Understanding COPD-overlap syndromes

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease accounts for a large burden of lung disease. It can ‘overlap’ with other respiratory diseases including bronchiectasis, fibrosis and obstructive sleep apnea (OSA). While COPD alone confers morbidity and mortality, common features with contrasting clinical outcomes can occur in COPD ‘overlap syndromes’.

Areas Covered: Given the large degree of heterogeneity in COPD, individual variation to treatment is adopted based on its observed phenotype, which in turn overlaps with features of other respiratory disease states such as asthma. This is coined asthma-COPD overlap syndrome (‘ACOS’). Other examples of such overlapping clinical states include bronchiectasis-COPD (‘BCOS’), fibrosis-COPD (‘FCOS’) and OSA-COPD (‘OCOS’). The objective of this review is to highlight similarities and differences between the COPD-overlap syndromes in terms of risk factors, pathophysiology, diagnosis and potential treatment differences.

Expert Commentary: As a consequence of COPD overlap syndromes, a transition from the traditional ‘one size fits all’ treatment approach is necessary. Greater treatment stratification according to clinical phenotype using a precision medicine approach is now required. In this light, it is important to recognize and differentiate COPD overlap syndromes as distinct disease states compared to individual diseases such as asthma, COPD, fibrosis or bronchiectasis.

Keywords: Chronic obstructive pulmonary disease; Overlap syndrome; Asthma; Bronchiectasis; Fibrosis; Idiopathic; Obstructive sleep apnea.

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1. INTRODUCTION

Overlap syndromes in health and disease

An overlap syndrome is a clinical situation where clinical and/or laboratory signs of two or more separate disease entities exist in a single patient. This adds complexities to an accurate diagnosis which in turn impacts therapeutic choices. Complex endo-phenotypes may emerge in such settings which are refractory to a conventional therapeutic approach. Whether overlap syndromes should be recognized as distinct clinical entities, as opposed to a mix of two separate disease states is an important and often-debated question, as treatment of individual symptoms may not suffice in an overlap patient. In addition to respiratory overlap syndromes, this concept is evident across different medical disciplines particularly rheumatology; where the overlapping symptoms of connective tissue disorders were among the first described. In mixed connective tissue disorder (MCTD) for instance, the signs and symptoms of other conditions including lupus, scleroderma and polymyositis may occur, an archetypical example of medical overlap [1]. Examples from gastroenterology include overlaps between Gastroesophageal reflux disease (GERD), functional dyspepsia (FD), and irritable bowel syndrome (IBS), while Primary biliary cirrhosis–autoimmune hepatitis overlap syndrome (PBC-AIH) is an emerging field for hepatology research [2,3].

In this current review, we focus on respiratory overlap syndromes, namely the overlaps that occur between COPD, asthma, bronchiectasis and OSA. Central to most of the respiratory overlap syndromes is COPD, a chronic inflammatory disease characterised by persistent airflow obstruction, accelerated loss of lung function and

irreversible pulmonary damage (**Figure 1**). Globally, COPD-related morbidity and mortality is increasing and the World Health Organization (WHO) estimates that 5% of all deaths worldwide can be attributed to COPD [4]. Based on current trajectories, COPD will be the 3rd leading cause of death internationally by 2030, a rank already reported in the United States and South-East Asia [4-7]. Interestingly, COPD incidence in Asia remains highest, three times more prevalent when compared to other continents [8]. While the primary inciter of COPD is usually tobacco smoke exposure, other risk factors of emerging importance include air pollution and occupational exposures [9,10]. Importantly, COPD is a heterogeneous disease often clinically presenting as different phenotypes some of which are now recognized in ‘overlap’ with asthma, bronchiectasis and obstructive sleep apnoea (OSA).

Overlap syndromes in respiratory medicine: ACOS, BCOS, FCOS and OCOS

Asthma and COPD are among the commonest respiratory diseases internationally [11,12]. While both share common features such as airway inflammation and airflow limitation, most agree that they are distinct disease states each with different etiology, pathophysiology, prognosis and treatment response (**Figure 1**) [13]. This was not always the case: in the 1960s, Orie and colleagues proposed that all airway diseases, including asthma, emphysema, and chronic bronchitis, should be considered the single entity of “chronic non-specific lung disease” that share common genetic origins – this became known as the “Dutch hypothesis” [14]. Expectedly, there was opposition from others who argued that asthma and COPD were distinctly different diseases with dissimilar causal mechanisms, the “British hypothesis” [15,16]. The debate persists even over half a

century later and to some extent both hypotheses have merit [16-18]. In recognition of the presence of both distinctive as well as overlapping features, the term “asthma–COPD overlap syndrome” (ACOS) has emerged to describe patients with clinical features of both diseases [11,12]. Both GINA and GOLD guidelines have acknowledged this and proposed that clinicians should assess for features of both asthma and COPD and where present, a diagnosis of ACOS considered. Consequently, early work on ACOS assessed for asthma symptoms in COPD populations however it is also important to consider the assessment of COPD feature in asthmatic populations, the latter being less commonly sought [19-24].

The true prevalence however of ACOS varies considerably due to the lack of standardized definitions that has more recently been addressed [19,25]. There is also substantial variation in the reported mortality in ACOS [26-29] due in large part to differences in study definitions. ACOS is therefore a heterogeneous group of disorders; where different subtypes result in diverse clinical outcomes. This is supported by a large prospective study that subdivided ACOS into early and late onset asthma groups. Higher mortality was observed in late onset asthma related ACOS compared to that in early onset asthma [29]. The potential difference in intrapulmonary pathology, delay in diagnosis and treatment and potential contribution of comorbidities in the late onset asthma group may account for the worse prognosis. Crucially, patients with ACOS have been excluded from most clinical trials hence the evidence base to inform optimal treatment for this specific group is lacking.

Bronchiectasis is an irreversible structural airway dilatation identified by high-resolution computed tomography (HRCT). This contrasts to COPD which is

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physiologically diagnosed on the basis of poorly reversible airflow obstruction, degree of symptoms and frequency of exacerbations [11,30,31]. Changes in the airway wall are usually milder and more diffuse in COPD as compared to bronchiectasis where etiology, severity and airway geometry all play important roles. Despite such differences, both diseases share common symptoms of dyspnea, chronic productive cough, airflow obstruction and susceptibility to recurrent exacerbations due to new or persistent infection. The presence of bronchiectasis in COPD is now recognized as a potential new phenotype of the COPD state [11]. The overlapping of these two conditions was first described by Barker in 2002 and since, prevalence has increased, now reported in up to 57.6% of COPD patients [32-37]. High levels of pro-inflammatory cytokines, lower airway bacterial colonization and longer symptom recovery time following exacerbation are described in BCOS [35]. Both severity of detected airflow obstruction and at least one hospital admission for an exacerbation in the previous year have been associated with bronchiectasis in moderate to severe COPD [34]. Intubated intensive care unit (ICU) patients with BCOS experience longer duration of both ICU and hospital stays, prolonged mechanical ventilation and increased risks of ventilator-associated pneumonia however no independent effect on mortality is clearly described [38]. Recent work however has described high mortality rates (28.5%) in individuals with BCOS over a prolonged period of 48 months suggestive of a poorer prognosis [39]. The geometric and anatomical variation to the bronchiectasis (tubular, varicose and cystic) described in BCOS has not been highlighted clearly in existing studies however, bronchiectasis in BCOS tends to localize to the lower lobes, is bilateral and spares central regions [34,35]. Importantly, a single study did show that tubular patterns of bronchiectasis were predominant over other

types in BCOS but further work is clearly needed to better understand this relationship [36]. While existing work in this field is varied and difficult to compare, it is clear that the mere existence of BCOS is associated with different clinical manifestations, treatment responses and prognosis compared to COPD alone, all factors warranting further work to better understand the BCOS-state.

Pulmonary fibrosis is an interstitial lung disease resulting in scarring. Overlap between the clinical features of pulmonary fibrosis and COPD (herein referred to as ‘fibrosis-COPD overlap syndrome’ – FCOS) is supported by emerging evidence linking the shared features of both conditions to a common underlying pathophysiology [40,41]. While FCOS awaits formal clinical definition, and is less broadly acknowledged in the clinical literature, it is clear that similarities between both idiopathic pulmonary fibrosis (IPF) and COPD do exist, and that overlap represents a potentially overlooked clinical phenomenon (**Figure 1**). Indeed, overlap between fibrosis and emphysema (a common diagnostic feature of COPD) has been given recognition as a newly defined ‘combined pulmonary fibrosis and emphysema syndrome’ (CPFE) [40]. This likely represents an important sub-category of FCOS encompassing patients with distinct features such as loss of alveolar parenchyma and apparent alveolar senescence, strongly associated with inhalation of noxious agents (most frequently tobacco smoke) [40,42]. Recent evidence further points to overlap between underlying factors of disease pathogenesis in patients with symptoms of FCOS [42]. The most striking of these is telomere length, reduced in familial IPF and of shorter length in COPD versus controls. Consequently, the senescence hypothesis has emerged for both COPD and IPF, highlighting similarities between the

conditions in terms of premature lung aging. Notably, dysregulation of pathways governing parenchymal tissue development and remodeling, including NOTCH and Wingless-related integration site (WNT), are implicated in both IPF and COPD pointing to a common endotype likely of relevance for the FCOS-state [42].

Arising from intermittent collapse of the upper airway consequently resulting in reduced or absent inspiratory airflow, OSA is characterized by obstructive sleep respiratory events (apneas, hypopneas and arousals), signs of disrupted sleep and daytime symptoms of poor sleep [43]. Patients with COPD also suffer from poor sleep quality primarily due to nocturnal coughing and breathlessness that hinders sleep initiation and maintenance [44]. The association of COPD with OSA, first described by Flenley, identifies patients with overlap to have greater degrees of nocturnal hypoxemia and hypercapnia when compared to patients with COPD or OSA in isolation [45]. Subsequent studies have further shown that daytime oxygen desaturations, hypercapnia and a reduced quality of life are greater in an OSA-COPD overlap versus COPD alone [46-48]. Patients with overlap untreated with continuous positive airway pressure (CPAP) appear to have higher all-cause mortality [49,50]. This is likely due to cardiopulmonary complications such as pulmonary hypertension and cardiac arrhythmias arising from prolonged and profound hypoxemia [51,52]. Clearly, OSA-COPD overlap syndrome (herein referred to as OCOS) represents an emerging disease group that requires attention and detailed study.

2. THE CHALLENGES OF COPD-OVERLAP SYNDROMES FOR SCIENTISTS, CLINICIANS AND PATIENTS

The emergence of COPD-overlap syndromes has posed particular, unique and differing challenges for scientists, clinicians and patients (Table 1). The major challenge for scientists in dissecting COPD-overlap syndromes lies in the ill-defined nature of these conditions. A more precise robust classification is critical from a research perspective as an inaccurate diagnosis can complicate cohort selection and confound data interpretation from clinical studies. The overlap patient is often overlooked by study exclusion criteria and as such, patients suffering from COPD-overlap syndromes have been less studied owing to clinical study design [19,53-55]. The classification of patients into a given disease category may be overly simplistic because of the heterogeneous clinical phenotypes observed in routine practice [56]. Therefore, an identification of distinct reproducible patient biomarkers that can satisfactorily discriminate patient groups remains the holy grail of scientific efforts dedicated to an improved understanding of COPD- overlap syndromes. Notwithstanding this and its associated major challenges, promising results from unsupervised clustering approaches involving proteomic and transcriptomic data from patient sputum samples have emerged in the context of asthma [57]. While the importance of the microbiome in predicting outcomes in COPD, asthma, bronchiectasis and IPF has been documented, a key challenge for future researchers is to distill from such molecularly rich-information a more granular clinician-friendly patient stratification system and thus provide scope for targeted precision medicine approaches for COPD-overlap syndromes [58-62].

Overlap syndromes pose several diagnostic and therapeutic challenges for the clinicians involved. The consensus definition for ACOS is relatively new and the lack of standardization in the past has limited a rigorous discussion of diagnosis, prevalence, pathophysiology, treatment and outcomes [19]. Additionally, a high index of suspicion is required for diagnosis and the monitoring of disease progression in ACOS. Therapeutic response is also more difficult to monitor due to complexities associated with physiologic variability in an overlap setting. For instance, detecting a preserved or slightly reduced lung volume does not rule out the presence of fibrosis in a patient with COPD or emphysema. Similarly in patients with fibrosis, forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO) measurements, used to monitor disease progression or therapeutic response are different in CPFE patients who tend to exhibit delays in the reduction of FVC and DLCO reducing their utility as surrogate markers for disease progression [63,64]. Serial FVC changes similarly lack prognostic significance in CPFE unlike other types of pulmonary fibrosis, and the rate of FEV1 decline is rather the strongest predictor of mortality in CPFE. Despite this, DLCO declines are important as they herald the development or progression of pulmonary hypertension, a feature commonly encountered in CPFE [63,65]. Patients with overlap syndromes have higher morbidity and mortality. Patients with ACOS have more frequent exacerbations, greater lung function decline, higher healthcare utilization and greater economic burden compared to those with asthma or COPD alone [28,29,66]. However conflicting results do exist, some of which report no significant differences [27,67,68]. This could be explained by smaller patient number, shorter duration of follow up and importantly differences in ACOS definition. Patients with OCOS illustrate severer

hypercapnia and pulmonary hypertension versus sleep apnea–hypopnea syndrome or COPD alone [69]. BCOS is associated with increased mortality especially in the setting of reduced FEV1 [70,71]. Compared to COPD, BCOS is twice more likely to have exacerbations, four times more likely to isolate potentially pathogenic microorganisms, and also more likely to have severe airway obstruction and higher mortality [72].

Patients with overlap syndromes themselves face unique challenges. Delays in diagnosis can sometimes occur because of the contrasting opinions from specialists. This results in both anxiety and potentially extra costs due to additional investigations and specialist visits. Specifically, ACOS patients have higher mortality rates [28,29], more frequent exacerbations, healthcare utilization and economic burden. Importantly, one must be cautious in the interpretation of the causal relationship between overlap and cost, given that patients with higher healthcare utilization may have increased opportunity for diagnosis leading to bias [73-79]. In this light, the parameters by which ACOS is defined also merit careful consideration when trying to quantify health care burden [19]. In addition to these increased challenges, patients also experience for unknown reasons higher risks of pulmonary embolism and tuberculosis [80,81]. OCOS patients have greater sleep disturbance, nocturnal desaturation, higher Epworth sleepiness scores, lower total sleep time and efficiency, higher arousal and poorer sleep quality [46,82]. Resting and exertional hypoxemia are more common in FCOS translating to greater symptomatology and poorer six minute walk distances as compared to smokers without interstitial lung abnormalities [40,83]. Patients with COPD-overlap syndromes are generally excluded from clinical trials and consequently don't benefit from newer drugs

or available interventions which, in turn, has been one reason for the lack of tangible progress in our understanding of these recognized syndromes.

3. THE EPIDEMIOLOGY OF COPD-OVERLAP SYNDROMES

Some key issues must be considered in the interpretation of epidemiological studies addressing COPD-overlap syndromes. First, the definitions of such overlap syndromes need greater clarity as currently no clear consensus exists on what specifically constitutes an overlap syndrome. An operational definition has recently been proposed [19] based on three major criteria and at least one minor criterion (**Table 2**), but this awaits wider adoption by future studies. Second, epidemiological studies addressing this field are heterogeneous particularly in their methodology and specifically case definitions. For example, in the case of ACOS, most studies have employed use of physician diagnoses, claims data, self-reported diagnosis or questionnaires, and few base their case definitions on spirometry. Even in cases of the latter, diverse pulmonary function criteria have been employed to diagnose ACOS. ACOS itself may also comprise of multiple phenotypes, for example, asthma preceding COPD, or COPD preceding asthma, or both diagnosed at the same time. Epidemiological work addressing ACOS also differs based on the population that forms the denominator, for instance whether it is an entire population, or a base population of COPD or asthma patients. There are further variations in the origin of the population being studied and whether this originates from primary or secondary care. Different case definitions therefore generate different prevalence estimates. The PLATINO study is a multicenter population-based study of ACOS where COPD was defined as post bronchodilator FEV1/FVC < 0.7 and asthma was defined as

wheezing or having a significant bronchodilator response (>12% and >200ml) [84]. ACOS prevalence was 1.8% (**Table 1**). A Spanish EPI-SCAN study, whose study met the proposed definition of ACOS [19], found that 17.4% of patients with spirometry-defined COPD had a prior asthma diagnosis [23]. Studies by Golpe *et al* found the prevalence of ACOS to be different where they assessed COPD caused by the effects of tobacco smoke versus that from biomass exposure (5% vs 21.3% respectively) [21]. Reported prevalence of ACOS ranges from 6.5% to 13% [85,86]. As compared to prevalence data derived from COPD populations, studies to determine ACOS prevalence using asthmatic populations are far less common. In a primary care setting, asthma patients with no prior reported history of COPD, but who were current or ex-smokers illustrated a high ACOS prevalence of 27.4% [20].

Less is known about the prevalence of BCOS, attributable at least in large part to a lack of uniform definition. Whether bronchiectasis and COPD are inter-related or independent entities that develop concurrently remains unclear, for example traction bronchiectasis cannot strictly be termed BCOS because of the interdependence of one process on the other. Wide varying prevalence rates of BCOS are reported (**Table 1**). In the ECLIPSE study, a longitudinal, observational, multinational COPD cohort, only 4% had radiological evidence of bronchiectasis as adjudicated by two independent radiologists [33]. In a separate primary care cohort of n=110 patients who received an initial diagnosis of acute exacerbation of COPD, 29% had HRCT evidence of co-existing bronchiectasis [36]. Importantly, 12.3% of this cohort did not have spirometric evidence of airflow limitation and 5% of these patients received a final diagnosis of chronic asthma.

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3 A similar retrospective study found that 69% of those admitted for the first time with a
4 diagnosis of COPD exacerbation had radiological evidence of bronchiectasis [87].
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6 Interestingly, in Asian COPD studies, up to 50% have been documented to have BCOS
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8 most likely because of the high population prevalence of post-infectious bronchiectasis
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10 [88,89].
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17 The prevalence of OCOS is difficult to estimate (**Table 1**). Sleep disordered
18 breathing occurs secondary to COPD itself and hence definitions require clarity and
19 specificity. Early studies that reported a strong overlap between OSA and COPD suffered
20 from selection bias because such patients were already referred to a sleep clinic at the
21 time of data collection. The most significant study to estimate the prevalence of OCOS,
22 the Sleep Heart Health Study, found no difference in the prevalence of OSA among
23 patients with and without an FEV1/FVC ratio < 0.7 . This applied spirometry-based
24 criterion encompasses a broader group of obstructive lung disease rather than specifically
25 COPD *per se*, and the study population importantly consisted solely of individuals with
26 relatively mild obstruction [46]. A European community population-based study reported
27 that only 1% of the total population and 9.2% of those with OSA, confirmed on
28 polysomnography, had COPD based on spirometry. While COPD was frequently
29 detectable in OSA patients in the general population, those with overlap had a more
30 severe course of sleep-disordered breathing suggestive of the disadvantageous effects
31 from overlap between the two clinical states [46].
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FCOS has been described more specifically as CPFE, with upper lobe emphysema coupled to lower lobe fibrosis and honeycombing [40]. The precise prevalence is unknown (**Table 1**) and almost all patients with CPFE have a smoking history, a mutual risk factor for both IPF and emphysema. Interestingly, connective tissue disease has also been described as a major risk factor suggestive of an autoimmune component to its etiology [90].

4. WHAT PREDISPOSES TO COPD-OVERLAP SYNDROMES?

Shared risk factors coupled to common pathways of pathogenesis predispose particular individuals toward the development of certain COPD-overlap syndromes. Once widely regarded as having distinct inflammatory patterns, more recent work has demonstrated several common inflammatory pathways in both asthma and COPD. Asthmatic patients with late-onset disease or a positive smoking history can exhibit COPD-associated characteristics such as airway neutrophilia, abundance of macrophages, high CD8 counts and airway epithelial remodelling [91-93]. Conversely, a subset of COPD patients may demonstrate a Th2-type eosinophilic inflammatory profile, a traditional asthma characteristic [94,95]. It however remains to be elucidated whether such inflammatory pathways translate and can explain some of the overlapping features of ACOS. Bronchial hyper-responsiveness, a recognised asthmatic feature, is in part driven by eosinophilic inflammation and predicts a greater rate of FEV1 decline in early COPD [96]. In long-standing and more severe asthma, structural factors such as fixed airway obstruction are detectable due to a loss of reversibility, decreased lung elastic recoil and the development of microscopic centrilobular emphysema [97]. Such

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3 pathophysiologic mechanisms occur in the absence of smoking and predispose to clinical
4 features similar to that observed in COPD (**Figure 2**). Several risk factors are recognized
5 in the pathogenesis of ACOS. Smoking promotes airway inflammation, increases
6 bronchial hyper-responsiveness and confers steroid resistance [93,98,99]. Over the long-
7 term, smoking accelerates lung function decline and increases respiratory symptoms
8 [100]. Recent population-based work has detected that high level exposures to air
9 pollution increases the risk of developing ACOS in an asthmatic cohort independent of
10 smoking [101]. While allergic phenotypes are well recognized in asthma, up to 30% of
11 COPD sufferers demonstrate aeroallergen sensitization [102]. The presence of such
12 allergic sensitization in COPD is independently associated with worse respiratory
13 symptoms and more exacerbations [102,103].
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32 Chronic airway inflammation, genetics and environmental influence all have
33 important and independent roles in the pathogenesis of both bronchiectasis and COPD.
34 The inflammatory response, in both cases, involves neutrophils, macrophages and CD8+
35 T-cells, which are responsible for attenuating airway damage [104]. In bronchiectasis,
36 pathology is largely attributed to recurring infection and inflammation that leads to
37 neutrophil proteinase extravasation. Consequently, bronchial damage ensues impairing
38 host defences and permitting further bacterial colonization and dilatation which in turn
39 incites the process again [105]. Risk factors for COPD include cigarette smoking;
40 exposure to indoor air pollution, occupational risks and recurrent childhood lower
41 respiratory tract infections [106]. Whilst some have suggested that outdoor air pollution
42 and COPD are linked, large prospective epidemiological studies are required before
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causality can be established. Inhalation of noxious aerosols leads to mucociliary dysfunction and loss of tight junctions between airway epithelia consequently resulting in inflammation, bacterial colonization and subsequent exacerbations. This repeated cycle of chronic infection and inflammation leads to microbe persistence that causes further tissue damage and airway remodelling (**Figure 2**). *Pseudomonas aeruginosa* is a key gram negative organism of importance in both bronchiectasis and COPD. It is associated with disease severity: up to one third of patients with bronchiectasis are colonized while it may be recovered from up to 20% of COPD airways conferring more exacerbations and worse prognosis [107-112]. The role of *P. aeruginosa* in the context of BCOS has yet to be elucidated [34,109]. Alpha-1 antitrypsin (AAT) deficiency (AATD) is a known genetic risk factor for COPD. The prevalence of COPD in AATD ranges from 1-4.5% in the homozygous PI*ZZ phenotype and 17.8% in heterozygous PI*MZ phenotype [113]. Importantly there are considerable discrepancies in pulmonary function abnormalities and the development of COPD in AATD, suggesting involvement of other risk factors such as cigarette smoking and environmental exposures. AATD is detectable in bronchiectasis however BCOS has not been specifically examined [114-117]. A significant association between emphysema and bronchiectasis caused by AATD has been described suggestive that bronchiectasis could be a consequence of emphysema [114]. Importantly, some patients with bronchiectasis do not demonstrate obvious emphysema and the precise mechanisms driving bronchiectasis in the context of COPD remain ill-defined. AATD patients with an element of reversibility also appear to have poorer prognosis suggestive of the key influence conferred when an overlap pattern exists [118]. Detailed and well-

designed future studies targeting mechanisms to better understand the pathogenesis of BCOS are clearly warranted.

Smoking has deleterious effects on both COPD and IPF [11,119]. Both conditions increase with age and have a male preponderance [24,40,120-122]. Despite the distinctive nature of both conditions, striking similarities exist. Both diseases occur later in life [24,120] with episodes of exacerbation punctuating their clinical course [123,124]. Deposition of collagen and the existence of fibrosis (small airways in COPD and the lung parenchyma in IPF) co-exist in the setting of FCOS. It has therefore been hypothesized that an accelerated biological lung aging or abnormal aging process predisposes individuals to either or both diseases concurrently resulting in FCOS (**Figure 2**) [42,125]. Mechanisms underlying FCOS remain poorly characterized however several factors, common to both diseases, likely play key roles that include smoking induced-oxidative stress [126,127], telomere length abnormalities or mutation [128-135], accelerated cellular and immunosenescence [122] and altered anti-aging molecular and extracellular matrix markers such as klotho and sirtuins [125]. Clearly, much is still to be done and remains unknown within the FCOS field.

The pathogenesis of OCOS is multifactorial. Mechanical factors predispose and play a significant and more prominent role in OCOS as compared to other overlap pathologies. Upper airways resistance is accentuated in both COPD and OSA such that a longer time constant is required for lung emptying (**Figure 2**) [136]. Lung hyperinflation produces diaphragmatic flattening and decreases its efficiency for generating sufficient

inspiratory force. A greater reliance on accessory inspiratory muscles increases both the work and oxygen requirements for breathing [136]. During Rapid Eye Movement (REM) sleep, a decreased accessory muscle tone further compromises a patient's ability to maintain ventilation. Obesity, commonly associated with both OSA and the 'blue-bloater' COPD clinical phenotype, can further exacerbate upper airway obstruction, respiratory muscle weakness and chest wall restriction [137]. Overall, more sustained and excessive hypoxemia and hypercapnia develops [82]. Consequently, hypoxemia predisposes to increased sympathetic activity and a higher frequency of cardiac dysrhythmias [138,139]. Pulmonary hypertension is also more pronounced and develops in the presence of factors such as airflow obstruction, hypoventilation, hypoxemia and obesity [51,82,140]. Increased right ventricular hypertrophy and remodeling with resultant right heart failure have been demonstrated in OCOS patients [52]. Systemic inflammation also contributes to OCOS. Elevated C-reactive protein (CRP), interleukins-6 (IL-6) and -8 (IL-8), and tumor necrosis factor-alpha (TNF- α) have all been found in OCOS patients and may be associated with cardiovascular disease [141-144]. In response to hypoxemia and smoking, oxidative stress leads to increased reactive oxygen species (ROS) production and resultant pulmonary vascular endothelial damage, an important vascular consequence of the overlap state [145].

5. THE MICROBIOME IN COPD-OVERLAP SYNDROMES

Host-microbe interactions are important drivers of respiratory disease, with the presence of pathogenic organisms often serving as prognostic markers for disease progression [146]. Respiratory pathogens such as *Pseudomonas aeruginosa* can

precipitate exacerbation and predict poorer clinical outcomes in bronchiectasis and COPD while stronger evidence surrounds the role of viral infection in the pathogenesis of IPF [146,147]. In asthma, infection by common respiratory viruses is often associated with exacerbations, while bacteria and even fungi are associated with severe forms of disease such as Severe Asthma with Fungal Sensitization (SAFS) [93,148].

As well as recognising specific pathogenic organisms, a growing appreciation exists for the role of the microbiome in human disease, laying the foundations for the development of novel diagnostic and therapeutic approaches [149]. This is becoming evident in respiratory medicine, where the composition of the microbiome (and perturbations therein) clearly plays an important role in respiratory infections, is now also implicated in asthma and COPD [122,150,151]. The pathogenesis of COPD, asthma, bronchiectasis and IPF have been subjected to lung-microbiome studies, with likely implication for the detection and management of COPD-overlap syndromes. Microbiome analysis has revealed the healthy lung to be predominated by bacterial genera including *Pseudomonas*, *Streptococcus*, *Prevotella* and *Fusobacterium* as well as *Haemophilus*, *Veillonella*, and *Porphyromonas* [152]. Changes in composition, bacterial load or the presence of specific pathobiont species within the microbiome may accompany chronic lung conditions including COPD, asthma, bronchiectasis and IPF [58,59,61,150]. It follows that specific changes may also predict sub-categories of disease including COPD-overlap syndromes and therefore permit a more refined patient stratification.

In tandem, the gut microbiome has also been implicated in disease pathogenesis via a gut-lung axis. This has been evaluated in asthma and work continues in other chronic respiratory disease settings making the gut microbiome a potentially key biomarker for lung disease including that in overlap syndromes [150]. Other sites, such as the oral cavity, may also prove important. For instance, it has been shown that the oral microbiome is significantly altered on exposure to cigarette smoke - a major risk factor for COPD - and that infiltration of these oral microbiota into the lung leads to increased inflammation [153]. Such metagenomic studies build on our knowledge base of associations between microbiome status and adverse clinical outcomes in lung diseases such as COPD where the presence of specific organisms can trigger acute exacerbations in addition to perpetuating immune responses during chronic colonisation. As the pathogenesis likely proceeds along several microbiome axes, an analysis of the microbiome at multiple body sites may ultimately provide the most informative picture. In addition, sampling of the patient's environment such as the home using metagenomic sequencing technologies may also be useful in terms of identifying known allergens such as fungi, contributing to disease pathogenesis in overlap syndromes [154]. Geographic variability in the respiratory human microbiome is another consideration as results must be interpreted in the context of regional and population-specific microbiome signatures that vary considerably [155].

6. THE DIAGNOSIS AND MANAGEMENT OF COPD-OVERLAP SYNDROMES

ACOS: GINA and GOLD guidelines focused on asthma and COPD respectively outline a description of ACOS as an “Asthma-COPD overlap syndrome (ACOS)

characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD (**Table 3**). ACOS is therefore identified by the features that it shares with both asthma and COPD.” The key variables to consider for diagnosis include age of onset, pattern and time course of symptoms, personal or family history of atopy, variable or persistent airflow limitation, symptomatic lung function change and the presence of hyperinflation on chest radiography [11,12,156,157]. More recently, a group of global experts agreed a consensus definition of ACOS that includes the presence of all three major criteria and at least one minor criterion for ACOS (**Table 2**) [19]. As opposed to traditional clinically-driven phenotypes, ACOS may be better defined by biological tools, such as fractional exhaled nitric oxide (FENO) and/or blood eosinophils. Three recent studies have found FENO to be a potential surrogate biomarker for identification of patients with ACOS [158-160]. Patients with ACOS differing by study definition had significantly higher FENO levels than those with COPD alone. In addition, blood eosinophils were also ascribed as a potential biomarker in a Japanese COPD cohort [158] with a blood eosinophil count of ≥ 300 cells/ μ L as a minor criteria in the recent consensus definition (**Table 2**) [19].

The presence of different ACOS phenotypes, such as eosinophilic, neutrophilic, asthma in smokers or non-smokers exposed to biomass has been suggested by Bateman *et al.* [161] while Barnes challenges the term “syndrome”, referring to it as misleading because it encompasses these particular phenotypes under a single umbrella (e.g. COPD and eosinophilic inflammation, smoking asthmatics or those with severe disease and predominantly neutrophilic inflammation, and patients with asthma and irreversible

airway obstruction due to structural change). He importantly proposes that it may be better to use asthma-COPD overlap (ACO), rather than ACOS to describe this clinical state [162]. Clearly, the concept of ACOS or ACO is evolving and further work including unbiased phenotyping studies of broad populations with chronic airways disease may prove useful for identifying ACOS phenotypes. ACOS patients have greater comorbidities (such as allergic rhinitis, anxiety, gastroesophageal reflux disease and osteoporosis) compared to COPD alone and the presence of cardiovascular diseases in ACOS patients is associated with hospitalization in a single study [163].

According to GINA guidelines, if syndromic assessment is equally balanced between asthma and COPD in ACOS, then treatment should be commenced as it would for asthma alone with low or moderate doses of ICS followed by the addition of a long-acting β -agonist (LABA) and/or long-acting muscarinic antagonists (LAMA) (**Table 3**). Critically, a lack of comprehensive therapeutic trial data persists in ACOS, except for a single study comparing the efficacy of once-daily fluticasone furoate/vilanterole (FF/VI) with twice-daily fluticasone propionate/salmeterol (FP/SAL) [164]. This twelve-week, randomized, open-label cross-over trial studied 16 patients and described a significant FEV1 improvement after four weeks of FF/VI treatment compared to the run-in period. Importantly, however other assessed parameters including FeNO levels, CAT scores, ACT scores, and other blood tests were not significantly different over the same period.

Of note however, regular use of ICS in ACOS is associated with an increased risk of pneumonia especially in those with severe COPD [11]. A recent study suggests that omalizumab improves asthma control and health-related quality of life in individuals with

severe allergic asthma and overlapping COPD. These findings provide the first real-world efficacy data for this patient population and suggest that omalizumab may be useful in the management of severe asthma with COPD overlap [165]. Despite the existing evidence base, much work remains to better understand the optimal methods for both the diagnosis and the effective treatment of ACOS.

BCOS: This syndrome is a particular clinical challenge to diagnose, as both conditions present with cough, sputum production, repeated exacerbations and dyspnea [11,31,166]. Obstructive airflow physiology is required for a COPD diagnosis but this may not always be present in bronchiectasis. As a suppurative structural lung disease, bronchiectasis is largely dependent on radiological evidence to detect features of airway dilatation, lack of peripheral airway tapering and cystic or varicose airway change. This is in contrast to COPD, where airway wall changes are more subtle, manifesting as generalized and mild thickening. It is therefore proposed that BCOS should have the following diagnostic features: history of exposure to inciting agents such as tobacco smoke, severe fixed airflow obstruction and airway wall CT abnormalities (**Table 3**) [34,53]. Microbiological investigations are useful in this particular overlap syndrome as the detection of colonization or infection by organisms such as *P. aeruginosa* may portend greater pulmonary function decline, more frequent exacerbations and higher mortality [146,167]. The optimal management of BCOS requires further work although antibiotics should certainly be considered if airway infection with *P. aeruginosa* is detected due to the higher risks of pneumonia and hospitalizations associated with this BCOS subgroup [38]. However, the route of administration and duration of such

antibiotic therapy remain uncertain [53]. Long term macrolide therapy for anti-inflammatory and anti-microbial effects may also reduce infectious bronchiectasis exacerbations, although the risk of antibiotic resistance is presumably high but remains uncertain (**Table 3**) [168]. Treatment options targeted at COPD, including inhaled corticosteroids and bronchodilators, may be indicated in BCOS particularly if patients frequently exacerbate.

FCOS: FCOS has male preponderance, and symptoms of exertional dyspnoea and cough are its most common presentation [90]. The radiological appearance is distinct with features of upper lobe emphysema and lower lobe fibrosis, traction bronchiectasis and honeycombing [40]. Due to the combined effects of pulmonary fibrosis and emphysema on pulmonary function, FCOS is characterized by normal to reduced lung volumes with disproportionately low oxygen saturation and severely reduced diffusion capacity (**Table 3**) [41,90,169]. Associations with connective tissue disease (CTD) are described and a CTD assessment should be performed in all cases [90]. Evaluation for pulmonary arterial hypertension (PAH) should be pursued due to its higher incidence in FCOS patients [170]. To date, no established treatment regime exists for FCOS. The deleterious effects of smoking on COPD and IPF are recognised and smoking cessation is therefore recommended [119]. In the presence of significant hypoxemia and pulmonary hypertension, oxygen therapy should be prescribed based on its benefits demonstrated in COPD [171]. The role of corticosteroids and immunosuppression remains unclear but may be a therapeutic option in CTD-related FCOS [90]. Newer anti-fibrotic agents such as pirfenidone and nintedanib have recently been approved for the treatment of IPF

however their role in FCOS requires dedicated evaluation and clinical study [54,172]. Despite a poor prognosis, there is currently insufficient evidence to recommend the use of pulmonary hypertension specific therapies in the setting of FCOS (**Table 3**) [173].

OCOS: Typically, OSA is defined as an Apnea-Hypopnea Index (AHI) of 5 or greater with associated symptoms (e.g., excessive daytime sleepiness, fatigue, or impaired cognition) or an AHI of 15 or greater, regardless of symptoms [174]. Generally, a high index of clinical suspicion is required to both consider and diagnose OCOS (**Table 3**). The presence of hypoxaemia, hypercapnia and pulmonary hypertension that is out of proportion to severity of either disease should prompt further assessment for the other disorder [175]. Continuous Positive Airway pressure (CPAP) is the first line treatment for OCOS (**Table 3**). Two large observational cohort studies have demonstrated its mortality benefit in this setting when compared to medical therapy alone [49,50]. Interestingly, CPAP-treated OCOS patients were less likely to have severe COPD exacerbations requiring hospitalization [49]. In stable chronically hypercapnic COPD patients, the use of bi-level positive airway pressure (BIPAP) is preferred to CPAP. This therapy targets a reduction of hypercapnia and improved survival particularly in GOLD stage IV COPD [176]. Importantly, no controlled studies have been performed in an OCOS population therefore limiting the evidence base available for clinicians.

7. EXPERT COMMENTARY

COPD-overlap syndromes are clearly emerging as a major challenge in respiratory medicine. Affecting clinicians, allied health professionals, scientists and most

of all patients, the forthcoming decade will undoubtedly reveal novel features of these disease overlaps with the potential for paradigm shift in our understanding of pulmonary health and disease trajectory. Only time will tell whether these overlap syndromes truly represent separate disease entities to the traditional classification of individual respiratory disease states such as asthma or COPD. What is more likely however is that they are mixed phenotypes, a combination of one or more established disease entities in a single individual.

There are several important challenges and opportunities for both clinicians and scientists as this field evolves. An improved clinical and molecular phenotyping method is required to better stratify these challenging patient cohorts and understand disease pathogenesis, one that could be addressed with a systems biology approach and the use of emerging ‘omics’ technologies including genomics, metabolomics and proteomics. We must however be extremely cautious that our increasing recognition of COPD-overlap syndromes in clinical practice does not simply result in greater patient ‘labelling’. It is critical that this improved endo-phenotyping of overlapping respiratory disease states translates to better patient management and facilitates the practice of precision medicine. One potential method by which this may occur is to focus on risk factors or co-morbidities unique to each ‘overlapping’ COPD-related state creating a management plan that is both patient and situation specific [177]. To better understand the clinical course and improve diagnostic and subsequently therapeutics for COPD-overlap syndromes, we must consider (a) challenges that currently exist for recruitment into both clinical trials and molecular studies, where to date most overlap patients have largely been excluded and (b) how to interpret results from large cohort studies where COPD-overlap

syndromes may be present or haven't been assessed for. Clearer guidelines based on definitions of these overlap states are now necessary to aid clinicians better identify and subsequently stratify these challenging patients with mixed pathologies. This work has already commenced for ACOS but is similarly necessary for other COPD-overlap states [19]. For instance, consensus is required in FCOS to determine what percentage or pattern of fibrosis constitutes an overlap syndrome and what does not. In BCOS, what is the role of dry bronchiectasis if clinical criteria to determine its existence are based on clinical symptoms such as cough productive of purulent sputum and how is this differentiated from chronic bronchitis? These are critical, difficult but key challenges that must be addressed if we are to make progress in better understanding COPD-overlap syndromes and more importantly pathogenic mechanisms common to a variety of respiratory disease states.

8. FIVE YEAR VIEW

It is now clear that in addition to genetic predisposition and environmental influences, that many other factors such as the host microbiome play a role in both the development and progression of a variety of respiratory pathologies (**Figure 3**). How such factors influence COPD-overlap syndromes are yet to be elucidated and future work should focus on this area. The precise contribution of genetics and environmental influences that contribute to the development of a COPD-overlap syndrome need to be better understood and studied to inform more accurate, economical and robust diagnostics that will subsequently influence therapeutics. It is likely that these identifiable factors or their combination in a particular COPD-overlap syndrome is individual hence

personalized and a more phenotype-driven precision approach to their management necessary, one that focus on risk factors and the management of co-morbidities [177]. Emerging data suggest that genetics and early-life change influences lung function trajectories followed in later life, which, in turn determines the occurrence of respiratory disease such as COPD [29,178]. Therefore, predictions may now be possible to determine the individuals most likely to develop a particular respiratory disease. It would be valuable in this context to assess cohorts prospectively and determine the development of COPD-overlap syndromes which provides insight into pathophysiological mechanisms that have been driven or influenced by either host, environmental or microbial factors. We are only at the beginning of our own learning trajectory in the complex field of COPD-overlap syndromes but with the appropriate rigour, investment and study designs, our understanding of not just COPD-overlap syndromes but the fundamental airway changes related to a range of respiratory pathologies will certainly be enhanced.

9. KEY POINTS

- Transition from a ‘single diagnosis’ for certain respiratory disease states is now clearly recognized with the emergence of COPD-overlap syndromes such as asthma-COPD overlap syndrome (ACOS), bronchiectasis-COPD overlap syndrome (BCOS), fibrosis-COPD overlap syndrome (FCOS) and OSA-COPD overlap syndrome (OCOS)
- COPD-overlap syndromes represent distinct and unique challenges for clinicians, scientists and patients

- A need for clear evidence-based approaches to diagnosis and treatment (including the development of guidelines) are now necessary for COPD-overlap syndromes to aid clinicians and scientists better identify, stratify and research this challenging patient group

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later life. Accelerated decline of FEV1 is not an obligate feature of COPD

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FIGURE LEGENDS

Figure 1: Non-proportional Venn diagram illustrating the centrality of COPD to the main currently described respiratory overlap syndromes including asthma, bronchiectasis, fibrosis and obstructive sleep apnea. COPD – chronic obstructive pulmonary disease, OSA – obstructive sleep apnea, ACOS – Asthma-COPD overlap syndrome, BCOS – Bronchiectasis-COPD overlap syndrome, FCOS – Fibrosis-COPD overlap syndrome and OCOS – OSA-COPD overlap syndrome, HRCT - High-resolution computed tomography.

Figure 2: Predisposing risk factors and their associated complications in the development of the various COPD-overlap syndromes. COPD – chronic obstructive pulmonary disease, OSA – obstructive sleep apnea, ACOS – Asthma-COPD overlap syndrome, BCOS – Bronchiectasis-COPD overlap syndrome, FCOS – Fibrosis-COPD overlap syndrome, OCOS – OSA-COPD overlap syndrome, ↑ - increased, ↓ - decreased, 6MWT - 6 minute walk test, PHT - Pulmonary hypertension and QOL – Quality of life.

Figure 3: A summary of the major factors that influence the development and progression of respiratory disease states.

TABLE LEGENDS

Table 1: (a) Summary of the major challenges encountered in the clinical care and research of patients with COPD-overlap syndromes (b) prevalence rates of COPD-overlap syndromes from the existing literature base.

Table 2: Criteria for diagnosis of Asthma-COPD overlap syndrome. FEV1: forced expiratory volume in the 1st second; FVC: forced vital capacity; Bronchodilator response using 400 µg of albuterol/salbutamol (or equivalent) [19].

Table 3: Summary of the diagnostic criteria and treatment approach for the various COPD-overlap syndromes. CT – Computed tomography, CPFE - Combined pulmonary fibrosis and emphysema, OSA - Obstructive sleep apnea, COPD – Chronic obstructive pulmonary disease, - GINA – Global Initiative for Asthma, GOLD - Global Initiative for Chronic Obstructive Lung Disease and AHI - Apnea–Hypopnea Index, LABA - Long-acting beta adrenoceptor agonists, LAMA - Long-acting muscarinic receptor antagonists and CPAP - Continuous positive airway pressure.

Reviewer comments for: [ERRX-2016-0164] [UNDERSTANDING COPD-OVERLAP SYNDROMES]		
Referee 1		
Comment	Author Response	Text Insertion (if applicable)/ page/ line number of change
General Comments:		n/a
1. In page 9–10 and Table 1, the authors described that the prevalence rate of ACOS are 1.8–55.2%. The GINA/GOLD joint document describes that current doctor-diagnosed asthma and COPD has been reported in approximately 15–20% of patients. The authors should carefully discuss the difference between epidemiological studies and COPD cohort studies.	We have now emphasized the differences between epidemiologic studies and disease cohort studies, to explain differences in prevalence estimates	Page 13 Line 262 – 266. It should be noted that cohort studies of asthma or COPD patients are also enriched patient populations and therefore vulnerable to selection bias. This could account for the interstudy discrepancies in prevalence estimates of ACOS, in contrast to random sampling methods of population-based epidemiological work.
2. In page 18, the authors described that ACOS might be better defines by biological tools, such as blood or sputum eosinophil counts. Blood eosinophil counts were reported as a biomarker of ACOS in a Japanese COPD cohort (Int J COPD. 2016;11:2117–23), but not in the ECLIPCE cohort (Eur Respir J. 2016;47:1559–62). Moreover, there is no good evidence to suggest that sputum eosinophil counts are one of biomarkers of ACOS. The authors should revise the description. Recent studies demonstrated that the fractional exhaled nitric oxide (FENO) was an inflammatory biomarker	This paragraph has been changed. Sputum eosinophils as biomarker of ACOS has been removed and discussion about FENO and blood eosinophil as a potential biomarker has been add with inclusion of the references as suggested by reviewer.	Page 22. Lines 465-472. As opposed to traditional clinically-driven phenotypes, ACOS may be better defined by biological tools, such as fractional exhaled nitric oxide (FENO) and/or blood eosinophils. Three recent studies have found FENO to be a potential surrogate biomarker for identification of patients with ACOS [158-160] . Patients with ACOS differing by study definition had significantly higher FENO levels than those with COPD alone. In addition, blood eosinophils were also ascribed as a potential biomarker in a Japanese COPD cohort [158] with a blood eosinophil count of ≥ 300 cells/uL as a minor criteria in the recent consensus definition (Table 2) [19].

<p>of ACOS (Int J COPD. 2016;11:2117–23, Int J COPD. 2016;11:2149–55, Int J COPD. 2016;11:2385–90). The author should reference these studies and discuss the novel potential biomarker.</p>		
<p>3. In page 20, the authors proposed that inhaled corticosteroids might be indicated. The GOLD 2017 document describes that inhaled corticosteroids may not be indicated in patients with bacterial colonization or recurrent lower respiratory tract infections. The sentence needs rephrasing.</p>	<p>This sentence has been added together with reference to the GOLD 2017 guideline</p>	<p>Page 23, line 500-501. Of note however, regular use of ICS in ACOS is associated with an increased risk of pneumonia especially in those with severe COPD [11]</p>
<p>4. In this review the authors coined new words, such as BCOS, FCOS and OCOS. The authors should comment that these terms are your original proposal.</p>	<p>We cannot fully claim to have coined the term "BCOS" as it has already emerged in the literature. This has been cited in the original manuscript (Hurst JR, Elborn JS, De Soyza A, Consortium B-U. COPD-bronchiectasis overlap syndrome. Eur Respir J, 45(2), 310-313 (2015)). The term "FCOS" is indeed our proposed term for overlap involving Pulmonary fibrosis and COPD - this was also noted in the original text, however, we have changed the wording to give further emphasis to the reviewer's point. While OSA-COPD</p>	<p>Page 7 Line 124-127. Pulmonary fibrosis is an interstitial lung disease resulting in scarring. Overlap between the clinical features of pulmonary fibrosis and COPD (herein referred to as 'fibrosis-COPD overlap syndrome' – FCOS) is supported by emerging evidence linking the shared features of both conditions to a common underlying pathophysiology [40,41].</p> <p>Page 8 Line 157-160 This is likely due to cardiopulmonary complications such as pulmonary hypertension and cardiac arrhythmias arising from prolonged and profound hypoxemia [51,52]. Clearly, OSA-COPD overlap syndrome (herein referred to as OCOS) represents an emerging disease group that requires attention and detailed study.</p> <p>BCOS - no change</p>

	overlap is well described in the literature, the term 'OCOS' is not yet a widely used in the literature (to our knowledge) and hence we have also clarified this.	
5. Some investigators claim that to call asthma–COPD overlap a “syndrome” is misleading (e.g. Chest 2016;149:7–8). The authors are recommended to be addressed these view point.	This viewpoint has been addressed and referenced together with another reviewer's comments about discussion of different phenoytpes within ACOS	Page 22. Line 474-481. The presence of different ACOS phenotypes, such as eosinophilic, neutrophilic, asthma in smokers or non-smokers exposed to biomass has been suggested by Bateman et al. [161] while Barnes challenges the term “syndrome” , referring to it as misleading because it encompasses these particular phenotypes under a single umbrella (e.g. COPD and eosinophilic inflammation, smoking asthmatics or those with severe disease and predominantly neutrophilic inflammation, and patients with asthma with irreversible airway obstruction due to structural change). He importantly proposes that it may be better to use asthma-COPD overlap (ACO), rather than ACOS to describe this clinical state [162].
Referee 2		
Comment	Author response	Text Insertion (if applicable)/ page/ line number of change
General Comments		n/a
1. The authors would be include their personal experience on the topic	We have added a section in the Five year view which addresses this point.	Page 28 Line 606 - 628
Referee 3		
Comment	Author response	Text Insertion (if applicable)/ page/ line number of change
General Comments		n/a
1. I do miss some discussion on the possible existence of different phenotypes within ACOS	This paper has been included with discussion on different phenotypes of ACOS.	Page 22. Line 474-481. The presence of different ACOS phenotypes, such as eosinophilic, neutrophilic, asthma in smokers or non-smokers exposed to

<p>(see Bateman et al, Lancet Respir Med 2015; 3(9):719-28 This should be added.</p>		<p>biomass has been suggested by Bateman et al. [161] while Barnes challenges the term “syndrome”, referring to it as misleading because it encompasses these particular phenotypes under a single umbrella (e.g. COPD and eosinophilic inflammation, smoking asthmatics or those with severe disease and predominantly neutrophilic inflammation, and patients with asthma with irreversible airway obstruction due to structural change). He importantly proposes that it may be better to use asthma-COPD overlap (ACO), rather than ACOS to describe this clinical state [162].</p>
<p>2. I do miss some discussion on the impact of comorbidities within ACOS (see Van Boven et al, Chest 2016; 149(4):1011-20). This should be added.</p>	<p>This study has been added</p>	<p>Page 22-23. Lines 484-487. ACOS patients have greater comorbidities (such as allergic rhinitis, anxiety, gastroesophageal reflux disease and osteoporosis) compared to COPD alone and the presence of cardiovascular diseases in ACOS patients is associated with hospitalization in a single study [163].</p>
<p>3. Page 8 (line 176-178, "Patients with...COPD alone"). This sentence is repeated on page 9 (line 188-190, "Specifically,...economic burden"). One of these two sentences could be deleted. Regarding this higher healthcare utilization and costs, one may wonder if this is causally related with overlap syndromes, given this may be patients that are seeking more healthcare and have more chance to get multiple diagnoses (see Mannino, Chest 2008; 134(1):1-2)</p>	<p>We have deleted the repeated statement (188-190). We thank the reviewer for drawing attention to the important point raised by the editorial of Mannino <i>et al.</i> We have addressed the comment of the reviewer in lines 189-192 and added the reference of Mannino <i>et al.</i></p>	<p>Page 11 Text insertion line 217-223. Importantly, one must be cautious in the interpretation of the causal relationship between overlap and cost, given that patients with higher healthcare utilization may have increased opportunity for diagnosis leading to bias [73-79]. In this light, the parameters by which ACOS is defined also merit careful consideration when trying to quantify health care burden [19]. In addition to these increased challenges, patients also experience for unknown reasons higher risks of pulmonary embolism and tuberculosis [80,81].</p>

4. Regarding the five year view: Creating overlap syndromes could result in more comprehensive labeling, while for true precision medicine we may actually have to focus on individual risk factors that can be treated ("Treatable traits", see Agusti et al. Eur Respir J 2016; 47(2):410-9). This could be emphasized a bit more.	This is indeed an important point. We have emphasised this in the five year view including the important reference of Agusti <i>et al.</i>	Page 27 Line 581-588. We must however be extremely cautious that our increasing recognition of COPD-overlap syndromes in clinical practice does not simply result in greater patient 'labelling'. It is critical that this improved endo-phenotyping of overlapping respiratory disease states translates to better patient management and facilitates the practice of precision medicine. One potential method by which this may occur is to focus on risk factors or co-morbidities unique to each 'overlapping' COPD-related state creating a management plan that is both patient and situation specific [177]. Page 28 Line 614-617. It is likely that these identifiable factors or their combination in a particular COPD-overlap syndrome is individual hence personalized and a more phenotype-driven precision approach to their management necessary, one that focus on risk factors and the management of co-morbidities [177].
5. Page 20: line 441: bur=but?	This typo has been corrected	Typo corrected line 441
6. Page 20: line 442: BOCS=BCOS I assume	This typo has been corrected	Typo corrected line 442
Referee 4		
Comment	Author response	Text Insertion (if applicable)/ page/ line number of change
General Comments		n/a
1. Line 47: "will be the 3rd leading cause of death internationally": is not it already the case, at least in some countries? Please comment on this within the manuscript.	It is true that this has been reported for other countries/ regions such as the United States and South-East Asia. We have made reference to this point and included a citations to support this.	Page 4 Text insertion line 52-54. Based on current trajectories, COPD will be the 3rd leading cause of death internationally by 2030, a rank already reported in the United States and South-East Asia [4-7].
2. Line 50: you should add a reference about occupational exposure	We have included the highly cited reference of Oxman and	Page 4 Line 55-57 Reference inserted - While the primary inciter of COPD is usually tobacco smoke exposure, other

and COPD	colleagues to support the link between occupational exposure and COPD	risk factors of emerging importance include air pollution and occupational exposures [9,10].
3. Lines 73-74: "patients with ACOS have higher mortality rates compared to those with asthma or COPD alone" There are some recent papers reporting equal or better mortality rates in ACOS; you must cite these papers and change this phrase accordingly. In the Lange paper, mortality rates are not higher in patients with early onset asthma. Please comment on this within the manuscript.	The paragraph has been changed now including the additional references, reporting differences in mortality rate and further discussion. Higher mortality was reported in ACOS with late onset asthma compared to early onset asthma by Lange <i>et al</i> , this may be explained by the differences in intrapulmonary pathology, delay in diagnosis and treatment and potential contribution of comorbidities in the late onset asthma group.	Page 5 Line change- 82-90. There is also substantial variation in the reported mortality in ACOS [26-29] due in large to differences in study definitions. ACOS is therefore a heterogeneous group of disorders; where different subtypes result in diverse clinical outcomes. This is supported by a large prospective study that subdivided ACOS into early and late onset asthma groups. Higher mortality was observed in late onset asthma related ACOS compared to that in early onset asthma [29]. The potential difference in intrapulmonary pathology, delay in diagnosis and treatment and potential contribution of comorbidities in the late onset asthma group may account for the worse prognosis.
4. Line 162: "The lack of standardized diagnostic criteria...in ACOS": In Ref 49, ACOS definition is very clear as reported in the commentary: persistent airflow obstruction in symptomatic individuals > 40 years, a history of asthma < 40 years, and a significant exposure history to cigarette or biomass smoke. This definition must be included in the manuscript and the discussion changed accordingly.	This sentence has been rephrased	Page 9. Lines 186-188. The consensus definition for ACOS is relatively new and the lack of standardization in the past has limited a rigorous discussion of diagnosis, prevalence, pathophysiology, treatment and outcomes [19].

5. Lines 175 to 178 (ref 21-28): Patients with ACOS have higher mortality rates and morbidity. Recent papers using ACOS definition reported above have found diferent results. You must discuss these papers and also change the last column of fig 2.	The paragraph has been change and additional references with different results on mortality and morbidity were added and discussed. The differences in reported morbidity and mortality of ACOS may be explained by the smaller numbers of patients, shorter followed up time and variation in definition of ACOS. We have edited Fig 2 to reflect the changes.	Page 10 Line change 202-207. Patients with ACOS have more frequent exacerbations, greater lung function decline, higher healthcare utilization and greater economic burden compared to those with asthma or COPD alone [28,29,66]. However conflicting results do exist, some of which report no significant differences [27,67,68]. This could be explained by smaller patient number, shorter duration of follow up and importantly differences in ACOS definition.
6. Lines 188-190: It is the same statement that reported in lines 175 to 178. These results are dependent on the definition of ACOS, as reported in lines 205 to 207. Please comment on this within the manuscript.	As per comment comment 3, referee 3, we have deleted the repeated statement (188-190). We have added a line addressing the issue of ACOS definition. And we have also dealt with this in the section " 3. THE EPIDEMIOLOGY OF COPD-OVERLAP SYNDROMES"	Page 11 Text insertion 217-223. Importantly, one must be cautious in the interpretation of the causal relationship between overlap and cost, given that patients with higher healthcare utilization may have increased opportunity for diagnosis leading to bias [73-79]. In this light, the parameters by which ACOS is defined also merit careful consideration when trying to quantify health care burden [19]. In addition to these increased challenges, patients also experience for unknown reasons higher risks of pulmonary embolism and tuberculosis [80,81]. Page 12. Text insertion Line 237-239. An operational definition has recently been proposed [19] based on three major criteria and at least one minor criterion (Table 2), but this awaits wider adoption by future studies.
7. Line 218: Studies detecting comparable ACOS prevalence (between 12 to 18%) have used ACOS definition reported above. This	We have rephrased the sentences to indicate most of these studies do not use the ACOS definition reported in Sin <i>et al</i>	Page 12-13. Text insertion Line 254-259. A Spanish EPI-SCAN study, whose study met the proposed definition of ACOS [19], found that 17.4% of patients with spirometry-defined COPD had a prior asthma diagnosis [23]. Studies by Golpe

must be clearly stated in the manuscript.	(2016) and removed those studies that do not meet the definition from this manuscript.	et al found the prevalence of ACOS to be different where they assessed COPD caused by the effects of tobacco smoke versus that from biomass exposure (5% vs 21.3% respectively) [21]. Reported prevalence of ACOS ranges from 6.5% to 13% [85,86].
8. Line 223: "ACOS prevalence from asthmatic populations": this is another way of defining ACOS. This definition must be included earlier in the manuscript (in opposition to ACOS from COPD patients), as reported in ref 49.	Thank you for the point. In the revised manuscript, we have included a statement to address definition and contrasted it with that for COPD (Ref 49) as highlighted by the reviewer.	Page 5. Line insertion 78-80. Consequently, early work on ACOS assessed for asthma symptoms in COPD populations however it is also important to consider the assessment of COPD feature in asthmatic populations, the latter being less commonly sought [19-24].
9. Line 295: "the major risks for developing COPD are exposure to cigarette smoke, biomass fuels, and air pollution" Is air pollution really a major risk factor for COPD? What about occupational factors? Please comment on this within the manuscript.	The sentence has been rephrased and occupational exposure is included as a risk factor for COPD. Whilst, there is some suggestion that outdoor air pollution is linked to the development of COPD development, a large prospective epidemiology study is required before any causal relationship can be assessed	Page 16 Line change- 342-346. Risk factors for COPD include cigarette smoking; exposure to indoor air pollution, occupational risks and recurrent childhood lower respiratory tract infections [106]. Whilst, some have suggested that outdoor air pollution and COPD are linked, large prospective epidemiological studies are required before causality can be established.
10. Line 305: "AATD is another key COPD risk factor" Is it true? What is the frequency of AATD in COPD cohorts? Please comment on this within the manuscript.	The point has been addressed and references added on the prevalence of AATD in COPD cohorts	Page 17 Line change- 354-360. Alpha-1 antitrypsin (AAT) deficiency (AATD) is a known genetic risk factor for COPD. The prevalence of COPD in AATD ranges from 1-4.5% in the homozygous PI*ZZ phenotype and 17.8% in heterozygous PI*MZ phenotype [113]. Importantly there are considerable discrepancies in pulmonary function abnormalities and the development of COPD in AATD, suggesting involvement of other risk factors such as cigarette smoking and environmental exposures.

11. Line 335: define REM	We have defined the acronym (REM - rapid eye movement)	Page 18 Line 391
12. Line 355: add in animals after “viral infection”	"in animals" has been added.	Page 19 Line 414
13. Line 364: “and the development” Are there prospective studies showing the association between lung microbiome and the development of asthma and COPD. If yes, these studies must be reported. If no “and the development” must be deleted.	We thank the reviewer for bringing this to our attention. Indeed, while interesting cross-sectional studies are reported, definitive prospective studies are lacking. We have re-worded to better reflect the strength of the evidence base and removed “and the development” from this section.	Page 20 Line 421-424. This is becoming evident in respiratory medicine, where the composition of the microbiome (and perturbations therein) clearly plays an important role in respiratory infections, is now also implicated in asthma and COPD [122,150,151]
14. ACOS: Lines 404 to 409: As reported in ref 49, there is no consensus on biomarkers in ACOS. The most promising is peripheral eosinophil count and an absolute threshold should be considered (minor criteria). Others biomarkers are useful only for research purposes. You must change your manuscript accordingly. Again, the consensus diagnosis definition must be reported in this section (Sin DD).	The consensus diagnosis definition has been added and the blood eosinophil count has also been mentioned (minor criteria)	Page 22. Lines 463-472. More recently, a group of global experts panel agreed a consensus definition of ACOS that includes the presence of all three major criteria and at least one minor criterion for ACOS (Table 2) [19]. As opposed to traditional clinically-driven phenotypes, ACOS may be better defined by biological tools, such as fractional exhaled nitric oxide (FENO) and/or blood eosinophils. Three recent studies have found FENO to be a potential surrogate biomarker for identification of patients with ACOS [158-160] . Patients with ACOS differing by study definition had significantly higher FENO levels than those with COPD alone. In addition, blood eosinophils were also ascribed as a potential biomarker in a Japanese COPD cohort [158] with a blood eosinophil count of ≥ 300 cells/uL as a minor criteria in the recent consensus definition (Table 2) [19]. Inserted a new TABLE 1 for major and minor criteria.

15. References 5-6: replace with more recent references about mortality and COPD	We have added more recent references. 4. World Health Organization. Chronic obstructive pulmonary disease (COPD), Available from: http://www.who.int/ mediacentre/factshee ts/fs315/en/ , [Accessed on (16/11/2016)] 5. Minino AM, Murphy SL, Xu J, Kochanek KD. Deaths: final data for 2008. National vital statistics reports : from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System, 59(10), 1-126 (2011). 6. World Health Organization. Global Health Observatory (GHO) data - Top 10 causes of death, Available from: http://www.who.int/g ho/mortality_burden_ disease/causes_death /top_10/en/ , [Accessed on (02/02/2017)] 7. Lopez-Campos JL, Ruiz-Ramos M, Soriano JB. Mortality trends in chronic obstructive pulmonary disease in Europe, 1994-2010: a joinpoint regression analysis. Lancet Respir Med, 2(1), 54-62 (2014).	Page 4 Line 52-54. Based on current trajectories, COPD will be the 3rd leading cause of death internationally by 2030, a rank already reported in the United States and South-East Asia [4-7].
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16. References 8-9: references with air pollution and COPD incidence, morbidity and mortality are out of the scope of this paper.	These references have been removed.	
Editors Comments		
Comment	Author response	Text Insertion (if applicable)/ page/ line number of change
1. Please restructure your abstract as below with the headings below and ensure it is no more than 200 words in length: - Introduction: Authors are required to provide a brief statement (one or two sentences) on the significance of the topic under discussion and the reason for the review - Areas covered: Authors are required to describe the research discussed and the literature search methodology undertaken. - Expert Commentary: Authors are required to provide one or two sentences summarising their Expert Commentary section.	We have restructured the abstract in line with recommendations.	Page 1-2 Line 1 - 25
2. Please separate the expert commentary and 5 year view sections. These should be two separate sections within the manuscript.	We have separated the 5 year view into separate sections.	Page 26 Line 568 and page 28 Line 606
3. Please provide 5-8 reference annotations (*=of importance, **= of considerable importance, followed by a brief sentence explaining why the reference is considered to be of interest).	8 references have been annotated and a brief sentence explanation have been provided.	13. Postma DS, Rabe KF. The Asthma-COPD Overlap Syndrome. N Engl J Med, 373(13), 1241-1249 (2015). ** - State of the art review describing the clinical management of ACOS 19. Sin DD, Miravittles M, Mannino DM et al. What is asthma-COPD overlap syndrome? Towards a consensus definition from a round table discussion.

Eur Respir J, 48(3), 664-673 (2016). ** - Consensus definitions for ACOS arising from round table discussions between expert clinicians.

29. Lange P, Colak Y, Ingebrigtsen TS, Vestbo J, Marott JL. Long-term prognosis of asthma, chronic obstructive pulmonary disease, and asthma-chronic obstructive pulmonary disease overlap in the Copenhagen City Heart study: a prospective population-based analysis. *Lancet Respir Med*, 4(6), 454-462 (2016). ** - Large scale cohort study assessing ACOS prevalence.

39. De Soyza A, McDonnell MJ, Goeminne PC et al. Bronchiectasis Rheumatoid overlap syndrome (BROS) is an independent risk factor for mortality in patients with bronchiectasis: A multicentre cohort study. *Chest*, (2017). ** - BCOS illustrates higher mortality rates

40. Cottin V, Nunes H, Brillet PY et al. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. *Eur Respir J*, 26(4), 586-593 (2005). * - One of the earliest descriptions of FCOS.

49. Marin JM, Soriano JB, Carrizo SJ, Boldova A, Celli BR. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. *Am J Respir Crit Care Med*, 182(3), 325-331 (2010). * - OCOS is associated with pulmonary hypertension, COPD exacerbations and mortality, which is improved with use of CPAP.

53. Hurst JR, Elborn JS, De Soyza A, Consortium B-U. COPD-bronchiectasis overlap syndrome. *Eur Respir J*, 45(2), 310-313 (2015). ** - International position on BCOS

178. Lange P, Celli B, Agusti A et al. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. *The New England journal of medicine*, 373(2), 111-122 (2015). ** - Early

		adulthood FEV1 is a key determinant of COPD in later life. Accelerated decline of FEV1 is not an obligate feature of COPD
4. Please clarify the figure permissions for this paper. Kindly list each figure and state whether they are original or require permission for their use. For the figures that have been previously published, permission will need to be obtained from the copyright holder to use them. Next to the figures that require permission for their use please send in the relevant documents and clearly state which documents are for which figures e.g. Figure 1: Original, no permission needed for use Figure 2: Permission needed for use and has been obtained, please see document entitled [insert document name here].	Figure 1 - Original, no permission needed for use Figure 2 - Original, no permission needed for use Figure 3 - Original, no permission needed for use	NA
5. Please provide source information for any data/information cited within figures and tables.	References have been cited in all figures and tables

Figure 1: Non-proportional Venn diagram illustrating the centrality of COPD to the main currently described respiratory overlap syndromes including asthma, bronchiectasis, fibrosis and obstructive sleep apnea. COPD – chronic obstructive pulmonary disease, OSA – obstructive sleep apnea, ACOS – Asthma-COPD overlap syndrome, BCOS – Bronchiectasis-COPD overlap syndrome, FCOS – Fibrosis-COPD overlap syndrome and OCOS – OSA-COPD overlap syndrome, HRCT - High-resolution computed tomography.

338x190mm (96 x 96 DPI)

Figure 2: Predisposing risk factors and their associated complications in the development of the various COPD-overlap syndromes. COPD – chronic obstructive pulmonary disease, OSA – obstructive sleep apnea, ACOS – Asthma-COPD overlap syndrome, BCOS – Bronchiectasis-COPD overlap syndrome, FCOS – Fibrosis-COPD overlap syndrome, OCOS – OSA-COPD overlap syndrome, ↑ - increased, ↓ - decreased, 6MWT - 6 minute walk test, PHT - Pulmonary hypertension and QOL – Quality of life.

338x190mm (96 x 96 DPI)

Figure 3: A summary of the major factors that influence the development and progression of respiratory disease states.

338x190mm (96 x 96 DPI)

Expert Review of Respiratory Medicine

(a) Challenges for clinicians and scientists when evaluating COPD – overlap syndromes

- Lack of standard diagnostic criteria
- Variations in definition
- Heterogeneous phenotypes
- Patients routinely excluded from clinical trials
- Complex physiological changes
- Higher morbidity and mortality

(b)

COPD – overlap Syndromes	Prevalence rate
ACOS	1.8%-27.4% [20-21, 23, 85-86]
BCOS	4-57.6% [33,36,87-89]
FCOS	Unknown
OCOS	9.2% [46]

URL: <https://mc.manuscriptcentral.com/erx> Email: Tasnim.Zahri@informa.com

3 major criteria	Either one minor criteria
<ul style="list-style-type: none">• ≥ 40 years old• Persistent airflow limitation (post-bronchodilator FEV1/FVC <0.70 or lower limit of normal) <p>Note: Preference using lower limit of normal</p>	<ul style="list-style-type: none">• Recorded history of atopy or allergic rhinitis
<ul style="list-style-type: none">• ≥ 10 pack-years of tobacco smoking <p>OR</p> <ul style="list-style-type: none">• equivalent indoor or outdoor air pollution exposure (e.g. biomass)	<ul style="list-style-type: none">• Bronchodilator response of FEV1 ≥ 200 mL and 12% from baseline values from ≥ 2 visits
<ul style="list-style-type: none">• Recorded history of asthma before 40 years old <p>OR</p> <p>Bronchodilator response of >400 mL in FEV1</p> <p>URL: https://mc.manuscriptcentral.com/errx</p>	<ul style="list-style-type: none">• Eosinophil count of ≥ 300 cells/uL in peripheral blood. <p>Email: Tasnim.Zahri@informa.com</p>

COPD-Overlap Syndrome	Diagnosis	Treatment
ACOS	<ul style="list-style-type: none">GINA and GOLD guidelines [11,12]Persistent airflow limitation with several features associated with both asthma and COPD [11,12]	<ul style="list-style-type: none">Commence standard asthma treatment [11,12]Inhaled corticosteroid followed by a long acting bronchodilator (LABA/LAMA) [11,12]
BCOS	<ul style="list-style-type: none">History of exposure to inciting agents e.g. tobacco smoke, post-tuberculosis, immunodeficiency etc. [34,53]Severe fixed airflow obstruction [34,53]CT abnormalities suggestive of bronchiectasis e.g. signet ring, tubular, varicose, cystic [34,53]	<ul style="list-style-type: none">Antibiotics for airway infection and exacerbations [38]Inhaled corticosteroids and bronchodilator therapy [38,168]Role of long term macrolide therapy requires further study [168]
FCOS	<ul style="list-style-type: none">CPFE → upper lobe emphysema with lower lobe fibrosis [40]	<ul style="list-style-type: none">Oxygen therapy [171]Anti-fibrotic agents (e.g. pirfenidone and nintedanib) require further evaluation [54,172]Corticosteroid and immunosuppressive therapy useful in CTD-related FCOS [90]
OCOS	<ul style="list-style-type: none">OSA → AHI>5 with symptoms or AHI>15 and COPD [174]	<ul style="list-style-type: none">CPAP [49-50]

ABSTRACT

Introduction: Chronic obstructive pulmonary disease accounts for a large burden of lung disease. It can ‘overlap’ with other respiratory diseases including bronchiectasis, fibrosis and obstructive sleep apnea (OSA). While COPD alone confers morbidity and mortality, common features with contrasting clinical outcomes can occur in COPD ‘overlap syndromes’.

Areas Covered: Given the large degree of heterogeneity in COPD, individual variation to treatment is adopted based on its observed phenotype, which in turn overlaps with features of other respiratory disease states such as asthma. This is coined asthma-COPD overlap syndrome (‘ACOS’). Other examples of such overlapping clinical states include bronchiectasis-COPD (‘BCOS’), fibrosis-COPD (‘FCOS’) and OSA-COPD (‘OCOS’). The objective of this review is to highlight similarities and differences between the COPD-overlap syndromes in terms of risk factors, pathophysiology, diagnosis and potential treatment differences.

Expert Commentary: As a consequence of COPD overlap syndromes, a transition from the traditional ‘one size fits all’ treatment approach is necessary. Greater treatment stratification according to clinical phenotype using a precision medicine approach is now required. In this light, it is important to recognize and differentiate COPD overlap syndromes as distinct disease states compared to individual diseases such as asthma, COPD, fibrosis or bronchiectasis.

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24 **Keywords:** Chronic obstructive pulmonary disease; Overlap syndrome; Asthma;
25 Bronchiectasis; Fibrosis; Idiopathic; Obstructive sleep apnea.

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For Peer Review Only

1. INTRODUCTION

Overlap syndromes in health and disease

An overlap syndrome is a clinical situation where clinical and/or laboratory signs of two or more separate disease entities exist in a single patient. This adds complexities to an accurate diagnosis which in turn impacts therapeutic choices. Complex endo-phenotypes may emerge in such settings which are refractory to a conventional therapeutic approach. Whether overlap syndromes should be recognized as distinct clinical entities, as opposed to a mix of two separate disease states is an important and often-debated question, as treatment of individual symptoms may not suffice in an overlap patient. In addition to respiratory overlap syndromes, this concept is evident across different medical disciplines particularly rheumatology; where the overlapping symptoms of connective tissue disorders were among the first described. In mixed connective tissue disorder (MCTD) for instance, the signs and symptoms of other conditions including lupus, scleroderma and polymyositis may occur, an archetypical example of medical overlap [1]. Examples from gastroenterology include overlaps between Gastroesophageal reflux disease (GERD), functional dyspepsia (FD), and irritable bowel syndrome (IBS), while Primary biliary cirrhosis–autoimmune hepatitis overlap syndrome (PBC-AIH) is an emerging field for hepatology research [2,3].

In this current review, we focus on respiratory overlap syndromes, namely the overlaps that occur between COPD, asthma, bronchiectasis and OSA. Central to most of the respiratory overlap syndromes is COPD, a chronic inflammatory disease characterised by persistent airflow obstruction, accelerated loss of lung function and

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irreversible pulmonary damage (**Figure 1**). Globally, COPD-related morbidity and mortality is increasing and the World Health Organization (WHO) estimates that 5% of all deaths worldwide can be attributed to COPD [4]. **Based on current trajectories, COPD will be the 3rd leading cause of death internationally by 2030, a rank already reported in the United States and South-East Asia [4-7].** Interestingly, COPD incidence in Asia remains highest, three times more prevalent when compared to other continents [8]. **While the primary inciter of COPD is usually tobacco smoke exposure, other risk factors of emerging importance include air pollution and occupational exposures [9,10].** Importantly, COPD is a heterogeneous disease often clinically presenting as different phenotypes some of which are now recognized in ‘overlap’ with asthma, bronchiectasis and obstructive sleep apnoea (OSA).

Overlap syndromes in respiratory medicine: ACOS, BCOS, FCOS and OCOS

Asthma and COPD are among the commonest respiratory diseases internationally [11,12]. While both share common features such as airway inflammation and airflow limitation, most agree that they are distinct disease states each with different etiology, pathophysiology, prognosis and treatment response (**Figure 1**) [13]. This was not always the case: in the 1960s, Orie and colleagues proposed that all airway diseases, including asthma, emphysema, and chronic bronchitis, should be considered the single entity of “chronic non-specific lung disease” that share common genetic origins – this became known as the “Dutch hypothesis” [14]. Expectedly, there was opposition from others who argued that asthma and COPD were distinctly different diseases with dissimilar causal mechanisms, the “British hypothesis” [15,16]. The debate persists even over half a

century later and to some extent both hypotheses have merit [16-18]. In recognition of the presence of both distinctive as well as overlapping features, the term “asthma–COPD overlap syndrome” (ACOS) has emerged to describe patients with clinical features of both diseases [11,12]. Both GINA and GOLD guidelines have acknowledged this and proposed that clinicians should assess for features of both asthma and COPD and where present, a diagnosis of ACOS considered. Consequently, early work on ACOS assessed for asthma symptoms in COPD populations however it is also important to consider the assessment of COPD feature in asthmatic populations, the latter being less commonly sought [19-24].

The true prevalence however of ACOS varies considerably due to the lack of standardized definitions that has more recently been addressed [19,25]. There is also substantial variation in the reported mortality in ACOS [26-29] due in large part to differences in study definitions. ACOS is therefore a heterogeneous group of disorders; where different subtypes result in diverse clinical outcomes. This is supported by a large prospective study that subdivided ACOS into early and late onset asthma groups. Higher mortality was observed in late onset asthma related ACOS compared to that in early onset asthma [29]. The potential difference in intrapulmonary pathology, delay in diagnosis and treatment and potential contribution of comorbidities in the late onset asthma group may account for the worse prognosis. Crucially, patients with ACOS have been excluded from most clinical trials hence the evidence base to inform optimal treatment for this specific group is lacking.

Bronchiectasis is an irreversible structural airway dilatation identified by high-resolution computed tomography (HRCT). This contrasts to COPD which is

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96 physiologically diagnosed on the basis of poorly reversible airflow obstruction, degree of
97 symptoms and frequency of exacerbations [11,30,31]. Changes in the airway wall are
98 usually milder and more diffuse in COPD as compared to bronchiectasis where etiology,
99 severity and airway geometry all play important roles. Despite such differences, both
100 diseases share common symptoms of dyspnea, chronic productive cough, airflow
101 obstruction and susceptibility to recurrent exacerbations due to new or persistent
102 infection. The presence of bronchiectasis in COPD is now recognized as a potential new
103 phenotype of the COPD state [11]. The overlapping of these two conditions was first
104 described by Barker in 2002 and since, prevalence has increased, now reported in up to
105 57.6% of COPD patients [32-37]. High levels of pro-inflammatory cytokines, lower
106 airway bacterial colonization and longer symptom recovery time following exacerbation
107 are described in BCOS [35]. Both severity of detected airflow obstruction and at least one
108 hospital admission for an exacerbation in the previous year have been associated with
109 bronchiectasis in moderate to severe COPD [34]. Intubated intensive care unit (ICU)
110 patients with BCOS experience longer duration of both ICU and hospital stays, prolonged
111 mechanical ventilation and increased risks of ventilator-associated pneumonia however
112 no independent effect on mortality is clearly described [38]. Recent work however has
113 described high mortality rates (28.5%) in individuals with BCOS over a prolonged period
114 of 48 months suggestive of a poorer prognosis [39]. The geometric and anatomical
115 variation to the bronchiectasis (tubular, varicose and cystic) described in BCOS has not
116 been highlighted clearly in existing studies however, bronchiectasis in BCOS tends to
117 localize to the lower lobes, is bilateral and spares central regions [34,35]. Importantly, a
118 single study did show that tubular patterns of bronchiectasis were predominant over other

types in BCOS but further work is clearly needed to better understand this relationship [36]. While existing work in this field is varied and difficult to compare, it is clear that the mere existence of BCOS is associated with different clinical manifestations, treatment responses and prognosis compared to COPD alone, all factors warranting further work to better understand the BCOS-state.

Pulmonary fibrosis is an interstitial lung disease resulting in scarring. Overlap between the clinical features of pulmonary fibrosis and COPD (herein referred to as ‘fibrosis-COPD overlap syndrome’ – FCOS) is supported by emerging evidence linking the shared features of both conditions to a common underlying pathophysiology [40,41].

While FCOS awaits formal clinical definition, and is less broadly acknowledged in the clinical literature, it is clear that similarities between both idiopathic pulmonary fibrosis (IPF) and COPD do exist, and that overlap represents a potentially overlooked clinical phenomenon (**Figure 1**). Indeed, overlap between fibrosis and emphysema (a common diagnostic feature of COPD) has been given recognition as a newly defined ‘combined pulmonary fibrosis and emphysema syndrome’ (CPFE) [40]. This likely represents an important sub-category of FCOS encompassing patients with distinct features such as loss of alveolar parenchyma and apparent alveolar senescence, strongly associated with inhalation of noxious agents (most frequently tobacco smoke) [40,42]. Recent evidence further points to overlap between underlying factors of disease pathogenesis in patients with symptoms of FCOS [42]. The most striking of these is telomere length, reduced in familial IPF and of shorter length in COPD versus controls. Consequently, the senescence hypothesis has emerged for both COPD and IPF, highlighting similarities between the

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conditions in terms of premature lung aging. Notably, dysregulation of pathways governing parenchymal tissue development and remodeling, including NOTCH and Wingless-related integration site (WNT), are implicated in both IPF and COPD pointing to a common endotype likely of relevance for the FCOS-state [42].

Arising from intermittent collapse of the upper airway consequently resulting in reduced or absent inspiratory airflow, OSA is characterized by obstructive sleep respiratory events (apneas, hypopneas and arousals), signs of disrupted sleep and daytime symptoms of poor sleep [43]. Patients with COPD also suffer from poor sleep quality primarily due to nocturnal coughing and breathlessness that hinders sleep initiation and maintenance [44]. The association of COPD with OSA, first described by Flenley, identifies patients with overlap to have greater degrees of nocturnal hypoxemia and hypercapnia when compared to patients with COPD or OSA in isolation [45]. Subsequent studies have further shown that daytime oxygen desaturations, hypercapnia and a reduced quality of life are greater in an OSA-COPD overlap versus COPD alone [46-48]. Patients with overlap untreated with continuous positive airway pressure (CPAP) appear to have higher all-cause mortality [49,50]. This is likely due to cardiopulmonary complications such as pulmonary hypertension and cardiac arrhythmias arising from prolonged and profound hypoxemia [51,52]. Clearly, OSA-COPD overlap syndrome (herein referred to as OCOS) represents an emerging disease group that requires attention and detailed study.

2. THE CHALLENGES OF COPD-OVERLAP SYNDROMES FOR SCIENTISTS, CLINICIANS AND PATIENTS

The emergence of COPD-overlap syndromes has posed particular, unique and differing challenges for scientists, clinicians and patients (**Table 1**). The major challenge for scientists in dissecting COPD-overlap syndromes lies in the ill-defined nature of these conditions. A more precise robust classification is critical from a research perspective as an inaccurate diagnosis can complicate cohort selection and confound data interpretation from clinical studies. The overlap patient is often overlooked by study exclusion criteria and as such, patients suffering from COPD-overlap syndromes have been less studied owing to clinical study design [19,53-55]. The classification of patients into a given disease category may be overly simplistic because of the heterogeneous clinical phenotypes observed in routine practice [56]. Therefore, an identification of distinct reproducible patient biomarkers that can satisfactorily discriminate patient groups remains the holy grail of scientific efforts dedicated to an improved understanding of COPD-overlap syndromes. Notwithstanding this and its associated major challenges, promising results from unsupervised clustering approaches involving proteomic and transcriptomic data from patient sputum samples have emerged in the context of asthma [57]. While the importance of the microbiome in predicting outcomes in COPD, asthma, bronchiectasis and IPF has been documented, a key challenge for future researchers is to distill from such molecularly rich-information a more granular clinician-friendly patient stratification system and thus provide scope for targeted precision medicine approaches for COPD-overlap syndromes [58-62].

Overlap syndromes pose several diagnostic and therapeutic challenges for the clinicians involved. **The consensus definition for ACOS is relatively new and the lack of**

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188 standardization in the past has limited a rigorous discussion of diagnosis, prevalence,
189 pathophysiology, treatment and outcomes [19]. Additionally, a high index of suspicion is
190 required for diagnosis and the monitoring of disease progression in ACOS. Therapeutic
191 response is also more difficult to monitor due to complexities associated with physiologic
192 variability in an overlap setting. For instance, detecting a preserved or slightly reduced
193 lung volume does not rule out the presence of fibrosis in a patient with COPD or
194 emphysema. Similarly in patients with fibrosis, forced vital capacity (FVC) and diffusing
195 capacity of the lungs for carbon monoxide (DLCO) measurements, used to monitor
196 disease progression or therapeutic response are different in CPFE patients who tend to
197 exhibit delays in the reduction of FVC and DLCO reducing their utility as surrogate
198 markers for disease progression [63,64]. Serial FVC changes similarly lack prognostic
199 significance in CPFE unlike other types of pulmonary fibrosis, and the rate of FEV1
200 decline is rather the strongest predictor of mortality in CPFE. Despite this, DLCO
201 declines are important as they herald the development or progression of pulmonary
202 hypertension, a feature commonly encountered in CPFE [63,65]. Patients with overlap
203 syndromes have higher morbidity and mortality. Patients with ACOS have more frequent
204 exacerbations, greater lung function decline, higher healthcare utilization and greater
205 economic burden compared to those with asthma or COPD alone [28,29,66]. However
206 conflicting results do exist, some of which report no significant differences [27,67,68].
207 This could be explained by smaller patient number, shorter duration of follow up and
208 importantly differences in ACOS definition. Patients with OCOS illustrate severer
209 hypercapnia and pulmonary hypertension versus sleep apnea–hypopnea syndrome or
210 COPD alone [69]. BCOS is associated with increased mortality especially in the setting

of reduced FEV1 [70,71]. Compared to COPD, BCOS is twice more likely to have exacerbations, four times more likely to isolate potentially pathogenic microorganisms, and also more likely to have severe airway obstruction and higher mortality [72].

Patients with overlap syndromes themselves face unique challenges. Delays in diagnosis can sometimes occur because of the contrasting opinions from specialists. This results in both anxiety and potentially extra costs due to additional investigations and specialist visits. Specifically, ACOS patients have higher mortality rates [28,29], more frequent exacerbations, healthcare utilization and economic burden. **Importantly, one must be cautious in the interpretation of the causal relationship between overlap and cost, given that patients with higher healthcare utilization may have increased opportunity for diagnosis leading to bias [73-79]. In this light, the parameters by which ACOS is defined also merit careful consideration when trying to quantify health care burden [19]. In addition to these increased challenges, patients also experience for unknown reasons higher risks of pulmonary embolism and tuberculosis [80,81].** OCOS patients have greater sleep disturbance, nocturnal desaturation, higher Epworth sleepiness scores, lower total sleep time and efficiency, higher arousal and poorer sleep quality [46,82]. Resting and exertional hypoxemia are more common in FCOS translating to greater symptomatology and poorer six minute walk distances as compared to smokers without interstitial lung abnormalities [40,83]. Patients with COPD-overlap syndromes are generally excluded from clinical trials and consequently don't benefit from newer drugs or available interventions which, in turn, has been one reason for the lack of tangible progress in our understanding of these recognized syndromes.

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234 **3. THE EPIDEMIOLOGY OF COPD-OVERLAP SYNDROMES**

235 Some key issues must be considered in the interpretation of epidemiological
236 studies addressing COPD-overlap syndromes. First, the definitions of such overlap
237 syndromes need greater clarity as currently no clear consensus exists on what specifically
238 constitutes an overlap syndrome. **An operational definition has recently been proposed**
239 **[19] based on three major criteria and at least one minor criterion (Table 2), but this**
240 **awaits wider adoption by future studies.** Second, epidemiological studies addressing this
241 field are heterogeneous particularly in their methodology and specifically case definitions.
242 For example, in the case of ACOS, most studies have employed use of physician
243 diagnoses, claims data, self-reported diagnosis or questionnaires, and few base their case
244 definitions on spirometry. Even in cases of the latter, diverse pulmonary function criteria
245 have been employed to diagnose ACOS. ACOS itself may also comprise of multiple
246 phenotypes, for example, asthma preceding COPD, or COPD preceding asthma, or both
247 diagnosed at the same time. Epidemiological work addressing ACOS also differs based
248 on the population that forms the denominator, for instance whether it is an entire
249 population, or a base population of COPD or asthma patients. There are further variations
250 in the origin of the population being studied and whether this originates from primary or
251 secondary care. Different case definitions therefore generate different prevalence
252 estimates. The PLATINO study is a multicenter population-based study of ACOS where
253 COPD was defined as post bronchodilator FEV1/FVC < 0.7 and asthma was defined as
254 wheezing or having a significant bronchodilator response (>12% and >200ml) [84].
255 ACOS prevalence was 1.8% (Table 1). **A Spanish EPI-SCAN study, whose study met the**
256 **proposed definition of ACOS [19], found that 17.4% of patients with spirometry-defined**

COPD had a prior asthma diagnosis [23]. Studies by Golpe *et al* found the prevalence of ACOS to be different where they assessed COPD caused by the effects of tobacco smoke versus that from biomass exposure (5% vs 21.3% respectively) [21]. Reported prevalence of ACOS ranges from 6.5% to 13% [85,86]. As compared to prevalence data derived from COPD populations, studies to determine ACOS prevalence using asthmatic populations are far less common. In a primary care setting, asthma patients with no prior reported history of COPD, but who were current or ex-smokers illustrated a high ACOS prevalence of 27.4% [20]. It should be noted that cohort studies of asthma or COPD patients are also enriched patient populations and therefore vulnerable to selection bias. This could account for the interstudy discrepancies in prevalence estimates of ACOS, in contrast to random sampling methods of population-based epidemiological work.

Less is known about the prevalence of BCOS, attributable at least in large part to a lack of uniform definition. Whether bronchiectasis and COPD are inter-related or independent entities that develop concurrently remains unclear, for example traction bronchiectasis cannot strictly be termed BCOS because of the interdependence of one process on the other. Wide varying prevalence rates of BCOS are reported (Table 1). In the ECLIPSE study, a longitudinal, observational, multinational COPD cohort, only 4% had radiological evidence of bronchiectasis as adjudicated by two independent radiologists [33]. In a separate primary care cohort of n=110 patients who received an initial diagnosis of acute exacerbation of COPD, 29% had HRCT evidence of co-existing bronchiectasis [36]. Importantly, 12.3% of this cohort did not have spirometric evidence of airflow limitation and 5% of these patients received a final diagnosis of chronic asthma.

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280 A similar retrospective study found that 69% of those admitted for the first time with a
281 diagnosis of COPD exacerbation had radiological evidence of bronchiectasis [87].
282 Interestingly, in Asian COPD studies, up to 50% have been documented to have BCOS
283 most likely because of the high population prevalence of post-infectious bronchiectasis
284 [88,89].

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286 The prevalence of OCOS is difficult to estimate (**Table 1**). Sleep disordered
287 breathing occurs secondary to COPD itself and hence definitions require clarity and
288 specificity. Early studies that reported a strong overlap between OSA and COPD suffered
289 from selection bias because such patients were already referred to a sleep clinic at the
290 time of data collection. The most significant study to estimate the prevalence of OCOS,
291 the Sleep Heart Health Study, found no difference in the prevalence of OSA among
292 patients with and without an FEV1/FVC ratio < 0.7. This applied spirometry-based
293 criterion encompasses a broader group of obstructive lung disease rather than specifically
294 COPD *per se*, and the study population importantly consisted solely of individuals with
295 relatively mild obstruction [46]. A European community population-based study reported
296 that only 1% of the total population and 9.2% of those with OSA, confirmed on
297 polysomnography, had COPD based on spirometry. While COPD was frequently
298 detectable in OSA patients in the general population, those with overlap had a more
299 severe course of sleep-disordered breathing suggestive of the disadvantageous effects
300 from overlap between the two clinical states [46].

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FCOS has been described more specifically as CPFE, with upper lobe emphysema coupled to lower lobe fibrosis and honeycombing [40]. The precise prevalence is unknown (**Table 1**) and almost all patients with CPFE have a smoking history, a mutual risk factor for both IPF and emphysema. Interestingly, connective tissue disease has also been described as a major risk factor suggestive of an autoimmune component to its etiology [90].

4. WHAT PREDISPOSES TO COPD-OVERLAP SYNDROMES?

Shared risk factors coupled to common pathways of pathogenesis predispose particular individuals toward the development of certain COPD-overlap syndromes. Once widely regarded as having distinct inflammatory patterns, more recent work has demonstrated several common inflammatory pathways in both asthma and COPD. Asthmatic patients with late-onset disease or a positive smoking history can exhibit COPD-associated characteristics such as airway neutrophilia, abundance of macrophages, high CD8 counts and airway epithelial remodelling [91-93]. Conversely, a subset of COPD patients may demonstrate a Th2-type eosinophilic inflammatory profile, a traditional asthma characteristic [94,95]. It however remains to be elucidated whether such inflammatory pathways translate and can explain some of the overlapping features of ACOS. Bronchial hyper-responsiveness, a recognised asthmatic feature, is in part driven by eosinophilic inflammation and predicts a greater rate of FEV1 decline in early COPD [96]. In long-standing and more severe asthma, structural factors such as fixed airway obstruction are detectable due to a loss of reversibility, decreased lung elastic recoil and the development of microscopic centrilobular emphysema [97]. Such

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325 pathophysiologic mechanisms occur in the absence of smoking and predispose to clinical
326 features similar to that observed in COPD (**Figure 2**). Several risk factors are recognized
327 in the pathogenesis of ACOS. Smoking promotes airway inflammation, increases
328 bronchial hyper-responsiveness and confers steroid resistance [93,98,99]. Over the long-
329 term, smoking accelerates lung function decline and increases respiratory symptoms
330 [100]. Recent population-based work has detected that high level exposures to air
331 pollution increases the risk of developing ACOS in an asthmatic cohort independent of
332 smoking [101]. While allergic phenotypes are well recognized in asthma, up to 30% of
333 COPD sufferers demonstrate aeroallergen sensitization [102]. The presence of such
334 allergic sensitization in COPD is independently associated with worse respiratory
335 symptoms and more exacerbations [102,103].

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337 Chronic airway inflammation, genetics and environmental influence all have
338 important and independent roles in the pathogenesis of both bronchiectasis and COPD.
339 The inflammatory response, in both cases, involves neutrophils, macrophages and CD8+
340 T-cells, which are responsible for attenuating airway damage [104]. In bronchiectasis,
341 pathology is largely attributed to recurring infection and inflammation that leads to
342 neutrophil proteinase extravasation. Consequently, bronchial damage ensues impairing
343 host defences and permitting further bacterial colonization and dilatation which in turn
344 incites the process again [105]. Risk factors for COPD include cigarette smoking;
345 exposure to indoor air pollution, occupational risks and recurrent childhood lower
346 respiratory tract infections [106]. Whilst some have suggested that outdoor air pollution
347 and COPD are linked, large prospective epidemiological studies are required before

causality can be established. Inhalation of noxious aerosols leads to mucociliary dysfunction and loss of tight junctions between airway epithelia consequently resulting in inflammation, bacterial colonization and subsequent exacerbations. This repeated cycle of chronic infection and inflammation leads to microbe persistence that causes further tissue damage and airway remodelling (**Figure 2**). *Pseudomonas aeruginosa* is a key gram negative organism of importance in both bronchiectasis and COPD. It is associated with disease severity: up to one third of patients with bronchiectasis are colonized while it may be recovered from up to 20% of COPD airways conferring more exacerbations and worse prognosis [107-112]. The role of *P. aeruginosa* in the context of BCOS has yet to be elucidated [34,109]. Alpha-1 antitrypsin (AAT) deficiency (AATD) is a known genetic risk factor for COPD. The prevalence of COPD in AATD ranges from 1-4.5% in the homozygous PI*ZZ phenotype and 17.8% in heterozygous PI*MZ phenotype [113]. Importantly there are considerable discrepancies in pulmonary function abnormalities and the development of COPD in AATD, suggesting involvement of other risk factors such as cigarette smoking and environmental exposures. AATD is detectable in bronchiectasis however BCOS has not been specifically examined [114-117]. A significant association between emphysema and bronchiectasis caused by AATD has been described suggestive that bronchiectasis could be a consequence of emphysema [114]. Importantly, some patients with bronchiectasis do not demonstrate obvious emphysema and the precise mechanisms driving bronchiectasis in the context of COPD remain ill-defined. AATD patients with an element of reversibility also appear to have poorer prognosis suggestive of the key influence conferred when an overlap pattern exists [118]. Detailed and well-

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370 designed future studies targeting mechanisms to better understand the pathogenesis of
371 BCOS are clearly warranted.

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373 Smoking has deleterious effects on both COPD and IPF [11,119]. Both conditions
374 increase with age and have a male preponderance [24,40,120-122]. Despite the distinctive
375 nature of both conditions, striking similarities exist. Both diseases occur later in life
376 [24,120] with episodes of exacerbation punctuating their clinical course [123,124].
377 Deposition of collagen and the existence of fibrosis (small airways in COPD and the lung
378 parenchyma in IPF) co-exist in the setting of FCOS. It has therefore been hypothesized
379 that an accelerated biological lung aging or abnormal aging process predisposes
380 individuals to either or both diseases concurrently resulting in FCOS (**Figure 2**) [42,125].
381 Mechanisms underlying FCOS remain poorly characterized however several factors,
382 common to both diseases, likely play key roles that include smoking induced-oxidative
383 stress [126,127], telomere length abnormalities or mutation [128-135], accelerated
384 cellular and immunosenescence [122] and altered anti-aging molecular and extracellular
385 matrix markers such as klotho and sirtuins [125]. Clearly, much is still to be done and
386 remains unknown within the FCOS field.

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388 The pathogenesis of OCOS is multifactorial. Mechanical factors predispose and
389 play a significant and more prominent role in OCOS as compared to other overlap
390 pathologies. Upper airways resistance is accentuated in both COPD and OSA such that a
391 longer time constant is required for lung emptying (**Figure 2**) [136]. Lung hyperinflation
392 produces diaphragmatic flattening and decreases its efficiency for generating sufficient

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10 396 maintain ventilation. Obesity, commonly associated with both OSA and the 'blue-bloater'
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12 397 COPD clinical phenotype, can further exacerbate upper airway obstruction, respiratory
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14 398 muscle weakness and chest wall restriction [137]. Overall, more sustained and excessive
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16 399 hypoxemia and hypercapnia develops [82]. Consequently, hypoxemia predisposes to
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18 400 increased sympathetic activity and a higher frequency of cardiac dysrhythmias [138,139].
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20 401 Pulmonary hypertension is also more pronounced and develops in the presence of factors
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22 402 such as airflow obstruction, hypoventilation, hypoxemia and obesity [51,82,140].
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24 403 Increased right ventricular hypertrophy and remodeling with resultant right heart failure
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26 404 have been demonstrated in OCOS patients [52]. Systemic inflammation also contributes
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28 405 to OCOS. Elevated C-reactive protein (CRP), interleukins-6 (IL-6) and -8 (IL-8), and
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30 406 tumor necrosis factor-alpha (TNF- α) have all been found in OCOS patients and may be
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32 407 associated with cardiovascular disease [141-144]. In response to hypoxemia and smoking,
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34 408 oxidative stress leads to increased reactive oxygen species (ROS) production and
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36 409 resultant pulmonary vascular endothelial damage, an important vascular consequence of
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38 410 the overlap state [145].
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48 412 5. THE MICROBIOME IN COPD-OVERLAP SYNDROMES

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52 414 presence of pathogenic organisms often serving as prognostic markers for disease
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54 415 progression [146]. Respiratory pathogens such as *Pseudomonas aeruginosa* can
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416 precipitate exacerbation and predict poorer clinical outcomes in bronchiectasis and
417 COPD while stronger evidence surrounds the role of **viral infection** in the pathogenesis of
418 IPF [146,147]. In asthma, infection by common respiratory viruses is often associated
419 with exacerbations, while bacteria and even fungi are associated with severe forms of
420 disease such as Severe Asthma with Fungal Sensitization (SAFS) [93,148].

421

422 As well as recognising specific pathogenic organisms, a growing appreciation
423 exists for the role of the microbiome in human disease, laying the foundations for the
424 development of novel diagnostic and therapeutic approaches [149]. **This is becoming**
425 **evident in respiratory medicine, where the composition of the microbiome (and**
426 **perturbations therein) clearly plays an important role in respiratory infections, is now also**
427 **implicated in asthma and COPD [122,150,151].** The pathogenesis of COPD, asthma,
428 bronchiectasis and IPF have been subjected to lung-microbiome studies, with likely
429 implication for the detection and management of COPD-overlap syndromes. Microbiome
430 analysis has revealed the healthy lung to be predominated by bacterial genera including
431 *Pseudomonas*, *Streptococcus*, *Prevotella* and *Fusobacterium* as well as *Haemophilus*,
432 *Veillonella*, and *Porphyromonas* [152]. Changes in composition, bacterial load or the
433 presence of specific pathobiont species within the microbiome may accompany chronic
434 lung conditions including COPD, asthma, bronchiectasis and IPF [58,59,61,150]. It
435 follows that specific changes may also predict sub-categories of disease including COPD-
436 overlap syndromes and therefore permit a more refined patient stratification.

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In tandem, the gut microbiome has also been implicated in disease pathogenesis via a gut-lung axis. This has been evaluated in asthma and work continues in other chronic respiratory disease settings making the gut microbiome a potentially key biomarker for lung disease including that in overlap syndromes [150]. Other sites, such as the oral cavity, may also prove important. For instance, it has been shown that the oral microbiome is significantly altered on exposure to cigarette smoke - a major risk factor for COPD - and that infiltration of these oral microbiota into the lung leads to increased inflammation [153]. Such metagenomic studies build on our knowledge base of associations between microbiome status and adverse clinical outcomes in lung diseases such as COPD where the presence of specific organisms can trigger acute exacerbations in addition to perpetuating immune responses during chronic colonisation. As the pathogenesis likely proceeds along several microbiome axes, an analysis of the microbiome at multiple body sites may ultimately provide the most informative picture. In addition, sampling of the patient's environment such as the home using metagenomic sequencing technologies may also be useful in terms of identifying known allergens such as fungi, contributing to disease pathogenesis in overlap syndromes [154]. Geographic variability in the respiratory human microbiome is another consideration as results must be interpreted in the context of regional and population-specific microbiome signatures that vary considerably [155].

6. THE DIAGNOSIS AND MANAGEMENT OF COPD-OVERLAP SYNDROMES

ACOS: GINA and GOLD guidelines focused on asthma and COPD respectively outline a description of ACOS as an "Asthma-COPD overlap syndrome (ACOS)

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461 characterized by persistent airflow limitation with several features usually associated with
462 asthma and several features usually associated with COPD (**Table 3**). ACOS is therefore
463 identified by the features that it shares with both asthma and COPD.” The key variables
464 to consider for diagnosis include age of onset, pattern and time course of symptoms,
465 personal or family history of atopy, variable or persistent airflow limitation, symptomatic
466 lung function change and the presence of hyperinflation on chest radiography
467 [11,12,156,157]. More recently, a group of global experts agreed a consensus definition
468 of ACOS that includes the presence of all three major criteria and at least one minor
469 criterion for ACOS (**Table 2**) [19]. As opposed to traditional clinically-driven phenotypes,
470 ACOS may be better defined by biological tools, such as fractional exhaled nitric oxide
471 (FENO) and/or blood eosinophils. Three recent studies have found FENO to be a
472 potential surrogate biomarker for identification of patients with ACOS [158-160].
473 Patients with ACOS differing by study definition had significantly higher FENO levels
474 than those with COPD alone. In addition, blood eosinophils were also ascribed as a
475 potential biomarker in a Japanese COPD cohort [158] with a blood eosinophil count
476 of ≥ 300 cells/ μ L as a minor criteria in the recent consensus definition (**Table 2**) [19].

477

478 The presence of different ACOS phenotypes, such as eosinophilic, neutrophilic,
479 asthma in smokers or non-smokers exposed to biomass has been suggested by Bateman *et*
480 *al.* [161] while Barnes challenges the term “syndrome” , referring to it as misleading
481 because it encompasses these particular phenotypes under a single umbrella (e.g. COPD
482 and eosinophilic inflammation, smoking asthmatics or those with severe disease and
483 predominantly neutrophilic inflammation, and patients with asthma and irreversible

airway obstruction due to structural change). He importantly proposes that it may be better to use asthma-COPD overlap (ACO), rather than ACOS to describe this clinical state [162]. Clearly, the concept of ACOS or ACO is evolving and further work including unbiased phenotyping studies of broad populations with chronic airways disease may prove useful for identifying ACOS phenotypes. ACOS patients have greater comorbidities (such as allergic rhinitis, anxiety, gastroesophageal reflux disease and osteoporosis) compared to COPD alone and the presence of cardiovascular diseases in ACOS patients is associated with hospitalization in a single study [163].

According to GINA guidelines, if syndromic assessment is equally balanced between asthma and COPD in ACOS, then treatment should be commenced as it would for asthma alone with low or moderate doses of ICS followed by the addition of a long-acting β -agonist (LABA) and/or long-acting muscarinic antagonists (LAMA) (Table 3). Critically, a lack of comprehensive therapeutic trial data persists in ACOS, except for a single study comparing the efficacy of once-daily fluticasone furoate/vilanterole (FF/VI) with twice-daily fluticasone propionate/salmeterol (FP/SAL) [164]. This twelve-week, randomized, open-label cross-over trial studied 16 patients and described a significant FEV1 improvement after four weeks of FF/VI treatment compared to the run-in period. Importantly, however other assessed parameters including FeNO levels, CAT scores, ACT scores, and other blood tests were not significantly different over the same period.

Of note however, regular use of ICS in ACOS is associated with an increased risk of pneumonia especially in those with severe COPD [11]. A recent study suggests that omalizumab improves asthma control and health-related quality of life in individuals with

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507 severe allergic asthma and overlapping COPD. These findings provide the first real-world
508 efficacy data for this patient population and suggest that omalizumab may be useful in the
509 management of severe asthma with COPD overlap [165]. Despite the existing evidence
510 base, much work remains to better understand the optimal methods for both the diagnosis
511 and the effective treatment of ACOS.

512

513 **BCOS:** This syndrome is a particular clinical challenge to diagnose, as both
514 conditions present with cough, sputum production, repeated exacerbations and dyspnea
515 [11,31,166]. Obstructive airflow physiology is required for a COPD diagnosis but this
516 may not be always be present in bronchiectasis. As a suppurative structural lung disease,
517 bronchiectasis is largely dependent on radiological evidence to detect features of airway
518 dilatation, lack of peripheral airway tapering and cystic or varicose airway change. This
519 is in contrast to COPD, where airway wall changes are more subtle, manifesting as
520 generalized and mild thickening. It is therefore proposed that BCOS should have the
521 following diagnostic features: history of exposure to inciting agents such as tobacco
522 smoke, severe fixed airflow obstruction and airway wall CT abnormalities (**Table 3**)
523 [34,53]. Microbiological investigations are useful in this particular overlap syndrome as
524 the detection of colonization or infection by organisms such as *P. aeruginosa* may
525 portend greater pulmonary function decline, more frequent exacerbations and higher
526 mortality [146,167]. The optimal management of BCOS requires further work although
527 antibiotics should certainly be considered if airway infection with *P. aeruginosa* is
528 detected due to the higher risks of pneumonia and hospitalizations associated with this
529 BCOS subgroup [38]. However, the route of administration and duration of such

antibiotic therapy remain uncertain [53]. Long term macrolide therapy for anti-inflammatory and anti-microbial effects may also reduce infectious bronchiectasis exacerbations, although the risk of antibiotic resistance is presumably high but remains uncertain (**Table 3**) [168]. Treatment options targeted at COPD, including inhaled corticosteroids and bronchodilators, may be indicated in BCOS particularly if patients frequently exacerbate.

FCOS: FCOS has male preponderance, and symptoms of exertional dyspnoea and cough are its most common presentation [90]. The radiological appearance is distinct with features of upper lobe emphysema and lower lobe fibrosis, traction bronchiectasis and honeycombing [40]. Due to the combined effects of pulmonary fibrosis and emphysema on pulmonary function, FCOS is characterized by normal to reduced lung volumes with disproportionately low oxygen saturation and severely reduced diffusion capacity (**Table 3**) [41,90,169]. Associations with connective tissue disease (CTD) are described and a CTD assessment should be performed in all cases [90]. Evaluation for pulmonary arterial hypertension (PAH) should be pursued due to its higher incidence in FCOS patients [170]. To date, no established treatment regime exists for FCOS. The deleterious effects of smoking on COPD and IPF are recognised and smoking cessation is therefore recommended [119]. In the presence of significant hypoxemia and pulmonary hypertension, oxygen therapy should be prescribed based on its benefits demonstrated in COPD [171]. The role of corticosteroids and immunosuppression remains unclear but may be a therapeutic option in CTD-related FCOS [90]. Newer anti-fibrotic agents such as pirfenidone and nintedanib have recently been approved for the treatment of IPF

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553 however their role in FCOS requires dedicated evaluation and clinical study [54,172].

554 Despite a poor prognosis, there is currently insufficient evidence to recommend the use of

555 pulmonary hypertension specific therapies in the setting of FCOS (**Table 3**) [173].

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557 **OCOS:** Typically, OSA is defined as an Apnea-Hypopnea Index (AHI) of 5 or

558 greater with associated symptoms (e.g., excessive daytime sleepiness, fatigue, or

559 impaired cognition) or an AHI of 15 or greater, regardless of symptoms [174]. Generally,

560 a high index of clinical suspicion is required to both consider and diagnose OCOS (**Table**

561 **3**). The presence of hypoxaemia, hypercapnia and pulmonary hypertension that is out of

562 proportion to severity of either disease should prompt further assessment for the other

563 disorder [175]. Continuous Positive Airway pressure (CPAP) is the first line treatment for

564 OCOS (**Table 3**). Two large observational cohort studies have demonstrated its mortality

565 benefit in this setting when compared to medical therapy alone [49,50]. Interestingly,

566 CPAP-treated OCOS patients were less likely to have severe COPD exacerbations

567 requiring hospitalization [49]. In stable chronically hypercapnic COPD patients, the use

568 of bi-level positive airway pressure (BIPAP) is preferred to CPAP. This therapy targets a

569 reduction of hypercapnia and improved survival particularly in GOLD stage IV COPD

570 [176]. Importantly, no controlled studies have been performed in an OCOS population

571 therefore limiting the evidence base available for clinicians.

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573 **7. EXPERT COMMENTARY**

574 COPD-overlap syndromes are clearly emerging as a major challenge in

575 respiratory medicine. Affecting clinicians, allied health professionals, scientists and most

of all patients, the forthcoming decade will undoubtedly reveal novel features of these disease overlaps with the potential for paradigm shift in our understanding of pulmonary health and disease trajectory. Only time will tell whether these overlap syndromes truly represent separate disease entities to the traditional classification of individual respiratory disease states such as asthma or COPD. What is more likely however is that they are mixed phenotypes, a combination of one or more established disease entities in a single individual.

There are several important challenges and opportunities for both clinicians and scientists as this field evolves. An improved clinical and molecular phenotyping method is required to better stratify these challenging patient cohorts and understand disease pathogenesis, one that could be addressed with a systems biology approach and the use of emerging ‘omics’ technologies including genomics, metabolomics and proteomics. We must however be extremely cautious that our increasing recognition of COPD-overlap syndromes in clinical practice does not simply result in greater patient ‘labelling’. It is critical that this improved endo-phenotyping of overlapping respiratory disease states translates to better patient management and facilitates the practice of precision medicine. One potential method by which this may occur is to focus on risk factors or co-morbidities unique to each ‘overlapping’ COPD-related state creating a management plan that is both patient and situation specific [177]. To better understand the clinical course and improve diagnostic and subsequently therapeutics for COPD-overlap syndromes, we must consider (a) challenges that currently exist for recruitment into both clinical trials and molecular studies, where to date most overlap patients have largely been excluded and (b) how to interpret results from large cohort studies where COPD-overlap

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599 syndromes may be present or haven't been assessed for. Clearer guidelines based on
600 definitions of these overlap states are now necessary to aid clinicians better identify and
601 subsequently stratify these challenging patients with mixed pathologies. This work has
602 already commenced for ACOS but is similarly necessary for other COPD-overlap states
603 [19]. For instance, consensus is required in FCOS to determine what percentage or
604 pattern of fibrosis constitutes an overlap syndrome and what does not. In BCOS, what is
605 the role of dry bronchiectasis if clinical criteria to determine its existence are based on
606 clinical symptoms such as cough productive of purulent sputum and how is this
607 differentiated from chronic bronchitis? These are critical, difficult but key challenges that
608 must be addressed if we are to make progress in better understanding COPD-overlap
609 syndromes and more importantly pathogenic mechanisms common to a variety of
610 respiratory disease states.

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613 **8. FIVE YEAR VIEW**

614 It is now clear that in addition to genetic predisposition and environmental
615 influences, that many other factors such as the host microbiome play a role in both the
616 development and progression of a variety of respiratory pathologies (Figure 3). How
617 such factors influence COPD-overlap syndromes are yet to be elucidated and future work
618 should focus on this area. The precise contribution of genetics and environmental
619 influences that contribute to the development of a COPD-overlap syndrome need to be
620 better understood and studied to inform more accurate, economical and robust diagnostics
621 that will subsequently influence therapeutics. It is likely that these identifiable factors or

their combination in a particular COPD-overlap syndrome is individual hence personalized and a more phenotype-driven precision approach to their management necessary, one that focus on risk factors and the management of co-morbidities [177]. Emerging data suggest that genetics and early-life change influences lung function trajectories followed in later life, which, in turn determines the occurrence of respiratory disease such as COPD [29,178]. Therefore, predictions may now be possible to determine the individuals most likely to develop a particular respiratory disease. It would be valuable in this context to assess cohorts prospectively and determine the development of COPD-overlap syndromes which provides insight into pathophysiological mechanisms that have been driven or influenced by either host, environmental or microbial factors. We are only at the beginning of our own learning trajectory in the complex field of COPD-overlap syndromes but with the appropriate rigour, investment and study designs, our understanding of not just COPD-overlap syndromes but the fundamental airway changes related to a range of respiratory pathologies will certainly be enhanced.

9. KEY POINTS

- Transition from a ‘single diagnosis’ for certain respiratory disease states is now clearly recognized with the emergence of COPD-overlap syndromes such as asthma-COPD overlap syndrome (ACOS), bronchiectasis-COPD overlap syndrome (BCOS), fibrosis-COPD overlap syndrome (FCOS) and OSA-COPD overlap syndrome (OCOS)
- COPD-overlap syndromes represent distinct and unique challenges for clinicians, scientists and patients

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- 645 • A need for clear evidence-based approaches to diagnosis and treatment (including
646 the development of guidelines) are now necessary for COPD-overlap syndromes
647 to aid clinicians and scientists better identify, stratify and research this
648 challenging patient group

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FIGURE LEGENDS

Figure 1: Non-proportional Venn diagram illustrating the centrality of COPD to the main currently described respiratory overlap syndromes including asthma, bronchiectasis, fibrosis and obstructive sleep apnea. COPD – chronic obstructive pulmonary disease, OSA – obstructive sleep apnea, ACOS – Asthma-COPD overlap syndrome, BCOS – Bronchiectasis-COPD overlap syndrome, FCOS – Fibrosis-COPD overlap syndrome and OCOS – OSA-COPD overlap syndrome, HRCT - High-resolution computed tomography.

Figure 2: Predisposing risk factors and their associated complications in the development of the various COPD-overlap syndromes. COPD – chronic obstructive pulmonary disease, OSA – obstructive sleep apnea, ACOS – Asthma-COPD overlap syndrome, BCOS – Bronchiectasis-COPD overlap syndrome, FCOS – Fibrosis-COPD overlap syndrome,

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3 1177 OCOS – OSA-COPD overlap syndrome, ↑ - increased, ↓ - decreased, 6MWT - 6 minute
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5 1178 walk test, PHT - Pulmonary hypertension and QOL – Quality of life.
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10 1180 **Figure 3:** A summary of the major factors that influence the development and
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12 1181 progression of respiratory disease states.
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17 1183 **TABLE LEGENDS**
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20 1184 **Table 1:** (a) Summary of the major challenges encountered in the clinical care and
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22 1185 research of patients with COPD-overlap syndromes (b) prevalence rates of COPD-
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24 1186 overlap syndromes from the existing literature base.
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29 1188 **Table 2:** Criteria for diagnosis of Asthma-COPD overlap syndrome. FEV1: forced
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31 1189 expiratory volume in the 1st second; FVC: forced vital capacity; Bronchodilator response
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33 1190 using 400 µg of albuterol/salbutamol (or equivalent) [19].
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38 1192 **Table 3:** Summary of the diagnostic criteria and treatment approach for the various
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40 1193 COPD-overlap syndromes. CT – Computed tomography, CPFE - Combined pulmonary
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42 1194 fibrosis and emphysema, OSA - Obstructive sleep apnea, COPD – Chronic obstructive
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44 1195 pulmonary disease, - GINA – Global Initiative for Asthma, GOLD - Global Initiative for
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46 1196 Chronic Obstructive Lung Disease and AHI - Apnea–Hypopnea Index, LABA - Long-
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48 1197 acting beta adrenoceptor agonists, LAMA - Long-acting muscarinic receptor antagonists
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50 1198 and CPAP - Continuous positive airway pressure.
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