NCT02352220) and the Early COPD Development Partnership (ClinicalTrials.gov identifier NCT03480347). In addition, the REdefining THerapy In Early COPD for the Pulmonary Trials Cooperative (RETHINC) study is assessing the effect of dual bronchodilator therapy in symptomatic current and former smokers with restricted spirometry. This subgroup of patients, excluded by the current COPD definition is included in the COPDGene 2019 definition [2], (ClinicalTrials.gov Identifier: NCT02867761). These studies may provide information on early COPD and determine therapies that may change the natural history of disease.

1.1.4. Mortality

COPD, with its comorbidities, is one of the five major causes of death

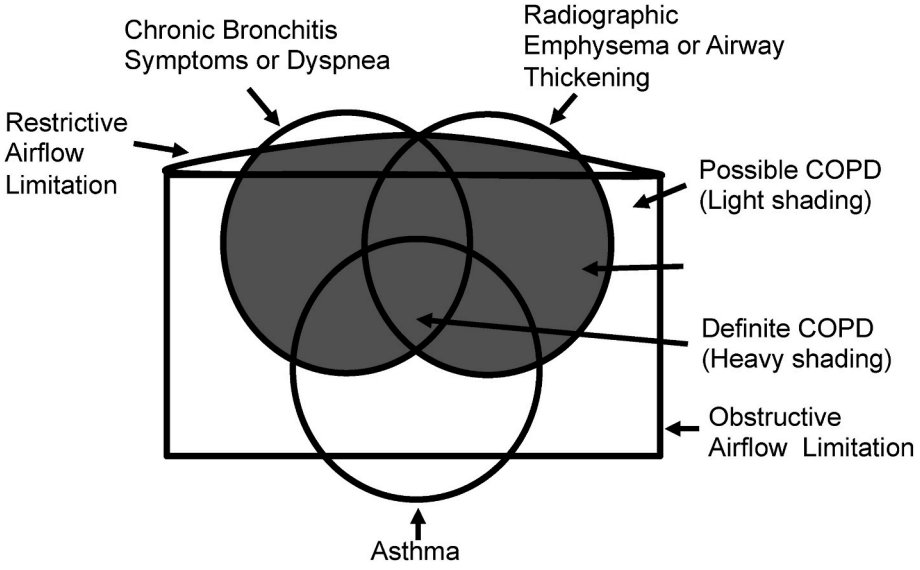

Fig. 1. Based on the COPDGene 2019 definition of COPD [2]. Possible, probable, or definite COPD is represented by the progressively darkening shaded sections.

worldwide [1,39,40]. Predictors of COPD mortality include: the level of FEV_1 [41], dyspnea [42], frequent exacerbations [43], weight loss [44], low exercise tolerance [45], age [46], a high BODE score [47], hospitalization history [46], high levels of biomarkers of Inflammation such as IL-6 or fibrinogen [48,49] and presence of comorbidities [17].

1.1.5. Conclusion

COPD is a preventable and treatable disease but, currently, not curable. There remain many unknowns about the natural history of lung function decline and the development of COPD. While the loss of FEV_1 relative to FVC has been an important part of this understanding, other factors such as breathlessness related to activities of daily living, exercise capacity, exacerbations, and peripheral muscle weakness are also important. These outcomes are often quite responsive to therapy of COPD [50]. Assessment of COPD severity and phenotype can be a valuable tool for adapting therapy to the clinical characteristics of each patient.

1.1.5.1. Key points.

- COPD represents a heterogeneous collection of diseases
- New definitions of COPD include components of imaging and symptoms, along with an expansion of the spirometric criteria
- Finding disease earlier in its course remains a priority in improving disease outcomes.

1.2. Prospects for treatment by COPD subtypes: Barry Make, Nicola Hanania

Since chronic obstructive pulmonary disease (COPD) is heterogenous, a "one size fits all" approach to its treatment is often unsuccessful in achieving optimal outcomes. A greater understanding of its phenotypes and endotypes is paving the way to more precise therapeutic approaches. These should ideally consider individual variability and incorporate clinical presentation, genetics, endotypes, and psychosocial aspects of the disease.

A phenotype as it pertains to COPD is defined as "disease attributes that describe differences between individuals as they relate to clinically meaningful outcomes, including symptoms, exacerbations, response to therapy, rate of disease progression, or death." [52] An endotype reflects the pathobiological mechanism leading to observable attributes of the disease. Few existing therapies for COPD have targeted specific phenotypes or endotypes attempting to employ a precision approach (Table 1). One of the biggest challenges is the fact that easy to measure, reproducible biomarkers to identify different subtypes of COPD are not widely available. More recently, there has been a call for the identification of treatable traits in COPD, which represents a unique approach to personalize its treatment [53]. Fig. 3illustrates some common COPD phenotypes. Below, we discuss some of the COPD phenotypes and their clinical relevance to different treatment strategies.

Table 1
Examples of treatable COPD subtypes.

Phenotype/Endotype	Treatment
Alpha 1- Antitrypsin Emphysema	Augmentation Therapy
Hypoxemia at rest	Supplemental oxygen
Upper lobe emphysema/low exercise tolerance	Lung volume reduction surgery (LVRS)
Emphysema/fissure integrity	Bronchoscopic lung volume reduction (BLVR)
Exacerbations/chronic bronchitis	Roflumilast
Exacerbations/eosinophilia	Inhaled corticosteroids, triple inhaled therapy
OSA/Hypercapnia	CPAP/NIV
Muscle fatigue/Exercise Intolerance	Pulmonary Rehabilitation

Chronic bronchitis is a clinical phenotype defined as the presence of cough and sputum production for at least three months in each of two consecutive years. This phenotype is associated with a greater symptom burden, greater lung function decline, and increased frequency and severity of exacerbations [54,55]. Roflumilast, an oral selective phosphodiesterase-4 inhibitor with anti-inflammatory properties, has been shown to reduce the frequency of exacerbations in a subset of these patients who have severe airway obstruction and frequent exacerbations [56,57]. Innovative bronchoscopic interventions to reduce excess mucus production, including liquid nitrogen metered cryospray, bronchial rheoplasty, and balloon desobstruction are currently being evaluated for patients with chronic bronchitis [58]. More recently, smokers with chronic bronchitis, even with preserved airway function have been shown to have a higher risk of exacerbations [59], and ongoing studies are underway to examine whether early pharmacologic therapy of such patients may influence clinical outcomes.

Characterizing *emphysema*, another phenotype of COPD, with lung function measurements and computed tomography (CT), can define underlying anatomical changes and correlate them with clinical outcomes. Data from the COPDGene trial [60] indicate that both bronchial wall thickness and total lung emphysema percentage, as assessed with CT imaging, are predictive of COPD exacerbation frequency. Notably, both associations were significant independent of the severity of obstruction.

Hyperinflation is a common occurrence in patients with emphysema and correlates with impaired cardiac and circulatory function because of

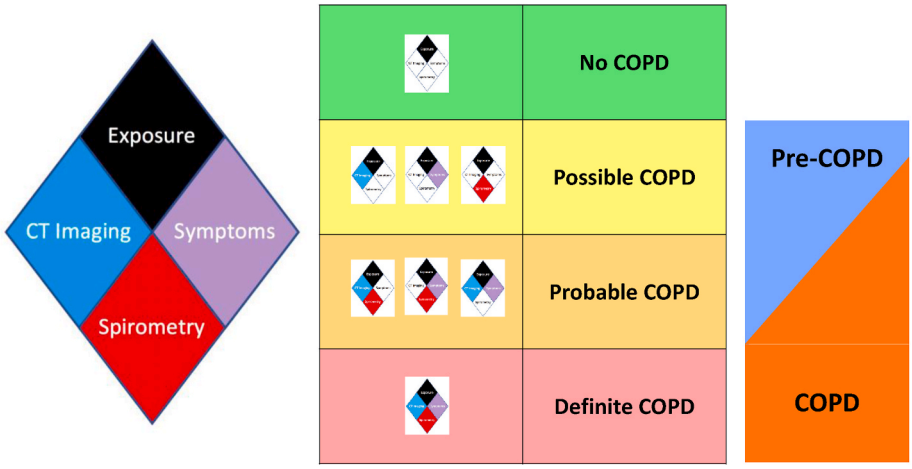

Fig. 2. The relationship between exposures, symptoms, imaging findings, and spirometry in the definition of COPD as defined by COPDGene 2019 [2]. In this definition exposure is at least 10 pack years of smoking, CT Imaging is evidence of emphysema or airway thickening, symptoms are either dyspnea or chronic bronchitis, and spirometry is either obstructive or restrictive impairment. Patients in the possible or probable COPD categories may be categorized as either COPD or Pre-COPD. With permission from the American Journal of Physiology, Lung Cellular and Molecular Physiology [51].

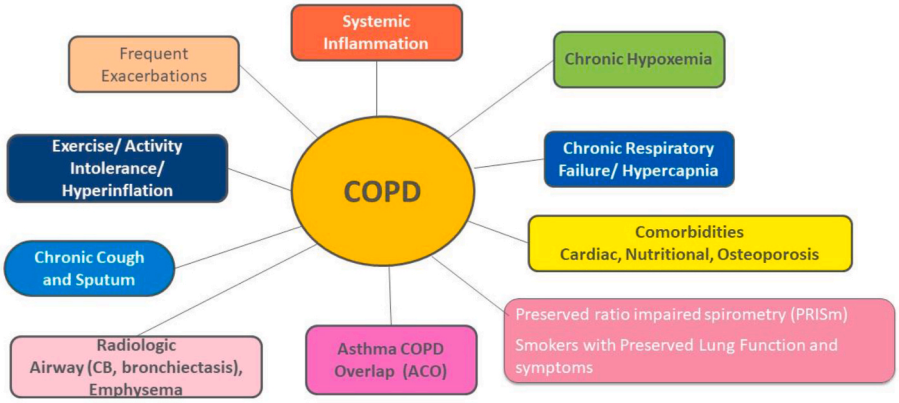

Fig. 3. Multiple identified and novel COPD phenotypes.

reduced ventricular preload and diastolic dysfunction [61,62]. As a result, therapies directed at reversing hyperinflation have become a target of intervention for this phenotype. Such therapies range from bronchodilators (mono- or dual-therapy) to lung volume reduction surgery (LVRS) and bronchoscopic lung volume reduction (BLVR). CT imaging has also been helpful to identify sub-populations that would preferentially benefit from such therapies. For example, diagnosis of upper lobe predominant emphysema may allow for selection of patients that would benefit from LVRS. The NETT trial demonstrated decreased mortality with LVRS in a subgroup of patients with upper-lobe predominant emphysema and low exercise capacity [63]. Although no large randomized controlled trials of BLVR have evaluated mortality as a primary outcome, significant improvements in FEV1 and 6 min walk distance have been demonstrated with BLVR in the subset of patients with severe, heterogenous emphysema and radiographically intact fissures [64].

Although there is no formally agreed upon definition for *asthma-COPD overlap* (ACO), it is well known that this phenotype does exist and has unique characteristics, outcomes, and treatment responses [65]. Patients within this phenotype have frequently been excluded from COPD or asthma trials and its optimal treatment approach is unknown. However, expert consensus generally advocated for a combination of bronchodilators and inhaled corticosteroids as first line therapy [66].

Another important clinical phenotype is referred to as the "*frequent exacerbator*". Although there is no uniform definition for this subgroup of patients, it has been suggested that patients belonging to this group usually have had 2 or more exacerbations in the preceding year and are at higher risk of subsequent exacerbations [67,68]. Several specific therapies have been evaluated in this subgroup of patients, including the use of inhaled corticosteroids - particularly in patients with high baseline eosinophil levels or those who fail dual bronchodilator therapy. More recently, several trials have demonstrated benefit from inhaled triple therapies (ICS/LABA/LAMA), resulting in decreased exacerbation frequency and a potential mortality benefit [69–71]. Roflumilast and maintenance treatment with azithromycin show promise in this patient population [72].

Multiple treatment strategies have focused on role of airway inflammation. Identification of the eosinophil-predominant phenotype is of clinical significance, as these patients tend to have a favorable response to corticosteroids [73,74]. Several biologic therapies are currently being evaluated to target patients with COPD and eosinophilia and those with a T2 inflammatory signature [75–77]. Although biomarkers such as blood and airway eosinophils and fraction of exhaled nitric oxide (FeNO) may have predictive and prognostic capabilities, utilization of advanced diagnostic testing such gene expression signature of biomarkers may also show promise in discriminating inflammatory phenotypes and may help predict exacerbation risk and corticosteroid responsiveness [78]. Targeting patients with non-T2 and neutrophilic inflammation in COPD has thus far been disappointing, but several targets are being evaluated by new therapies in different stages of development [79]. Finally, systemic inflammation is present in some COPD patients and linked to extrapulmonary comorbidities and increased risk of exacerbation; to date, it has not yet been effectively targeted.

Comorbidities are common to COPD and significantly influence prognosis., and optimization of therapy must take them into account. For example, there is a consistent correlation between the presence of bronchiectasis in COPD and severity of airflow obstruction [80,81]. COPD patients with this comorbid condition have increases in sputum production, frequency of exacerbations, airflow obstruction, bacterial colonization, levels of inflammatory markers and (possible) mortality risk. Despite evidence of worse clinical outcomes within this phenotype, there is currently limited evidence to support specific therapies for this population, although medications targeting CFTR gene dysfunction are being examined [82]. For now, inhaled bronchodilators are considered a mainstay of therapy, but use of ICS remains controversial, with current GOLD guidance suggesting that avoidance of ICS may be indicated in the case of bacterial colonization or frequent respiratory infections. Several studies of chronic macrolide therapy in bronchiectasis and COPD have demonstrated significant reduction in exacerbations and improvement in quality of life. Patients with this phenotype may benefit from a longer duration of antibiotic therapy during acute infectious exacerbations and some may benefit from cyclical antibiotic therapy [83,84].

Comorbid *cardiovascular disease (CVD)* is highly prevalent in patients with COPD and has significant clinical consequences [85,86]. These patients have increased all-cause mortality and risk of hospitalization. The association between CVD and COPD may be related to systemic inflammation. However, chronic infection, shared risk factors (especially smoking), or reduced lung function may also contribute to cardiovascular mortality [85]. Chronic low grade systemic inflammation is thought to be a significant factor contributing to the complex pathogenesis of atherosclerosis and has also been implicated in the development of COPD. The observation that patients with comorbid ischemic heart disease are at increased risk of myocardial infarction within 30 days of COPD exacerbation further supports an inflammatory link between the two diseases.

Obstructive sleep apnea (OSA) is common comorbidity in COPD patients, especially in those with more severe disease [87], although this association may be confounded by age. Furthermore, those with advanced COPD may have a lower threshold for hypopnea events due to a higher propensity to desaturate overnight. Airway inflammation also appears to be higher in patients with this OSA-COPD overlap phenotype, with increased proportion of neutrophils, TNF alpha and IL-8 in the bronchoalveolar lavage of patients with both diseases compared to patients with COPD alone [88]. The clinical consequences of comorbid OSA and COPD are significant, including high risk of death, increased

risk of exacerbations (if OSA remains untreated) and more profound hypoxemia, which may predispose to pulmonary hypertension [89]. Treatment with continuous positive airway pressure in this population is associated with reduction in inflammation levels, healthcare utilization, and mortality [90].

1.2.1. Key points

- COPD is heterogeneous, and a "one size fits all" approach to treatment is usually insufficient to optimize outcomes
- Identifying COPD phenotypes and using this information to target therapy is a rapidly developing science; novel approaches will enhance precision therapy
- Comorbidities play a significant role in morbidity and mortality in COPD; these must be recognized and treated accordingly

1.3. COPD is a systemic disease: Carolyn Rochester, Alvar Agusti

Defining COPD as a systemic disease has two different interpretations. The first is that rather than being considered a self-inflicted lung disease caused by tobacco smoking, COPD has a systemic origin. The second is that COPD is not only a lung disease, but a systemic disease with frequent and relevant extra-pulmonary manifestations (multimorbidity). Both interpretations are correct. With respect to the first interpretation, recent research has shown that many environmental (including but not restricted to tobacco smoking), host, genetic and epigenetic risk factors all contribute to the pathogenesis of COPD by determining the lung function trajectory followed by each person over the lifetime (trajectome), a new pathogenic understanding termed, "GETomics" [91]. Regarding the second one, there is plenty of evidence that multimorbidity occurs almost invariably in all COPD patients [92–97], including cardiovascular disease, depression, anxiety, skeletal muscle dysfunction, osteoporosis, anemia, diabetes, metabolic syndrome, obstructive sleep apnea, lung cancer, infection, cognitive impairment, frailty and nutritional disturbances (both cachexia and obesity) [17,28,94,98–102]. Importantly, systemic multimorbidity worsens symptoms and quality of life, increases disability, and poses increased risk of hospitalization and mortality [36,91,94,103,104]. In fact, up to two thirds of COPD patients die from non-respiratory causes, especially cardiovascular disease and lung cancer [93,100,104].

These two interpretations of COPD as a systemic disease are complementary and interrelated. On the one hand, the array of environmental, host, genetic and epigenetic risk factors that combine to alter lung function can also contribute to the pathogenesis of multimorbidity [1].(91) Conversely, the lung disease itself can contribute to multimorbidity through systemic inflammation, sedentarism, obesity, and other mechanisms [16–18,105–107]. For instance, persistent systemic inflammation is associated with a higher prevalence of comorbidities, exacerbations and increased all-cause mortality [19].([108]) Recent novel work using factor analysis and multidimensional network analysis has begun to unravel the interrelationships between various comorbidities/systemic manifestations of COPD and other patient characteristics [95]. Five distinct subgroups of patients with different clusters of features associated with different prognoses were identified in a cohort of 2164 patients in the ECLIPSE study [109]. Likewise, in another study of 208 patients with severe COPD and 200 controls without COPD, five clusters ("less comorbidity", "cardiovascular", "metabolic", "psychologic" and "cachectic") were identified; the "psychologic" and "cachectic" clusters were specific to COPD [110]. The linkages between comorbidities are complex, but groups of comorbidities cluster in a manner beyond that expected to occur by chance, thereby suggesting possible linked pathogenic origins [95,111]. Network analysis has recently also begun to assess the genes, proteins, and biological pathways that underlie the interrelationship between COPD and its comorbidities [112]. Collectively, this work will likely lead to better understanding of the pathogenesis of COPD and its systemic manifestations and may ultimately help to guide personalized therapies through use of validated biomarkers [113].

Importantly, in addition to biologic factors, societal factors such as poverty, socioeconomic deprivation, living environment, food insecurity, harmful substance use, and other environmental factors also impact the development and severity of comorbidities and systemic manifestations of COPD. Collectively included among the environmental factors in the "GETomics" concept of COPD [91], these issues also potentially impact patients' access to health care.

Considering COPD as a systemic disease has implications for the diagnosis and personalized management of the disease. COPD patients develop comorbidities at a younger age than individuals in the general population [17,95]. Those who eventually develop COPD after failing to achieve normal peak lung function in early adulthood develop more comorbidities and have higher all-cause mortality than those who achieve normal lung function [114]. A wider and earlier use of spirometry may help to identify this high-risk group of individuals in the general population at a young age (infancy, adolescence) [115], thus allowing monitoring and earlier treatment [116].

The comprehensive care of patients with COPD requires identification and management of each individual's "treatable traits" throughout the course of their disease [117]. Common comorbidities should be considered within the context of a broad-based patient assessment [92]. Computerized tomography of the thorax is helpful to characterize the intrathoracic features of COPD, as well as to identify comorbidities such as cancer, coronary artery disease, osteoporosis, body composition abnormalities and pulmonary vascular disease [118–122], and to exclude other conditions. Other testing to assess for systemic manifestations of COPD, including blood work, electrocardiogram echocardiogram, and/or body composition/nutritional assessment among others, depends on each patient's symptoms, medical history, radiologic and physiologic findings, physical and functional limitations, disease stability as well as shared decision making between patients and their health care providers regarding potential benefits vs. risks and associated costs of testing.

Notably, some comorbidities such as skeletal muscle dysfunction, cardiovascular deconditioning, anxiety, and depression can be stabilized and improved by pulmonary rehabilitation [98,123,124]. Moreover, previously unrecognized comorbidities such as cardiac disease, peripheral vascular disease, arrythmia, musculoskeletal issues (and others) may be recognized for the first time in the context of pulmonary rehabilitation [125,126]. The timing, content and setting of PR should be tailored, i.e., "personalized", to target the specific combination of respiratory and non-respiratory factors contributing to each person's symptoms and physical, functional and psychosocial limitations [127,128]. If implemented early in the course of the disease, including early in life among those at risk of future COPD, pulmonary rehabilitation has potential to change the disease trajectory, by optimizing health enhancing behaviors, minimizing risk (e.g., avoiding harmful exposures), preventing and/or hastening recovery from disease exacerbations and reducing risk of developing comorbidities.

A better understanding of disease "phenotypes" and "endotypes" resulting from differing disease trajectories and types of exposures (GETomics) [91], and the interrelationships between host susceptibility, environment and changes over time [129] should help to guide the development of more personalized, targeted and effective therapies for people with COPD in the future [130].

1.3.1. Key points

- COPD is a systemic disease … "systemic" can refer to its systemic origin or the concept that COPD is a systemic disease with frequent and relevant extrapulmonary manifestations
- Environmental, host, genetic, and epigenetic risk factors can contribute to the pathogenesis of COPD

- Considering COPD as a system disease has implications for its diagnosis and personalized management

1.4. Disease modification in COPD: Daniel Gerardi, Bartolome Celli

1.4.1. Introduction

Until recently, a diagnosis of COPD was thought to be a disease of the elderly associated with a progressive functional decline that responded poorly to different therapies. Under this paradigm, its management focused on reducing symptoms and improving functional status, conceding that little could be done to prevent its progression. However, recent developments, including results from large clinical trials of bronchodilators and inhaled steroids (ICS) (alone or in combination), implementation of pulmonary rehabilitation programs, therapies focused on exacerbation prevention, and treatment of its systemic manifestations have shown that disease modification is possible. This discussion will highlight the advances that have altered the progression of COPD.

1.4.2. COPD as a progressive disease

The Cambridge Dictionary defines *progression* as "the act of changing to the next stage of development." [131] In 1995, the American Thoracic Society (ATS) emphasized the central role of progressive airflow obstruction in its definition of COPD [132]. A decade later, an ATS–European Respiratory Society (ERS) Task Force provided a more positive statement indicating that, "[it] is a preventable and treatable disease state characterized by airflow limitation that is not fully reversible." [133] These definitions appropriately focused on airflow limitation, but underemphasized its symptom burden, functional limitations, exacerbation frequency, and mortality risk [134].

The classical perspective on COPD progression was influenced by the prospective study by Fletcher and colleagues of working men in London [135,136]. They observed that: 1) Non-smokers and those smokers not destined to develop COPD had a gradual, mild decline in airflow obstruction; 2) Smokers who developed COPD had a steeper rate of decline over time – eventually leading to disability and death; and 3) Quitting smoking reduced the rate of lung function decline, with early quitters having greater benefit. This view was later modified by adding the saw tooth effect of exacerbations on the slope of decline [137], and a greater emphasis on lung development early in life [36]. What this classic paradigm lacked is the fact that a relatively small proportion of smokers go on to develop clinically significant COPD, leading to the conclusion that genetics must also play a major role in progression [138].

Recent studies have challenged the concept that COPD is invariably a progressive disease. Vestbo and colleagues, in a study of 2163 patients over three years (*Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE)*), reported the decline of forced expiratory volume in 1 s (FEV1) to be "highly variable", with only 38% of the patients having a drop in FEV1 of more than 40 ml/year [139]. Similarly, Casanova and colleagues, who followed COPD patients for 5 years, demonstrated heterogeneity in progression of airways obstruction [140]: only 18% of their 1198 patients were "fast decliners," characterized by a mean FEV1 loss of 86 ml/yr, with significant slope changes occurring at any GOLD spirometric stage. Additionally, the Hokkaido COPD cohort study had very similar results, but also found an association between emphysema severity and rapid decline in FEV1 [21]. Finally, de-Torres and colleagues, in a long-term observational cohort study demonstrated that less than 30% of patients had worsening GOLD spirometric staging while 10% had improvement in this parameter, leading the authors to conclude that "… once diagnosed, COPD is usually a non-progressive disease." [141].

1.4.3. Modification of the "natural course" of the disease

Modification is "a change to something, usually to improve it" [131]. In COPD, this argues for a reduction of progression that is maintained over time [142]. For a disease with systemic consequences, we must recognize that disease modification should encompass not only stabilization or improvement of lung structural and functional parameters, but also its extra-pulmonary manifestations [116]. Disease modification approaches in COPD include smoking cessation, pharmacological interventions, oxygen supplementation, lung volume reduction, exacerbation mitigation, and pulmonary rehabilitation.

Accepting this expanded concept of disease modification, the evidence favoring modification of the natural course of COPD is substantial, as underscored by a continued reduction in worldwide COPD mortality. The 2017 Global Burden of Disease report demonstrated an annual decline in the mortality rate of 2.36% over the 27 years of the study [143], although – as for many chronic diseases - those countries with lower socioeconomic status continue to face a more severe burden.

Fletcher and colleagues appropriately pointed to the central role of cigarette smoking as a cause of COPD in developed countries. Now, the use of biomass in cooking and heating, is even more important in vast regions of the world [14]. Eliminating these exposures remains of primary importance in COPD disease modification [144]. Smoking cessation not only prevents progression of airflow limitation [145,146], it also provides a reduction in mortality risk [147]. Favorably modifying the progression of airflow limitation in COPD is not limited to avoiding or reducing noxious particle or gas exposure. Other potentially modifying therapies include alpha-one antiprotease replacement in those with deficiency [148], and regular use of inhaled long-acting bronchodilators and corticosteroids in patients with frequent exacerbations [69,70].

Supplemental oxygen therapy for COPD has long been known to reduce mortality for those COPD patients with resting hypoxemia, representing our most significant disease modification therapy in terms of mortality [149–151] - although adherence and inconvenience issues still remain a problem.

Inhaled therapy represents an essential pharmacological treatment for COPD. Large-scale pharmaceutical trials evaluating therapy with ICS and long-acting bronchodilators, while assessing lung function, dyspnea and health status, also provide valuable information on modifying COPD progression. Calverley and colleagues compared the combination the long-acting beta agonist (LABA) salmeterol plus the ICS, fluticasone proprionate, to placebo in 6112 COPD patients. While the study failed to meet the primary outcome of mortality reduction at three years, significant reductions were demonstrated in annual rates of exacerbations, along with improvements in health status and lung function [152]. In a 4-year trial comparing the long-acting muscarinic antagonist (LAMA), tiotropium to usual care including placebo, Tashkin and colleagues demonstrated improvements in lung function, quality of life, and exacerbation frequency. However, the primary endpoint of the study, a reduction in the rate of decline of FEV1, was not achieved. In another trial, Vestbo and colleagues confirmed that "triple therapy" (LABA, LAMA and ICS) was superior to LAMA alone in 2691 COPD patients [153]. Other studies have also demonstrated the beneficial effect of triple therapy for COPD [154], including an important reduction in all-cause mortality [155]. Precision therapy is also possible with studies showing that ICS is most effective when used by patients with high blood eosinophil counts [144]. The role of biologic therapy remains under investigation and a potential future therapy option. Azithromycin or roflumilast are non-inhaled therapies available to alter disease exacerbation rates in selected patients [141].

Pulmonary rehabilitation, a combination of exercise training, patient education, psychosocial support, self-management strategies, and nutritional intervention, has become the most essential non-pharmacologic intervention in symptomatic patients with COPD [123]. Although pulmonary rehabilitation has limited effect on lung physiology, its beneficial effects in reversing physical deconditioning [156] results in improvements in dyspnea, quality of life and exercise capacity [124]. Beneficial effects in these outcomes typically are greater than from standard medical therapy. Evidence from observational and

randomized controlled trials points to the importance of pulmonary rehabilitation in reducing mortality risk and health care utilization, especially when it is provided after an exacerbation [157,158], leading to recommendations for its implementation in this setting [144].

Finally, lung volume reduction (LVR) offers benefits to selected COPD patients with emphysema. Long-term follow up of patients undergoing surgical treatment (LVR) demonstrated that those with the combination of upper-lobe predominant emphysema and low exercise capacity, not only had increased exercise tolerance and health-related quality of life, but also a survival advantage at five years after the procedure [159]. More recently, less invasive bronchoscopic lung volume reduction, has also resulted in improvements lung function, dyspnea, health-related quality of life, and exercise tolerance in patients with heterogeneous emphysema and hyperinflation [160].

Taken together, the evidence presented above shows that the downward trajectory of individuals with COPD can be favorably modified. A challenge for clinicians and researchers is to move upstream, to implement stronger primary prevention programs in younger persons, to increase efforts to diagnose at-risk subjects at an earlier age, and to use precision therapies for various subgroups of patients presenting with clinical evidence of the disease. With all therapeutic resources brought to bear, a nihilistic approach to patients with COPD is no longer justified.

1.4.4. Key points

- The broader concept of disease modification in COPD extends beyond stabilization or improvement in structural and functional parameters
- Disease modification approaches in COPD include smoking cessation, pharmacological interventions, oxygen supplementation, lung volume reduction, exacerbation mitigation, and pulmonary rehabilitation
- The challenge for clinicians and researchers is to move upstream, to implement stronger primary prevention programs in younger persons, increase efforts to diagnose at-risk subjects at an earlier age, and use precision therapies for various subgroups of patients presenting with clinical evidence of the disease.

2. Enhancing outcomes in COPD

2.1. Improving exercise capacity in COPD: Richard Casaburi, Francois Maltais

Improving the ability of COPD patients to participate in activities of daily living without discomfort is one of the premier benefits of rehabilitative exercise training. It is instructive to view the arc of pulmonary rehabilitation research from the perspective of progress in improving exercise capacity.

It can be argued that pulmonary rehabilitation research can be divided roughly into eras, where one thrust or another dominated:

- Before 1970 – Prehistory, featuring the concepts put forward by Alvan Barach, positing that, contrary to previous recommendations that COPD patients avoid activities associated with dyspnea, increased activity should be promoted [161].
- 1970–1990 – Starting with the demonstration of the beneficial effects of an organized program of pulmonary rehabilitation by Petty et al. [162], programs began to proliferate. Symptomatic benefits were demonstrated in well-designed clinical trials and pulmonary rehabilitation began to be incorporated as a standard of care for symptomatic COPD patients.
- 1990–2005 – Towards the end of the preceding period, the opinion proliferated that benefits of PR were principally psychological [163]. Well-controlled interventional studies appeared, demonstrating that COPD patients reaped clear physiologic benefits from a program of rehabilitative exercise [164]. Muscle biopsy studies confirmed that improvements in muscle aerobic metabolism occurred that were similar to those seen in healthy younger studies [5]([165]). Skeletal muscle dysfunction was established as an important (and remediable) COPD comorbidity [98]. Frequency, duration and intensity principles utilized in athletics were adopted and higher intensity programs were found to be more effective in inducing physiologic adaptations. Rationally designed adjuncts to exercise training (e.g., oxygen supplementation, ventilatory support) were shown to improve its effectiveness.
- 2005–2015 – Chronic inactivity was recognized as an important feature of COPD. The development of activity monitors that patients could wear during everyday activity facilitated long-term assessment of activity patterns. Studies demonstrated that inactivity was an important, perhaps the most important, predictor of death in COPD [166]. Pulmonary rehabilitation was demonstrated to have variable effects on activity levels [167]. Motivational strategies were explored [168].
- 2015-present – In recognition of the abysmally low participation rate in pulmonary rehabilitation [169], strategies were sought to increase availability … and palatability. A variety of virtual rehabilitation modalities were explored to see whether these could be demonstrated to be safe and effective. The unavailability of center-based rehabilitation during the pandemic lent urgency to this research.

It is possible to argue that the focus of rehabilitative research has moved away from efforts to improve exercise capacity in general … and from physiologic research in particular. Two lines of evidence point to this conclusion.

- Many research studies have “retreated” to emphasizing symptomatic outcomes. While, for example, quality of life improvement is clearly to be desired, relying on it as a sole focus recalls an era when symptomatic benefits were the only ones considered.
- When exercise outcomes are included, the outcome usually incorporated is the 6-min walk. The 6-min walk, however, does not generally bring patients to their maximal exertion. As such, it is strongly influenced by motivation and coaching and has a distinct learning effect. It has been argued that this test should be viewed as a measure of functional exercise performance, rather than of exercise capacity. A recent guideline recommendation that the test be performed in duplicate in an attempt to overcome the learning effect [170] has mostly been ignored. Further, physiologic responses are generally not recorded, meaning that the mechanism of any observed improvement cannot be defined.

Once recognized, this tendency should be corrected. Developing new exercise training modalities aimed at improving exercise capacity must be based on a sound physiological rationale. Physiologic principles allowed PR to go from being considered “alternative medicine” to being acknowledged as the most effective symptomatic therapy for COPD. De-emphasizing these principles will have adverse consequences.

2.1.1. Key points

- Over the course of a few decades, pulmonary rehabilitation has evolved from what was considered an alternative medicine to being acknowledged as the most effective symptomatic therapy for COPD
- A large body of evidence demonstrates clear physiologic benefits from a program of rehabilitative exercise for COPD
- When exploring new modalities of pulmonary rehabilitation, it will be important to evaluate whether the physiologic benefits demonstrated in current programs are preserved

2.2. Symptoms and quality of life in COPD. Sue lareau, Paula Meek

COPD patients report several symptoms (anxiety, depression, pain,

etc.), the most common being dyspnea [171] and fatigue [172]. Like dyspnea, fatigue results from complex physiological and psychological factors, therefore, a single treatment, cannot be identified for all patients. In a major statement on dyspnea by the American Thoracic Society, [173] has been recommended that the measurement of dyspnea be made based on the associated domains of dyspnea. These can be categorized as: a) *sensory–perceptual* experience (what breathing feels like to the individual), b) *affective distress* (how unpleasant breathing feels), and c) symptom/disease *impact or burden* (how breathing affects activities or quality of life). This distinction is important, because for example, dyspnea may be measured based on instruments measuring only the impact or burden domain, which may fail to identify crucial sensory or affective information about the patient.

The inter-relationship between different symptoms and health related quality of life (HRQoL) is under-appreciated. Symptoms, and HRQoL are not necessarily separate issues, as HRQoL instruments often rely on symptoms as part of the quality of life assessment. HRQoL scores are often a summation of symptoms and physical limitations, (depending on the instrument). The inter-relationship of symptoms and quality of life can often be revealed in the distribution of scores on various measurement domains. To illustrate, 70% of the variance in a HRQoL measure, may be influenced by one domain on a measure e. g. dyspnea or fatigue. So, while the total score of a measure may be high, it may be attributable primarily to one domain, symptoms. One must therefore, examine what contributes to the evaluation of domains contributing to the total score. Furthermore, many use these subscales as surrogate measures for a symptom, resulting in misrepresentation of symptoms in the COPD population. This was underscored by a recent systematic review of fatigue, in which the prevalence of fatigue was found to range from 17 to 95%, based on the 28 different assessment measures used [174]. The fatigue instruments included both single domain surrogate HRQOL measures of fatigue (CRQ *fatigue* subscale and Short Form Health Survey-SF36 *vitality* subscale) as well as more comprehensive fatigue-specific instruments (e. g., FSS-Fatigue Severity Scale, MFI-Multidimensional Fatigue Inventory).

The prevalence of symptoms is also made difficult due to study specifics. Specifically, results vary among studies not only due to the instruments used, but also a) the lack of cutoff for the presence of the symptoms, b) small sample sizes, and c) the population studied (acute vs chronic). The prevalence of symptoms in COPD patients unsurprisingly varies widely. Ranges for dyspnea are from 32 to 65% [175], fatigue 17–95% [174] and depressive symptoms 27–79% [176].

It is challenging for clinicians to address these issues with individual patients. Assuming patients are on therapeutic doses of medications, an important next step in treatment can be pulmonary rehabilitation (PR) programs. As part of PR identifying various sources of symptoms and impact on HRQOL can occur. For example, if fatigue contributes to the intensity of dyspnea, a supervised and supportive exercise program, monitored by the staff can assure patients that their dyspnea with exercise is not harmful and can improve both dyspnea and fatigue. Improvements in exercise on the other hand, have repeatedly been shown to occur, such that Cochrane Reviews no longer accepts systematic reviews of exercise in PR.

In summary, symptoms and HRQoL must be evaluated in patients with COPD. Symptoms and HRQoL measurement should be used as part of the plan of evaluation and treatment consideration.

2.2.1. Key points

- The most common symptoms in people with COPD are dyspnea and fatigue
- These symptoms result from complex physiological and psychological factors, therefore a single treatment cannot be identified for all patients
- Symptoms and health related quality of life are not necessarily separate issues, as health related quality of life instruments often rely on symptoms as part of the assessment

2.3. Promoting physical activity across the spectrum of COPD severity. Martijn Spruit, Thierry Troosters

Maintaining and improving physical activity is an important challenge in the long-term management of patients with COPD, irrespective of the degree of airflow limitation [177]. Indeed, physical inactivity may already be present in newly-diagnosed patients with mild-to-moderate COPD [178]. Moreover, physical activity is poorly related to the forced expiratory volume in the first second in patients with an established diagnosis of COPD [179].

While healthy levels of physical activity in terms of volume and intensity are required to prevent inactivity-related comorbidities [180], physical activity requires an increase in pulmonary ventilation, and may inevitably lead to distressing symptoms of dyspnea [181]. Increasing physical activity can only be a consequence of patients' changing behavior. Therefore successful programs should include behavior change strategies. In symptomatic patients such behavioral change programs are likely best combined with optimal symptom management including interventions that maximize pulmonary function (e.g., bronchodilator therapy) and interventions that reduce pulmonary ventilation for a given activity (e.g., exercise training). Behavior change interventions can be complex in design. However, simple and easy to implement interventions, such as the use of a step counter by patients in combination with provision of a physical activity goal are available and seem effective in subgroups of patients [182], particularly in those with sufficient exercise tolerance [183] (the so-called "can do-don't do" phenotype [184].

In patients with a very poor exercise tolerance the likelihood of being successful in changing physical activity is low, and perhaps in these patients the main focus of programs should be to enhance exercise tolerance prior to 'pushing' patients towards a more active life style [185]. In that paradigm, it is important to take into account that a simple increase in the volume of physical activity does not constitute a training stimulus sufficient to enhance exercise tolerance. If an increase in exercise capacity is desired, exercise training at sufficient intensity is required.

Connecting the dots, it seems important to classify patients based on their exercise tolerance and physical activity level. In patients with insufficient physical activity, improving physical activity is an important goal for therapy using behavioral change techniques. If, however, patients lack exercise tolerance this will be a difficult task and clinicians may want to focus first on enhancing exercise tolerance using optimal pharmacotherapy and exercise training. Once the capacity of patients is optimized clinicians need to shift the focus to optimizing physical activity.

2.3.1. Key points

- Maintaining and improving physical activity is an important challenge in the long-term management of patients with COPD, irrespective of the degree of airflow limitation
- Exercise capacity is necessary for physical activity, but behavior change is a key component of increasing physical activity
- Since both exercise capacity and physical activity are related to long term outcome, patient assessment and treatment strategies should address both

2.4. Pushing pulmonary rehabilitation education for meaningful impact. Felicity Blackstock, Chris Garvey

As with many aspects of healthcare, the COVID-19 pandemic that commenced in 2020 has led to innovation in education for people with

chronic respiratory conditions. Of significant note is the embedding of technology in connecting patients with healthcare providers and each other to learn about their condition. In addition to technology enabled learning, a greater breadth of countries from non-western orientated cultures have commenced evaluating the impact of patient education for people with COPD, paving the way for culturally and linguistically adapted education models. With healthcare services being stretched by COVID-19, a strong emphasis on self-management has emerged for patient education, moving beyond traditional models of information delivery to models that look at skills acquisition, coaching/mentoring, and application of knowledge for behavior change. The line between self-management intervention and education has been further blurred. A focus on new approaches to evaluation of the impact of education has also emerged.

The rate of uptake of technology-enabled patient education has been increasing exponentially in the last 10 years, made even more rapid with the public health requirements instigated to stem the spread of COVID-19 from early 2020 onwards. In chronic respiratory disease, upwards of 80% of papers examining the impact of technology enable patient education have been published since [186]. The early papers focused on website delivery of information, but more recently social media, smart phone applications, virtual reality/gaming, and 1:1 or group telehealth have been used to engage patients in education on their respiratory condition [187–191]. Technology enabled patient education has comparable improvements to more traditional education models for knowledge acquisition and health outcomes, with improvements observed in quality of life, physical activity and self-care [186]. Overall using technology for learning was well received by the majority of patients with COPD, including reporting ease of use, ready access any time of day, relevant activities and information, and saved time not needing to travel to see healthcare providers [186]. Although, patients did raise concerns that it was harder to form a relationship with their healthcare provider and peers [188], and mechanisms that facilitate interaction with the learning materials and people through technology platforms need to be considered in all technology enabled patient education.

A shift has been observed in patient education for people with chronic respiratory conditions from focusing on didactic content delivery to individualization and the need to develop self-management capabilities. The new models emerging include mentoring/coaching in applying new skills in everyday life [192], peer-to-peer learning through social media and applications [193], and a strong focus on psychomotor skill development [194]. Studies have begun to look beyond a patient knowing information to supporting patients to apply their new knowledge and skills in the context of pulmonary rehabilitation. The delineation between self-management interventions and patient education in pulmonary rehabilitation has been blurred [195]. New education models include providing feedback to ensure the learning that is occurring is correct. Such an approach has been recently demonstrated effective in the systematic review by Jia et al. [194], where pharmacist led education that incorporated feedback to the patient for correct inhaler technique and medication routine adherence was provided and improved home medication routines. Studies have also explored the learning needs of people with differing chronic respiratory conditions, allowing healthcare providers to think beyond the “one size fits all model” of education in pulmonary rehabilitation. Specifically, educational focus for interstitial lung disease (Holland et al., 2019) and bronchiectasis have been established [196].

There has been a significant increase in the number of countries studying the impact of patient education for people with chronic respiratory conditions. Globally, research evaluating patient education remains predominately from Northern American, Australia and Europe, however in the last five years studies have emerged from China, Oceania, Nepal, Korean, Sri Lanka, Iran, India, Hong Kong, and Saudi Arabia. Unfortunately details on the models are not well reported and therefore lessons learnt on cultural adaptations of patient education are not obvious in the literature. A future direction for reporting of studies of patient education needs to include more details on learning outcomes, curriculum design, and educational approaches of facilitators. This will allow deeper comparison of approaches across different cultures and healthcare models to determine best practice for culturally and linguistically diverse communities.

Evaluation of impact remains focused on knowledge and health outcomes, which unfortunately continues to limit scope of the impact that education can have. Studies continue to examine the core outcomes of note in rehabilitation for people with COPD and other chronic respiratory conditions, including quality of life, physical activity levels, and healthcare utilization. A small number of studies have examined new impacts like behavior change, patient activation and attendance and completion of healthcare interventions, like pulmonary rehabilitation. Attendance and completion of pulmonary rehabilitation appears to improve with patient education [195,197,198], suggesting that while education may not improve healthcare outcomes compared to exercise alone [199] if more people are completing pulmonary rehabilitation when education is provided, education is having a significant impact on population health.

Future directions for new models of patient education appear to include technology-enabled learning, enhancing face-to-face education, and overcoming geographical barriers for accessibility and flexibility to when learning can occur. Models of education should focus on not just knowledge acquisition, but also application of knowledge for behavior change in daily life with motivational and mentoring/coaching support. True individualization, where patient learning needs, motivations and cultural orientation are being thought of is present, but further work is needed. Educational approaches that confirm optimal learning has occurred by assessing the patient’s knowledge, skill and behavior change, with subsequent provision of feedback to ensure understanding. Finally, the evaluation of patient education looking at new outcomes that education can impact such as confidence, motivation and adherence with health behavior change, will direct pulmonary rehabilitation education models for the next 10 years.

2.4.1. Key points

- The COVID-19 pandemic has served as a catalyst to innovation in education for individuals with COPD and other chronic respiratory conditions.
- The addition of technology-enabled learning has paved the way for individualized, culturally appropriate education models
- Models of education should focus on not just knowledge acquisition, but also application of this knowledge (with motivational and mentoring/coaching support) to optimize behavior change in daily life

3. Non-pharmacologic management of COPD

3.1. Pulmonary rehabilitation: state of the science. Sally Singh, Rebecca Crouch

There is overwhelming evidence to support the delivery of pulmonary rehabilitation, the most recent Cochrane Review [124] evidenced significant improvements in exercise capacity, health related quality of life and breathlessness. Indeed, they concluded that no further trials were required, and suggested that researchers should focus their efforts on understanding the optimal duration, components, and delivery of rehabilitation services. The focus of the Cochrane Review was on center based supervised rehabilitation, commonly as an outpatient in either a hospital or community-based facility. There have been subsequent reviews describing the benefit of pulmonary rehabilitation in diseases other than COPD, for example interstitial lung disease or bronchiectasis [123,200]. The evidence for rehabilitation has its origins in the early 1900’s where rehabilitation started as an intervention in post TB lung disease and COPD [201]. More recently in an ATS Workshop Report

pulmonary rehabilitation was acknowledged as a key priority for low-and-middle income countries [202]. It may be an important scientific development to consider the appropriate cultural adaptation of pulmonary rehabilitation in these settings [203,204]. Early work has been described in Kyrgyzstan for example where the fundamental principles of exercise training have been intertwined with singing and ball games after detail qualitative work to understand the needs of the post TB lung disease population [205].

The science of pulmonary rehabilitation is constantly evolving; perhaps the most obvious development over the last couple of years has been the development of alternative modes of delivery not least because of the impact of the pandemic [206–208]. The science of developing technological solutions is potentially different to the traditional model of developing and refining rehabilitation programmes and may deploy approaches, to collaborate with software engineers, healthcare providers and payers to facilitate successful implementation [209]. Furthermore, there has been international acknowledgement that, with adaptations, Pulmonary Rehabilitation may service as the basis for an intervention for those with Long Covid/post Covid syndrome [210,211]. To date there has been one randomised controlled trial reported [212] and several other cohort trials that must be considered positively [213,214]. The challenge currently with the Long Covid population appears to be the complex symptom of fatigue although data from the COPD population and early data from the long Covid population would suggest that a symptom titrated exercise programme can favorably influence this symptom.

There has been an increasing literature describing alternative formats of rehabilitation, from simple home-based programmes [215,216] through to more complex digital programmes. The latter could involve video conferencing [217], web-based applications through to smart phone applications [218].These developments have yielded mixed results but may be considered as an alternative to centre-based rehabilitation, especially if there are challenges of accessibility and timing of the supervised programme. Increased choice of modes of delivery inevitably required a collaborative shared decision-making process to identify the most appropriate mode of delivery [219]. The extension of this principle is personalized rehabilitation, where the intervention is matched to the phenotype of the individual. This requires a comprehensive assessment at baseline to describe the deficits or 'treatable traits' [117], it is likely that the 'science' of pulmonary rehabilitation will develop in this direction and become a more sophisticated intervention rather than the 'one size fits all approach'. The science will be supported by the exploration of adjuncts, novel interventions, and new pharmaceutical therapeutics to be delivered alongside conventional exercise training.

3.1.1. Key points

- Novel and emerging pulmonary rehabilitation models in clinical practice have promise in improving access and widening participation
- Models of pulmonary rehabilitation must be adapted to better serve individuals in low-and-middle income countries
- Personalizing pulmonary rehabilitation will enable health care providers to match the need of the individual and move away from the 'one size fits all approach'

3.2. Morphologic treatments of emphysema. Jerry Criner, Antarpreet Kaur

Alterations in lung structure that occur with COPD may be important contributors to patient's symptoms, especially dyspnea. Dyspnea results from increased airflow limitation due to increased airway wall inflammation and thickness, bronchoconstriction, mucous hypersecretion, and emphysematous destruction of the lung parenchyma. Morphologic changes in lung structure causes lung hyperinflation. Excessive gas trapping can follow normal expiration and further worsen during exercise [220]. Hyperinflation not only leads to dyspnea, but exercise limitation and respiratory failure as well as physiological changes to the thorax impairing cardiac function. Hyperinflation is also associated with an increase in COPD exacerbations, impaired cardiopulmonary function, and skeletal muscle dysfunction [221,222]. Severe emphysema causes pruning of the pulmonary capillary bed, as well as impaired ventilation and perfusion matching causing hypoxemia and hypercapnia and pulmonary hypertension. Increased intrathoracic pressure may also lead to cardiac dysfunction [223].

These airway and lung parenchyma morphological changes provide potential targets for treatment that may alleviate dyspnea, reduce cough and mucous production, and improve quality of life. Morphological treatments for COPD range the spectrum from airway predominant to emphysematous treatments. Airway predominant treatments are currently the subject of Phase III clinical trials; emphysematous based treatments include bullectomy, lung volume reduction surgery, bronchscopic lung reduction and in select cases, lung transplantation. Each of these therapies are succinctly reviewed below.

3.2.1. Bullectomy

Giant bullectomy is a rare, but effective procedure for removing bulla that occupies more than one-third of a hemithorax and compresses adjacent viable lung tissue. Reductions in dyspnea, and improved lung and cardiac performance, as well as exercise tolerance has been reported [224].

3.2.2. Lung volume reduction surgery

Lung volume reduction surgery improves lung mechanics and functional capacity, but also pulmonary artery pressures and ventricular function.

Lung volume reduction surgery (LVRS) resects 20–35% of emphysematous tissue in each hemithorax via sternotomy or video-assisted thoracoscopic surgery (VATS). Removal of the emphysematous lung tissue improves hyperinflation and lung function. Results of National Emphysema Treatment Trial (NETT) have demonstrated improvement in symptoms, physiology, and mortality in a specific group of COPD individuals with upper lobe predominant emphysema, low exercise capacity and FEV1 and DLCO >20%. 90-day mortality was higher in the surgical group (7.9% versus 1.3%), however, this leveled out by the end of 5-year period (0.11 deaths per person here in both groups). Subgroup analysis in patients with upper lobe predominant disease, and low exercise capacity, (<40 W in males, <25W in females) had lower risk of death with LVRS and a significant increase in exercise capacity and health-related quality of life improvement at 2 years. Patients with more severe disease evident by FEV1 < 20%, and DLCO <20% or homogenous emphysema had higher perioperative mortality compared to standard care [151]. Benefits seen in dyspnea scores and health-related quality of life for long-term, and even demonstrated at 4 years after surgery. Long-term survival benefit was demonstrated in patients with upper lobe predominant disease and low exercise profile following rehabilitation [159].

3.2.3. Bronchoscopic lung volume reduction (BLVR)

Multiple modalities for minimally invasive lung volume reduction have been trialed for lung volume reduction. These include thermal vapor ablation, biologic agents like foam sealant, airway bypass stents, self-activating metallic coils, and endobronchial valves. The only FDA approved modality currently available is endobronchial valves.

3.2.4. Foam sealant

Aeriseal is a form like liquid used in bronchioles to create an inflammatory reaction that subsequently leads to fibrosis to achieve lung volume reduction. Initial study for this technique included 14 patients in whom the treatment yielded a significant improvement in FEV1, walk distance and quality of life [225]. Subsequently in 2015, ASPIRE study aimed at comparing standard of care with medical therapy and foam

sealant in 95 patients. The study was terminated early for high morbidity, 43% hospitalization and mortality, 2 deaths in the treatment group [226]. This treatment is not currently recommended or approved for use.

3.2.5. Thermal vapor ablation

Bronchoscopic thermal vapor ablation involves instillation of heated vapor to induce inflammatory reaction and subsequent volume loss in the area with emphysema. A dedicated software is used to determine the target and dose of steam vapor for inducing lung volume reduction. Initial study that evaluated this therapy included 44 patients with for upper lobe predominant emphysema. It showed a significant improvement in lung volume, 48% reduction, along with 17% increase in FEV1. Exercise tolerance in terms of 6-min walk distance (improvement by 46.5 m) and quality of life (SGRQ reduction by 14 points) was also demonstrated at 6-month follow-up [227]. Serious adverse events related to the procedure correlated with the volume of the treated lobe in its incidence and severity [228]. The subsequent study known as the STEP-UP trial used stepwise treatment to bilateral lungs in a sequential fashion. At 6-month follow-up, vapor ablation resulted in a statistically significant increase in FEV1 (14.7%) and reduction in SG RQ (decreased by 9.7 points). However, adverse effects included higher rates of COPD exacerbation (24% versus 4%) and higher rates of pneumonia (18% versus 8%) in treatment group [229]. This therapy is not widely available for clinical use.

3.2.6. Airway bypass stents

Expandable silicone coated, paclitaxel eluting stents are placed endobronchially from emphysematous tissue into airways to promote emptying of trapped air and hence achieve reduction in lung volumes. The EASE trial (Exhalation airway stents for emphysema), published in 2011, included patients with homogeneous emphysema, with FEV1<50%, and air trapping with RV >150% [230]. The trial showed an improvement in FEV1, and dyspnea scores at 1 month, which did not sustain at 12 months. Mucous plugging and tissue granulation leads to blockage of stents and lack of efficacy at 12 months. Adverse effects included higher rates of COPD exacerbation and infection as compared to controls (15.9% versus 8.4%.). These stents are not currently approved for treatment.

3.2.7. Self-activating coils

PneumoRx coils are self-activating nitinol coils that work by compressing lung parenchyma once they are deployed leading to volume reduction with atelectasis. There are reduced airflow interrogated segments of the lung because increased distribution to healthy parenchyma, hence improving elastic recoil. Treatment involves between 8 and 14 coils in one session in each lung under fluoroscopic guidance.

The placement of coils does not require absence of collateral ventilation. The biggest trial that looked at efficacy of these coils was the RENEW trial, which was a multinational, randomized control trial involving 315 patients [231]. It demonstrated that patient treated with growth and increase in FEV1 (increased by 7%), increase in exercise capacity (10.3 m increase in 6-min walk distance), and improvement in quality of life (SGRQ decreased by 8.9 points). The rate of complications including major complications (hospitalization and life-threatening or fatal events, (34.8%), pneumonia (20%), and pneumothorax (9.7%) was higher in patients with coil placement [232]. A gradual decrease in therapeutic benefit was observed after 1 year [233]. Post-hoc analysis of RENEW trial revealed that patients with highest emphysema scores and worse air trapping benefited the most from the treatment. This therapy is not FDA approved at this time.

3.2.8. Endobronchial valves (EBV)

Endobronchial valves are one-way valves that allow air to escape the lung during expiration but prevented from entering during inspiration. In absence of collateral ventilation, the valves induce lobar atelectasis and lung volume reduction consequently. The Zephyr endobronchial valve and Spiration valve system are both approved by the FDA. The Zephyr valve is a duckbill shaped valve with a silicone membrane supported by a nickel titanium frame. This design involves airflow and mucus to egress from the target lobe bronchus. The Spiration valve system is an umbrella shape valve with Nitinol struts and a polyurethane umbrella.

VENT trial (Endobronchial Valve for Emphysema palliation Trial) was the initial trial published in 2010 that demonstrated statistically but not clinically significant improvement in FEV1 (6.8% improvement), 6 MW distance (20 m improvement) and SGRQ score (3.4-point reduction). However, this trial did not screen patients based on absence of CV or heterogeneity in emphysema distribution and post hoc analysis revealed clinical benefit only in patient with fissure integrity [234]. This led to modification of selection criteria based on absence of collateral ventilation, and multiple subsequent trials that excluded patients with collateral ventilation. The two pivotal studies that led to FDA approval for the valves were the LIBERATE trial for Zephyr valves [235] and EMPROVE trial [236] for the Spiration valve system.

LIBERATE was the first multicentric randomized controlled trial conducted at 24 international sites to evaluate the efficacy and safety of the Zephyr valve in patients with heterogenous emphysema and no collateral ventilation. 190 patients between 40 and 75 years, with bronchodilator FEV1 between 15% and 45% predicted greater than 100% of predicted, with a longer than 175% predicted, diffusion capacity greater than 20% predicted, and 6-min walk distance between 100 and 500 m after completion of supervised pulmonary rehabilitation program were randomized to valve or standard of care arms. More than 50% obstruction of target lobe defined by percentage of voxels less than −910 Hounsfield units on CT, and heterogeneous emphysema defined by absolute difference of more than 15% and destruction scores between target and ipsilateral lobes. Eligible patients were assessed with the Chartis System to rule out CV. At 12 months after procedure, 47.7% EBV patients had a greater than 15% increase in postbronchodilator FEV1 as compared to 16.8% of standard care patients. Increase in 6-min walk distance by more than 25 m was seen with 41.8% EBV patients and reduction in SGRQ by more than 4 points were seen in 56.2% patients 12 months. Reduction in supplemental oxygen use and gas exchange were also achieved at 12 months. Respiratory adverse effects were significantly higher in EBV treatment group (35.2% versus 4.8%, $p < 0.001$) in the immediate postoperative phase (up to 45 days). However, between 45 days and 12-month period, the frequency of events was comparable between groups (33.6% versus 30.6%). Lower incidence of COPD exacerbation, pneumonia and respiratory failure was seen in the EBV group. Significantly higher pneumothorax rate, 46 pneumothoraces (34.4% rate) was seen in EBV group at 12 months. 38 required a chest tube and 12 required removals of at least 1 valve. 76% pnemothoraces happened within the first 3 days post-procedure [235].

EMPROVE trial published in 2019 was a multicentric randomized controlled trial to evaluate the efficacy and safety of Spirations valve system. 172 individuals aged 40 years or older with severe obstruction, post-bronchodilator FEV1 <45%, hyperinflated with TLC>100% and Residual volume >150% of predicted, with >40% emphysematous destruction in the target lobe (−920 HU) and >10% diseases severity difference between ipsilateral lobes and fissure integrity >90% defined by HRCT were randomized. At 6 months, average improvement in FEV1 in treatment group was 99 mL (69–128 mL) as compared to 2 mL (−30 to 26 mL) change in the control group. At 12 months, treatment group improved significantly in FEV1 as opposed to the control group (+67 mL vs. −32vmL) with a between group difference of 99 mL [19]. Responders defined as >15% change in FEV1 were significantly higher in the treatment group (30.4%, 95%CI, 16.8%–42.5%). SGRQ had a reduction of 9.5 points (−14.4 to-4.7) in the treatment group as well as improvement in dyspnea with decreased in mMRC by −0.9 (−1.2 to −0.6) at 12 months. 6 MW distance although improved did not reach statistical significance (6.9 m, 95% CI -14.2 to 28.2).

Serious adverse events in short-term (0–6 months) were significantly higher in treatment group as compared to control (31% vs.11.9%,95% CI, 5.9–29.7). There was a 12.4% (95% CI, 4.6–18.6) increased incidence of pneumothoraxes in treatment group with 66% of these happening within 3 days of the procedure. 69% patients had one or more valves removed for pneumothorax management. In the long-term phase, (6–12 months post-procedure), there was no statistically significant difference in serious adverse events between the treatment and the control groups (21.4% vs 10.7%).

Overall, in all trials, any respiratory complication rate was 31–35% of patients compared to 5–12% in controls [237]. Pneumothoraces occurred most in the immediate post-operative phase and happen due to rapid re-expansion after effective targeted lobe volume reduction.

A framework for referral for the eligible patients has been defined by the GOLD committee as follows (Fig. 1).

The images of all the bronchoscopic LVRS devices are shown in Fig. 2.

3.2.9. Airway predominant treatments

Chronic bronchitis is a common and significant contributor to a worsening of patient's symptoms and quality of life with associated increases in mortality. No specific medical intervention has been shown to alleviate chronic bronchitis in any clinically meaningful way. New interventions have been proposed to address this clinical void by using either metered dose nitrogen cryospray [238]or rheoplasty [239] to eliminate airway epithelium goblet cell hyperplasia and reduced mucous hypersecretion. Phase III randomized clinical trials are currently underway to evaluate the efficacy of these therapies. Targeted lung denervation is another therapy currently undergoing phase III clinical trial study to determine its impact of frequent moderate or severe exacerbations in patients already on maximal inhaled respiratory treatment [240,241].

3.2.10. Lung transplantation

In patients with severe impairment in lung function, associated pulmonary hypertension or combinations of severe airway and parenchymal morphological damage, no specific airway or parenchymal, interventional is feasible and only lung transplantation is a viable option [224]. Lung transplantation has been shown to improve health status and functional capacity but not prolong survival in patients with COPD [242]. Most transplants in patients with COPD are double not single transplants; bilateral transplant have been shown to increase survival greater than single transplant ins patients with COPD especially those less than 60yrs of age. Median survival has increase to 5.5 years post lung transplantation in patients with COPD [243]. Lung transplantation is limited by donor organ supply and complications are similar to patients receiving lung transplantation without underlying COPD [244].

3.2.11. Summary

A variety of morphological treatments have been studied and continue to be studied in the care of patients with COPD. Future works hopefully will identify newer, less invasive therapies than lung transplantation or lung volume reduction surgery to interventionally treat patients with a variety of lung and airway abnormalities.

3.2.11.1. Key points.

- Morphologic treatments for COPD span the spectrum from airway-predominant to emphysematous treatment
- Emphysema-based treatments include bullectomy, LVRS, bronchoscopic lung reduction, and (in select cases) lung transplantation
- Airway predominent treatments currently under investigtion include metered-dose nitrogen cryospray or rheoplasty and targeted lung dennervation

3.3. Noninvasive ventilation in COPD. Nicolino Ambrosino, Michael Dreher

3.3.1. Acute exacerbations of COPD

About 20% of patients with Chronic Obstructive Pulmonary Disease (COPD) exacerbations may show acute hypercapnic respiratory failure, an indicator of respiratory muscle insufficiency associated with increased death risk [245]. Acute respiratory acidosis develops when respiratory muscles fail to achieve adequate alveolar ventilation and the respiratory pump decompensates [246].

Noninvasive ventilation (NIV) should be considered in exacerbations of COPD when pH $\leqslant$ 7.35 due to increased $PaCO_2$ >45 mmHg. In addition, when respiratory rate >20–24 breaths·min^{-1} despite standard medical therapy and co-existing type 2 (hypercapnic) respiratory failure to prevent acute respiratory acidosis, to prevent or as an alternative to invasive mechanical ventilation (MV), to provide ventilatory support in do not intubate patients [247,248].

It is the preferred choice for hospitalized COPD patients developing respiratory acidosis: a NIV trial prior to invasive MV, should be attempted unless immediate deterioration. It should not be used in non-acidotic hospitalized hypercapnic patients [248].

An improvement in either pH or respiratory rate, or both, is a good predictor of a successful outcome: the response is usually seen within the first 1–4 h after initiation [249]. There is no lower limit of pH below which a NIV trial is inappropriate, however hypercapnic encephalopathy can be a contraindication. In addition, the lower the pH, the greater the risk of NIV failure, and patients must be closely monitored with rapid access to invasive ventilation if not improving. The patient selection must consider the available location. There is evidence of effectiveness in ICU, general ward and emergency department depending on severity. Different modalities of ventilation and types of interfaces can be used [6] [250]. The expertise of professionals is crucial and overall, NIV is cost-effective [250–253].

3.3.2. Chronic hypercapnic respiratory failure due to COPD: the importance of addressing PaCO2

Up to 25% of patients with COPD, GOLD stage 3 and 4 suffer from chronic hypercapnia [254], with treatment of chronically elevated PaCO2 performed mainly using long-term nighttime non-invasive ventilation (NIV) [255]. A goal of NIV is to effectively reduce elevated $PaCO_2$ levels, through applying sufficient levels of inspiratory positive airway pressure (IPAP) [256,257]. However, controversy exists whether stable hypercapnic COPD patients should be treated with NIV [258,259], no doubt reflecting a disparity in effectiveness among several studies: some were unable to demonstrate significant benefit [260,261], while other, smaller physiological studies did [262]. Arguably, the discrepancy in outcome reflects the ability or inability of the intervention to reduce elevated PaCO2 levels with NIV. With a titrating approach to stepwise increases in IPAP levels, NIV may result in improvements in quality of life and reduction in mortality [263]. Furthermore, long-term NIV can be associated with a reduction in hospitalizations when initiated in patients after successful treatment of acute-on chronic respiratory failure [264].

There is no global recommendation on when to start long-term NIV in stable hypercapnic COPD patients. The German respiratory society recommends: 1) to start long-term NIV in patients with COPD and symptoms of chronic hypercapnia when $PaCO_2$ is > 50 mmHg during daytime spontaneous breathing or >55 mmHg during nighttime spontaneous breathing [265,266]; 2) to start long-term NIV in patients after acute hypercapnic exacerbation with dependency on MV during the hospitalization phase if there is persistency of hypercapnia (defined as $PaCO_2$ >53 mmHg at least 14 days following acute MV).

The American Thoracic Society guidelines recommend with various grades of certainty [267]: 1) the use of nocturnal NIV in addition to usual care for stable hypercapnic patients with COPD; 2) a screening for obstructive sleep apnea before initiation; 3) not initiating long-term NIV during an admission for acute-on-chronic hypercapnic respiratory failure, but after reassessment at 2–4 weeks after resolution; 4) not using an in-laboratory overnight polysomnogram to titrate NIV in patients initiating NIV; and 5) NIV with targeted normalization of $PaCO_2$ in these patients.

Lastly, tele-monitoring programs may be useful for safety and effectiveness of long-term NIV [268].

3.3.2.1. Key points.

- NIV is the preferred option to treat hospitalized COPD patients with acute respiratory acidosis as it improves outcomes through preventing invasive mechanical ventilation
- NIV should be considered in exacerbations of COPD when, despite standard medical therapy, pH is equal or less than 7.35 resulting from elevations of $PaCO_2$ >45 mmHg. and respiratory rate is greater than 20–24 breaths·min^{-1}
- NIV for chronic hypercapnic respiratory failure has had mixed outcomes, arguably resting on its ability or inability to reduce PaCO2; potential benefits include improvements in quality of life and reductions in hospitalizations and mortality

3.4. Prolonging life and reducing health care utilization in COPD. Peter Lindenauer, Dick ZuWallack

Traditional goals in treating the COPD patient include decreasing symptom burden, improving functional and health status, and reducing the frequency and impact of respiratory exacerbations [269]. Adding to these are reducing the rate of further decline of lung function in current-smokers and improving survival by prescribing long-term, supplemental oxygen therapy in those with significant hypoxemia [149,150]. More recently, reducing healthcare utilization and decreasing mortality risk have risen to the forefront, based on their obvious importance to the patient and society plus the realization through ongoing clinical studies that they are at least partially achievable.

Patients with COPD experience dramatic and prolonged deterioration in health status following a hospitalization for a respiratory exacerbation and remain at high risk for rehospitalization and death for weeks to months. Consequently, this period has become a focus of interventions intended to achieve positive outcomes. Comprehensive pulmonary rehabilitation, which includes individual goal setting, an interdisciplinary approach to patient care, exercise training, education, self-management strategies, and integration of care, is well-suited to meet the increased risks in this setting. This view is supported by several small, randomized trial, as well as more recent observational studies.

A recent meta-analysis on the effects of pulmonary rehabilitation following an exacerbation included a total of 13 trials, involving some 801 patients. In four of the studies the PR intervention was limited to supervised exercise, while the remainder involved a comprehensive, multi-component interventions. Four of the studies, including 319 patients, reported on mortality, while 6 studies, including 365 patients, reported on readmission. At the end of the PR intervention the pooled relative risk of mortality was 0.58 favoring early PR (95% CI 0.35–0.98), whereas at the longest follow-up was 0.55 (95% CI 0.12–2.37). Similarly, at 3–12 months of follow-up, the pooled effect of pulmonary rehabilitation on readmission was 0.47 (95% CI 0.29–0.75).

In a large observational study Lindenauer and colleagues [157] reported on the association between initiation of pulmonary rehabilitation within 90 days of a COPD discharge following an exacerbation and all-cause mortality over the subsequent year. Of 197,376 Medicare beneficiaries discharged, only 2721 (1.5%) of this group initiated pulmonary rehabilitation within 90 days. Of the total group, 19.4% died within one year. However, compared to those not receiving pulmonary rehabilitation, the hazard ratio for mortality in the rehabilitation group was 0.63 (95% CI: 0.57 to 0.69), suggesting a dramatic survival benefit that few, if any, interventions can match. Furthermore, there was a dose-response relationship between the number of rehabilitation sessions completed and increased survival benefit.

Second, in a subsequent study by the same investigators using multistate modeling techniques [270], those initiating pulmonary rehabilitation within 90 days of the hospital discharge had a hazard ratio for all-cause rehospitalization at one-year of 0.83 (95% confidence interval: 0.77–0.90) compared to those not receiving this treatment.

These studies point towards impressive benefits from pulmonary rehabilitation in the area of survival and hospitalization in the COPD patient following an exacerbation. Prominent effects such as these naturally lead to inquiry of the mechanistic underpinnings of its success. Unfortunately, there is no strict standardization of the pulmonary rehabilitation intervention, and pulmonary rehabilitation is almost universally provided as a "package." Thus, it is nearly impossible to make inferences on which of its components is (are) effective in this regard. Furthermore, it is not out of the question that *emergence* (when an entity has properties its components on their own do does not have) is operative here. Having stated the above limitations, several elements integral to the rehabilitative process have, on their own, been demonstrated to improve survival or reduce health care utilization. To name a few: 1) reductions in dyspnea and improvements in functional status and exercise capacity from exercise training [42,45,271,272]; 2) decreased sedentary lifestyle through promotion of physical activity [29,273–275]; 3) improved adherence to therapies, including supplemental oxygen, through educational and self-management strategies [276]; 4) improved lean body mass associated with nutritional support and exercise training [277–281]; 5) early recognition and prompt, appropriate treatment of the respiratory exacerbation via self-management strategies [282]; integration and coordination of care [283,284]; and 6) addressing common comorbidities that increase total disease burden and prognosis [285].

3.4.1. Key points

- The COPD exacerbation is bad, resulting in dramatic and prolonged deterioration in health status and high risk for rehospitalization and death
- Comprehensive pulmonary rehabilitation, which includes individual goal setting, an interdisciplinary approach to patient care, exercise training, education, self-management strategies, and integration of care, is well-suited to meet the increased risks in this setting
- A systematic review of pulmonary rehabilitation following COPD exacerbations and a large propensity study of discharged Medicare beneficiaries in this setting demonstrate health care utilization and survival benefits

4. Optimizing delivery of care for COPD

4.1. Telemedicine: managing severe COPD and its exacerbations. Jean-Luis Pepin, Roberto Dal Negro

4.1.1. Rationale for telemedicine for COPD exacerbations

The exacerbation of COPD, best defined as a *"sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations that is acute in onset and may warrant additional treatment in a patient with underlying COPD,"* [286] often causes profound increases in symptoms, impairment in health status, and increases in risk for health care utilization and mortality [1,287]. Implementation of collaborative self-management strategies within the scope of disease management,

including education and use of written exacerbation action plans, health coaching, and coordination of care [288] can reduce the negative impact of exacerbations [282]. Patients who might benefit most from these strategies include those with severe respiratory disease, high symptom burden, prominent systemic and co-morbid conditions, increased frequency of exacerbations, and high risk of hospitalization. Meeting the needs of this heterogeneous population can be daunting. Adding to this problem is heterogeneity of medical care, both locally and across systems, with some patients having suboptimal access to appropriate and timely interventions.

Telemedicine interventions for those COPD patients at high risk for exacerbations, poor outcome, or suboptimal access to medical interventions might provide benefit through facilitating the transfer of information in two directions: from the patient to the health care providers and from the health care providers to the patient and family (telemonitoring and tele-education, respectively). Examples of monitoring include respiratory symptoms, such as cough and dyspnea, and vital signs, including oxygen saturation measurements and weight measurements. Examples of information transferring from the health care provider to the patient include changes in care necessary to treat the exacerbation or complications, such as instituting corticosteroid and/or antibiotic treatment or increasing diuretic therapy. Optimal benefits of telemedicine rest on timeliness and accuracy of information transfer.

Despite the potential of telemedicine interventions for early recognition of exacerbations (and dealing with emerging complications such as heart failure) and prompt initiation of appropriate treatments, a systematic review and meta-analysis of randomized trials of this form of treatment had mostly negative results [289]. Because of the heterogeneity of trials, more knowledge is necessary to determine which aspects of telemedicine may prove beneficial in specific situations. For illustrative purposes, what follows is the concept, implementation, and general results of one practically successful intervention.

4.1.2. An example of a regional telemedicine system for the management of COPD exacerbations

4.1.2.1. Background. A pioneer project utilizing telemedicine, supported by the Department for Public Health of the Veneto Regional Government and the National Research Council, was initiated in 1990; its general aim was to provide patients with novel therapeutic options in the home that may reduce hospitalization risk and improve quality of life. Industry and clinicians worked together to develop and refine technical support, that included exacerbation monitoring and management of long-term oxygen treatment (LTOT) for patients with severe respiratory disease.

The telemedicine system consisted of one central unit (CU) and several peripheral units (PU's) located in the patient's home. Transmission of data to the CU occurred several times a day, with the type and timing of information (e.g., vital signs and functional data) set by the protocol, individualized to each patient (reflecting the disease and its severity) and agreed to by the specialist staff. When needed, patients also had the opportunity to directly send additional information to the CU, transmit a priority message to the specialist group, or call for an immediate intervention (SOS) by pushing a red button which was easily visible on the top of the domiciliary equipment. The latter priority message resulted in both visual and acoustic signals which remained until addressed by the CU operator(s). If needed, an ambulance would be dispatched immediately from the Hospital Lung Department to the patient's home.

4.1.2.1.1. PU's could include the following.

- Pulse-oximetry, to record peripheral blood oxygen saturation and heart rate; this has a minimum recording time of 5 min
- Electrocardiogram (ECG) tracings
- Spirometry
- Capnography
- For those using mechanical ventilation, data from these devices
- Daily adherence with the oxygen prescription and use for those treated with LTOT
- Visual, face-to-face contact with the healthcare providers

Emphasis was given to prompt and thorough training of patients and their caregivers (approximately 95% were relatives) in the use of the PU's. In general, devices utilized at home were well-accepted and did not require a high level of skill or training on the part of patients or their caregivers [290–292]. Patients' and care-givers' suggestions and fulfilments were periodically solicited by questionnaire.

In their analysis of outcomes over a 10-year period, patients with severe COPD treated with long-term supplemental oxygen [293] were divided into two groups: those treated with standard medical therapy (n = 218) and those with telemedicine complementing standard therapy (n = 185). The later included exacerbation and clinical deterioration monitoring. The two groups were well-matched with respect to sex, age, FEV-1% predicted, PaO2 and PaCO2. While this analysis was not a randomized, controlled trial and therefore subject to potential selection and other biases, survival in the telemedicine group was significantly longer: 1240 versus 483 days, $p < 0.01$. While this result must be interpreted with caution in view of the non-randomized design, it nonetheless suggests that telemedicine has the potential to have beneficial effects for severe COPD patients with chronic respiratory failure who would be at high risk for exacerbations and poor outcomes.

In summary, telemedicine as a tool holds promise for managing care and improving outcomes in patients with COPD at increased risk for exacerbations. However, the mostly negative systematic reviews of this intervention indicate that – if it is to become consistently successful more research is needed in both optimizing patient selection and refining the intervention. The latter will undoubtedly require an approach based on the characteristics and needs of the patient as well as resources available in the particular health care system.

4.1.2.1.2. Key points.

- Telemedicine holds promise as a tool for the early recognition and initiation of treatment of COPD exacerbations, especially in those at increased risk and poor outcomes
- Despite its promise, a strong evidence base for its effectiveness is still lacking
- More research is needed in both optimizing patient selection and refining the intervention

4.2. Making pulmonary rehabilitation more accessible. Michael steiner, Anne holland

The enormous gulf between the scientific evidence underpinning the benefits of pulmonary rehabilitation (PR) and its delivery to patients with COPD in clinical practice is well-recognized. In the United States, less than 4% of Medicare beneficiaries with COPD have access to PR [169]. Many patients who are referred to PR never attend, and dropout rates are substantial [294]. Barriers related to health system organization include: 1) Inadequate funding based on policy; 2) Insufficient numbers of trained staff; 3) Geographic disparities in program access; and 4) Poor awareness of the benefits of PR amongst referrers. There are also important patient-level barriers, including travel to center-based outpatient programs for individuals with high symptom burden [200]. Even before the COVID-19 pandemic forced the closure of PR services across the globe, the PR community was beginning to address these barriers using remotely delivered program models. The aim of these developments has been to widen patient choice, and thereby enhance

access and uptake of PR. Given the well documented beneficial effects of completion of PR on subsequent healthcare use, this objective should be a priority for health policymakers.

A variety of novel models of PR have been tested in clinical trials, including virtual groups with real-time remote supervision and monitoring, telephone-based coaching models, and 'light touch' models using apps and websites. A Cochrane review including 15 randomized controlled trials and 1904 participants, 99% of whom had COPD, found similar outcomes of remotely delivered PR and the traditional center-based model [295]. Completion rates were higher for remotely delivered PR (93% vs 70%), which may be some indication of where the additional value of such programs lies. This emerging scientific knowledge has been timely to inform our response to the pandemic. By necessity, the uptake of remotely delivered PR in clinical practice has accelerated over the last 2 years, and it is likely that this has substantially reduced the time between generation and implementation of these research findings.

As PR services establish their future (post pandemic) models of care, it is timely to consider how remotely delivered models could be optimized to improve access, whilst maintaining the excellent patient outcomes for which center-based PR is justifiably known. Whilst it is clear that remotely delivered models led to clinically important benefits for patients with COPD in clinical trials [296], outcome testing differed in some respects from center-based programs. For example, models implemented during the pandemic frequently did not include exercise testing - a key to prescription of an effective exercise training load [297].

Some patients will not engage in remotely delivered PR programs for a variety of reasons, including comorbidities (e.g., those at high risk of falls, poor hearing or vision, cognitive impairment), lack of access to an internet-enabled device, low confidence in using the internet, or a preference for in-person care [298]. These patients are likely under-represented in existing research. The challenge for the PR community and healthcare providers more broadly is to support and accelerate innovation in the way PR is delivered whilst at the same time ensuring the efficacy of the therapy is preserved. This will require robust Quality Assurance of program components against accepted standards, and benchmarking of clinical benefit against expected outcomes or regional or national data (Quality Control).

Whilst randomized controlled trials have provided confidence that remotely delivered models will be a useful addition to the PR playbook, answering the outstanding clinical and scientific questions may require a different approach. The degree of supervision provided by remote models varies widely (e.g., real time supervision via videoconferencing vs text messaging and apps), and we do not yet understand which patient will do best under which model. Personalized or stratified therapy ensuring the program delivery model is matched to individual patient needs may best be developed through adaptive trial designs, in which participants are allocated to one of several PR models based on underlying characteristics. An understanding of the stratification metrics that will identify these characteristics is a key research requirement. Conventional patient-level randomized trials (whereby definition, patient choice is limited) may not be sufficient to move the field forward. Alternatives such as cluster randomization at a center level, or preference-based research, may offer greater insight. Future research which understands and incorporates patient choice of PR model is likely to be a critical driver of successful outcomes for this patient-centered intervention.

4.2.1. Key points

- Implementation of remotely delivered PR in clinical practice has accelerated during the COVID-19 pandemic
- Robust Quality Assurance and Quality Control are required to ensure that remote PR models deliver the excellent outcomes for which center-based PR is known
- A variety of PR models are now available; there is an urgent need to establish which patients are likely to do best using each model
- Future clinical trials should consider designs which offer opportunities for patients to choose their preferred model.

4.3. Collaborative Care Model (CCM) for COPD management. Jeffrey D. Marciniuk, Roger Goldstein, Jean Bourbeau

Management of COPD cannot be optimized in the acute care system, which is highly focused on the short-term treatment of unpredicted events [299]. Patient care is especially disrupted in the transition from acute to community care, at which time poor communication, limited self-management, and inadequate follow-up all negatively affect outcomes [300]. CCMs address health outcomes for defined diagnostic and demographic populations [299,301] and have been used with success in several chronic conditions [302,303]. Enrollment in CCMs must meet specific criteria, and care is measurement-based, including outcomes for system metrics and patient reported specific outcomes (PROMs) and experiences (PREMs). Key features of the CCM include the care manager (navigator, coach, care co-ordinator), who co-ordinates the care team, comprised of the patient and family, primary, and specialist care. This team develops a care plan which links the patient to relevant community inter-professional healthcare providers and resources. The care manager co-ordinates interdisciplinary conferences, especially for higher risk patients, to review and modify the care plan. This model of care is adaptable and responsive to patients' needs [304]. A unique feature is the early and ongoing involvement of primary care in the initial plan and follow-up [305]. The CCM has the advantages of a multisite team with care continuity, familiarity, and ongoing communication (Figs. 4 and 5). Upon program completion, the patient returns to the primary care provider.

Aspects of the CCM have been described in COPD [192,276,282,306,307]. [308,309] Examples of criteria-based enrollment include spirometry-proven COPD, recent hospitalization for acute exacerbation, and patient coaching, self-management and community follow-up to varying extents. COPD self-management has been associated with improved quality of life and reduced healthcare resource utilization, although program heterogeneity in content, design and duration have challenged making broad conclusions [310,311]. Important and successful components include: 1) Accountability tools to self-manage toward set goals; 2) Patient centered behavioral changes using motivational communication; and 3 A dedicated case manager [192,276].

Keys to the success of CCM are effective clinical information systems to enable learning and continuous improvement, health care delivery redesign and decision support, and adequate community resources. CCM's can be facilitated by the availability of PR programs, which contain many of the essential components. Models to manage chronic respiratory disease have been encouraging in several jurisdictions, including the UK [312], the European Union [313] and Canada [314]. A recent ATS workshop on integrated care of the COPD patient encourages research, development, and implementation of this approach, including guidelines for the multi-morbid COPD patient, large randomized controlled trials of integrated care, and development of information technologies and increased community resources for education, exercise, and social support [315].

CCM models promote closer relationships between primary and secondary care as well as care integration across the disease trajectory, encouraging teamwork, partnerships, and continuity of care [316]. Such models must be scalable to tackle population health and should include methods to maintain fidelity to the model with ongoing quality improvement. Adopting a CCM for those with chronic respiratory conditions will undoubtedly improve population health.

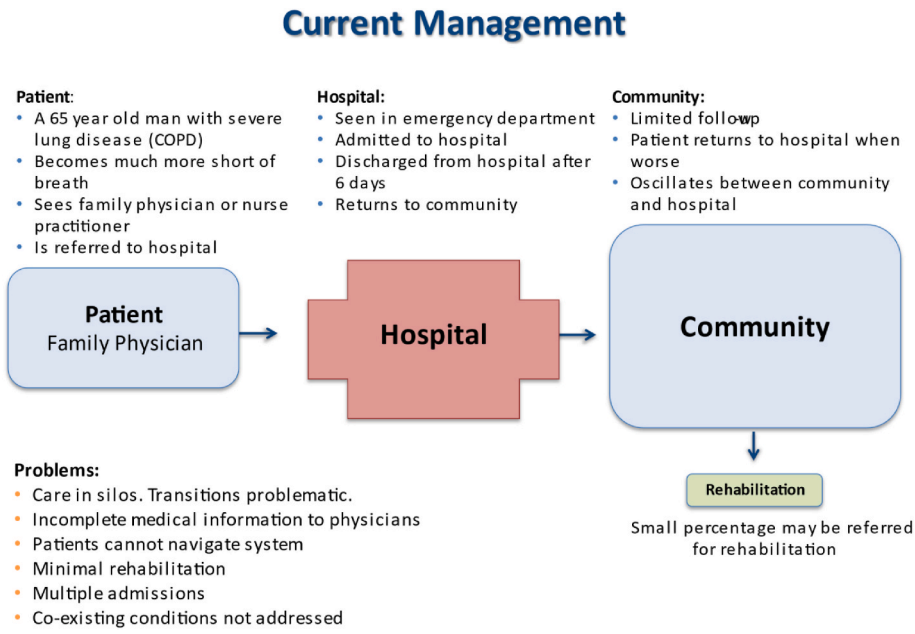

Fig. 4. Silo model for management of the COPD patient in the peri-hospital period.

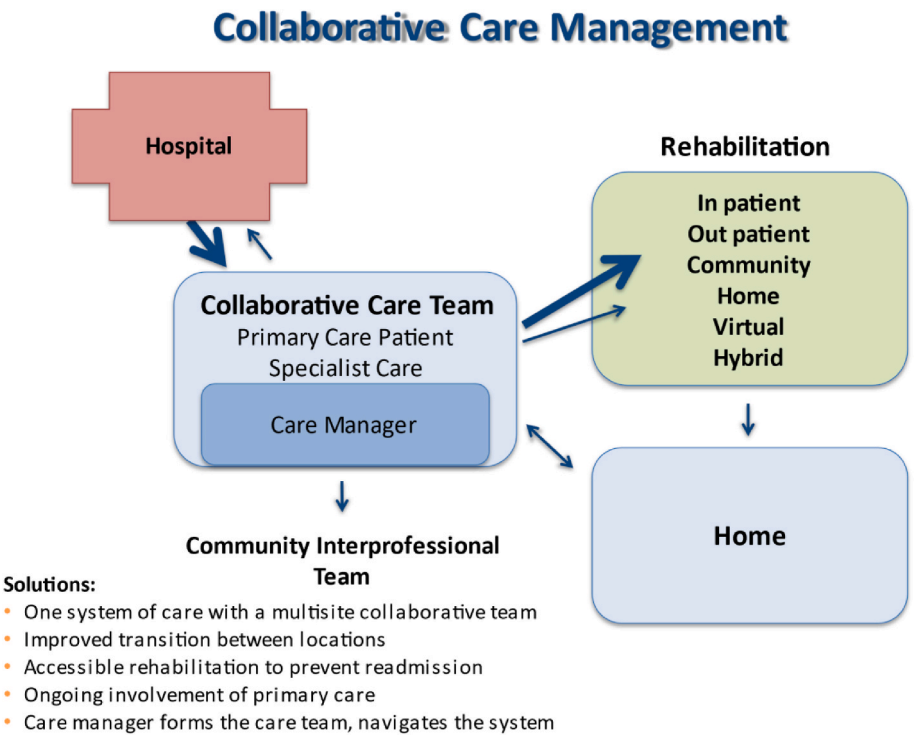

Fig. 5. Collaborative care model for COPD management.

4.3.1. *Key points*

- Key team members of the Collaborative Care Model (CCM) include the patient and family, the care manager/navigator, and primary and specialist health care providers
- The CCM is based on a care plan that is adaptable and responsive to individual patient's needs, is reviewed and modified by the inter-professional healthcare team, and coordinates services based on ongoing input from the primary care provider
- Keys to the success of CCM are effective clinical information systems to enable learning and continuous improvement, health care delivery redesign and decision support, and adequate community resources

4.4. *Integrating COPD care across Disciplines and systems. Mike morgan, Jane Reardon*

Integrate (v): 'To combine two or more things so that they work together; to combine with something else in this way' (The Oxford Dictionary).

At first glance, the concept of integrated care for people with chronic diseases such as COPD seems obviously beneficial. It has, however, been

surprisingly difficult to demonstrate the benefit of integrated care formats in clinical trials. One reason for this has been the lack of a unified definition of the term. Integrated care means different things to different people. For example, for the clinician, the term may describe multi-component therapy, multi-disciplinary care, and provision of care in different physical settings. The commissioners (payers)of services may describe integrated care as multiple providers working with a single budget across hospital and community boundaries or the delivery of services for all chronic diseases under a single umbrella. The picture has been additionally complicated by the COVID-19 pandemic, which has introduced remote or virtual consultation into the mix. It is also important not to forget the patient's involvement in their care. From their perspective, they can expect to be involved in any decision about their care through a dialogue with a knowledgeable health care professional.

Clinical trials in this area have been complicated by the lack of unified or standardize outcome measures. They have included subjective measures of health status, dyspnea, and exercise capacity. The impact on health care usage has also been variously addressed in terms of the frequency of hospital admissions, length of stay or emergency visits.

The accepted conceptual framework for the integrated care of people with chronic disease is the Chronic Care Model. This outlines the necessary components of service delivery which includes amongst others, patient self-management, service delivery design and the application of clinical guidelines [317]. An early study showed that if patients received at least two components of the Chronic Care Model then the frequency of hospital admissions was reduced [318]. There have been many further studies examining the effect of multi-professional, multi-component care but the results have been a little disappointing. The most recent Cochrane review of 52 trials concludes that the integrated care approach in various settings probably results in improved quality of life and exercise capacity (from rehabilitation), and reduced hospital attendances, but the evidence is not overwhelming in spite of the large study population [311]. An earlier conclusion from the *Randomised Clinical trial on Effectiveness of integrated COPD Management in Primary CarE* (RECODE study) also failed to find a health economic benefit in a primary care setting [319].

Based on the above, integrated care approaches to the management of COPD do not appear to have the dramatic effect that was expected. This does not obviously make a lot of sense since the individual components such as rehabilitation or self-management training have shown clear improvements in single intervention trials [124,320]. Pulmonary rehabilitation, which should be considered a mandatory component of any integrated care structure, does on its own result in significant improvements in all relevant parameters. Possible reasons for this paradox could be that we are not looking at the right outcome measures or that the approach is applied too late in the patient pathway. Both the American and British Thoracic societies have produced position statements recommending the integrated care approach across primary and secondary care [315,321]. It simply does not seem sensible to accept that taking steps to avoid fragmented care, provide proven components by expert health care staff to an informed patient cannot be anything but beneficial. In the next decade we need to be a little clearer about how we define the topic and think more carefully about how we assess the benefits. Furthermore, it seems that formal pulmonary rehabilitation needs to be a mandatory component of any integrated care system for people with COPD.

4.4.1. Key points

- Uniformity in the concept of integrated care for chronic respiratory disease is lacking and studies in this area suffer from a lack of standard outcome measures
- Despite a strong rationale, the benefits of the integrated care model have not been established via randomized, controlled trials
- Pulmonary rehabilitation should be a mandatory component of any integrated care system for people with COPD

Author contributions

David Amann: Study design, data collection, data analysis
Sara R Tabtabai: Study design, editing of manuscript.
Dorothy Wakefield: Statistical analysis, study design, editing of manuscript.
Antarpreet Kaur: Study design.
Muhammad Yasir Adeel: Study design.
Richard Soucier: Study design.
Richard ZuWallack: Study design, editing of manuscript, statistical analysis.

Declaration of competing interest

To the best of my knowledge as editor and corresponding author for the above manuscript, neither I nor any of the coauthors or editor have any perceived conflict of interest with respect to the subject matter of this paper. This, by necessity, must be a preliminary statement, as I assume each author must at a later date submit a personal COI statement.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.rmed.2022.107041.

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