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REVIEW

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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.

1. Introduction

1.1. 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 endophenotypes 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 characterized 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 USA 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 apnea (OSA).

1.2. 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,
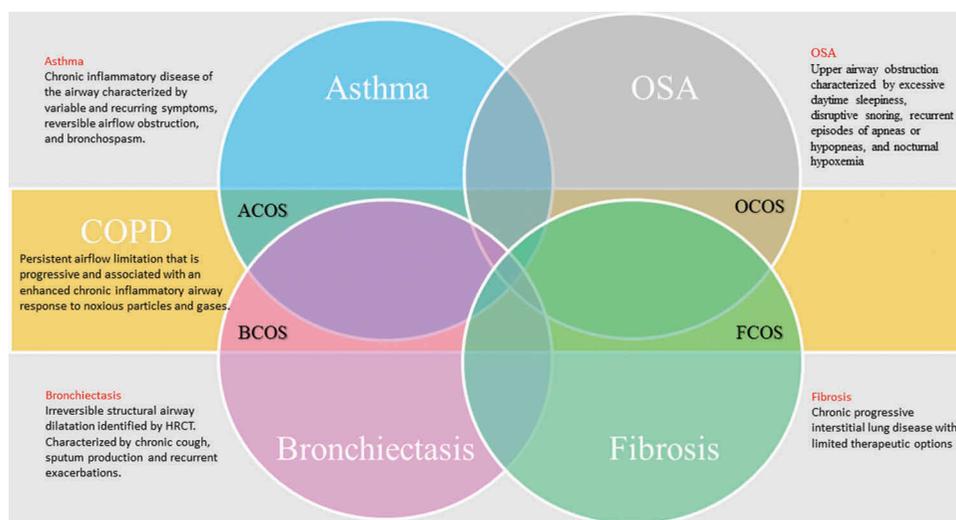
Figure 1. Non-proportional Venn diagram illustrating the centrality of COPD to the main currently described respiratory overlap syndromes including asthma, bronchiectasis, fibrosis and obstructive sleep apnea. COPD – chronic obstructive pulmonary disease, OSA – obstructive sleep apnea, ACOS – Asthma-COPD overlap syndrome, BCOS – Bronchiectasis-COPD overlap syndrome, FCOS – Fibrosis-COPD overlap syndrome and OCOS – OSA-COPD overlap syndrome, HRCT – High-resolution computed tomography.

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 nonspecific 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 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 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 proinflammatory 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 subcategory 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 distil 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].

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.

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

Effects

Diagnosis   Therapy
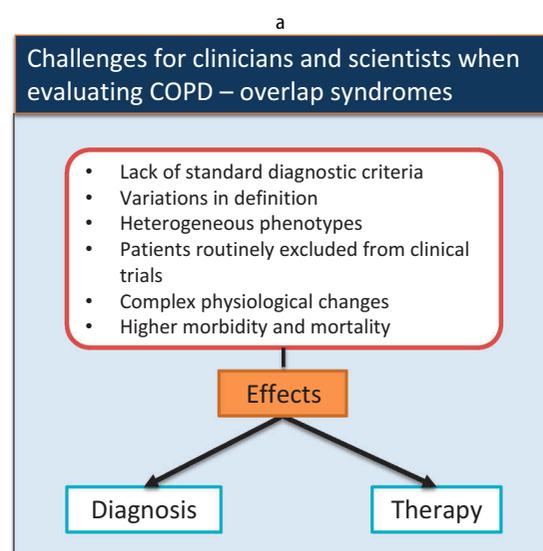
b

COPD – overlap Syndromes	Prevalence rate
ACOS	1.8–27.4% [20,21,23,63,64]
BCOS	4–57.6% [33,36,65–67]
FCOS	Unknown
OCOS	9.2% [46]

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 [68,69]. 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 [68,70]. 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 [28,29,71]. However, conflicting results do exist, some of which report no significant differences [27,72,73]. This could be explained by smaller patient number, shorter duration of follow up, and importantly differences in ACOS definition. Patients with OCOS illustrate more severe hypercapnia and pulmonary hypertension versus sleep apnea–hypopnea syndrome or COPD alone [74]. BCOS is associated with increased mortality especially in the setting of reduced FEV1 [75,76]. 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 [77].

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 [78–84]. In this light, the parameters by which ACOS is defined also merit careful consideration when trying to quantify healthcare burden [19]. In addition to these increased challenges, patients also experience for unknown reasons higher risks of pulmonary embolism and tuberculosis [85,86]. OCOS patients have greater sleep disturbance, nocturnal desaturation, higher Epworth sleepiness scores, lower total sleep time and efficiency, higher arousal, and poorer sleep quality [46,87]. Resting and exertional hypoxemia are more common in FCOS translating to greater symptomatology and poorer 6-minute walk distances as compared to smokers without interstitial lung abnormalities [40,88]. Patients with COPD-overlap syndromes are generally excluded from clinical trials and consequently do not 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 >200 ml) [89].

Table 2. Criteria for diagnosis of asthma-COPD overlap syndrome.

3 major criteria	Either one minor criteria
• ≥40-years old • Persistent airflow limitation (post-bronchodilator FEV1/FVC <0.70 or lower limit of normal) Note: Preference using lower limit of normal	• Recorded history of atopy or allergic rhinitis
• ≥10 pack-years of tobacco smoking OR equivalent indoor or outdoor air pollution exposure (e.g. biomass) • Recorded history of asthma before 40-years old OR Bronchodilator response of >400 mL in FEV1	• Bronchodilator response of FEV1 ≥ 200 mL and 12% from baseline values from ≥2 visits • Eosinophil count of ≥300 cells/μL in peripheral blood.

FEV1: forced expiratory volume in the 1st second; FVC: forced vital capacity; bronchodilator response using 400 μg of albuterol/salbutamol (or equivalent) [19].

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% [63,64]. 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 interrelated 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 coexisting 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. A similar retrospective study found that 69% of those admitted for the first time with a diagnosis of COPD exacerbation had radiological evidence of bronchiectasis [65]. Interestingly, in Asian COPD studies, up to 50% have been documented to have BCOS most likely because of the high population prevalence of post-infectious bronchiectasis [66,67].

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

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

Chronic airway inflammation, genetics, and environmental influence all have important and independent roles in the pathogenesis of both bronchiectasis and COPD. The inflammatory response, in both cases, involves neutrophils, macrophages, and CD8+ T cells, which are responsible for attenuating airway damage [104]. In bronchiectasis, pathology is largely attributed to recurring infection and inflammation that leads to neutrophil proteinase extravasation.
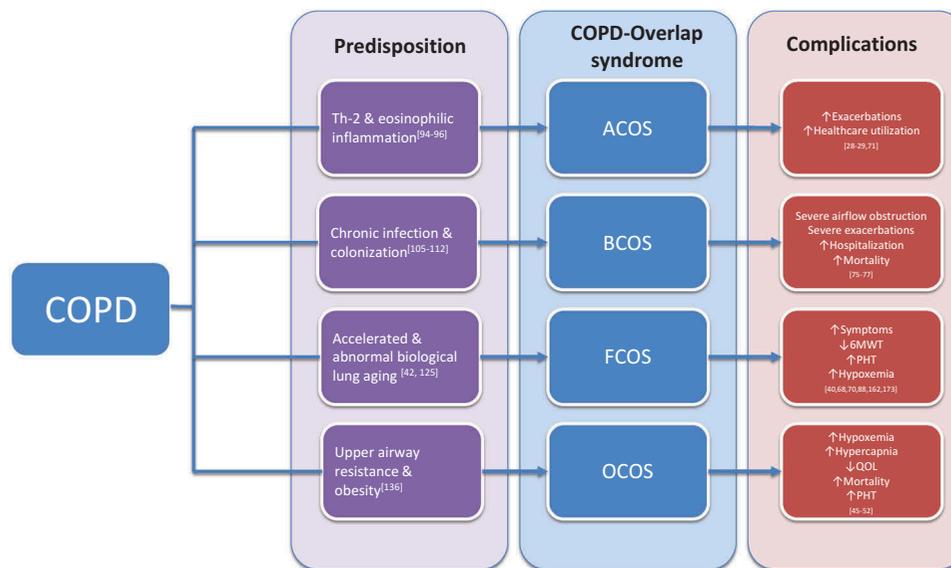
Figure 2. Predisposing risk factors and their associated complications in the development of the various COPD-overlap syndromes. COPD – chronic obstructive pulmonary disease, OSA – obstructive sleep apnea, ACOS – Asthma-COPD overlap syndrome, BCOS – Bronchiectasis-COPD overlap syndrome, FCOS – Fibrosis-COPD overlap syndrome, OCOS – OSA-COPD overlap syndrome, ↑ – increased, ↓ – decreased, 6MWT – 6 min walk test, PHT – Pulmonary hypertension and QOL – Quality of life.

Consequently, bronchial damage ensues impairing host defenses and permitting further bacterial colonization and dilatation which in turn incites the process again [105]. 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. 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 remodeling (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% to 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) coexist 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 develop [87]. 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 [51,87,140]. 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 recognizing 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 play an important role in respiratory infections, and is now also implicated in asthma and COPD [122,150,151]. The pathogenesis of COPD, asthma, bronchiectasis, and IPF has 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 subcategories 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 colonization. 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

Table 3. Summary of the diagnostic criteria and treatment approach for the various COPD-overlap syndromes.

COPD-overlap syndrome	Diagnosis	Treatment
ACOS	• GINA and GOLD guidelines [11,12] • Persistent airflow limitation with several features associated with both asthma and COPD [11,12]	• Commence standard asthma treatment [11,12] • Inhaled corticosteroid followed by a long acting bronchodilator (LABA/LAMA) [11,12]
BCOS	• 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]	• Antibiotics for airway infection and exacerbations [38] • Inhaled corticosteroids and bronchodilator therapy [38,161] • Role of long-term macrolide therapy requires further study [161] • Oxygen therapy [162]
FCOS	• CPFE → upper lobe emphysema with lower lobe fibrosis [40]	• Antifibrotic agents (e.g. pirfenidone and nintedanib) require further evaluation [54,163] • Corticosteroid and immunosuppressive therapy useful in CTD-related FCOS [90]
OCOS	• OSA → AHI>5 with symptoms or AHI>15 and COPD [164]	• CPAP [49,50]

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.

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

6.1. Asthma-COPD overlap syndrome (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/μL 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 nonsmokers exposed to biomass has been suggested by Bateman et al. [165] 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 [166]. 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, GERD, and osteoporosis) compared to COPD alone and the presence of cardiovascular diseases in ACOS patients is associated with hospitalization in a single study [167].

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) [168]. This 12-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 [169]. Despite the existing evidence base, much work remains to better understand the optimal methods for both the diagnosis and the effective treatment of ACOS.

6.2. Bronchiectasis-COPD overlap syndrome (BCOS)

This syndrome is a particular clinical challenge to diagnose, as both conditions present with cough, sputum production, repeated exacerbations, and dyspnea [11,31,170]. Obstructive airflow physiology is required for a COPD diagnosis but this may not be 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 [146,171]. 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 antimicrobial effects may also reduce infectious bronchiectasis exacerbations, although the risk of antibiotic resistance is presumably high but remains uncertain (Table 3) [161]. Treatment options targeted at COPD, including inhaled corticosteroids and bronchodilators, may be indicated in BCOS particularly if patients frequently exacerbate.

6.3. Fibrosis-COPD overlap syndrome

FCOS has male preponderance, and symptoms of exertional dyspnea 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) [41,90,172]. 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 [173]. To date, no established treatment regime exists for FCOS. The deleterious effects of smoking on COPD and IPF are recognized 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 [162]. The role of corticosteroids and immunosuppression remains unclear but may be a therapeutic option in CTD-related FCOS [90]. Newer antifibrotic 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 [54,163]. 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) [174].

6.4. OSA-COPD overlap syndrome (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 [164]. Generally, a high index of clinical suspicion is required to both consider and diagnose OCOS (Table 3). The presence of hypoxemia, hypercapnia, and pulmonary hypertension that is out of proportion to severity of either disease should prompt further assessment for the other disorder [175]. 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 'labeling.' It is critical that this improved endophenotyping 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 have not 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.
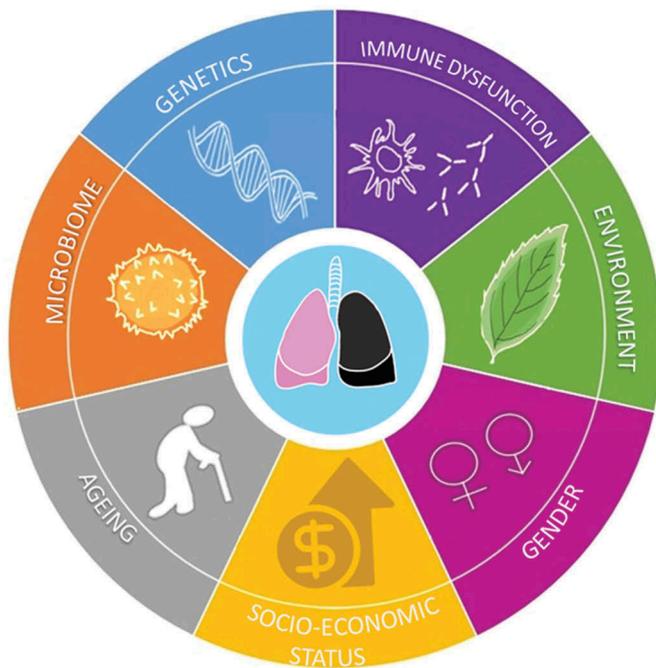
Figure 3. A summary of the major factors that influence the development and progression of respiratory disease states.

The precise contribution of genetics and environmental influences 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 rigor, 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.

Key issues

- 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

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Venables PJ. Mixed connective tissue disease. Lupus. 2006;15(3):132–137.
2. Kaji M, Fujiwara Y, Shiba M, et al. Prevalence of overlaps between GERD, FD and IBS and impact on health-related quality of life. J Gastroenterol Hepatol. 2010;25(6):1151–1156.
3. Lohse AW, zum Buschenfelde KH, Franz B, et al. Characterization of the overlap syndrome of primary biliary cirrhosis (PBC) and auto-immune hepatitis: evidence for it being a hepatitic form of PBC in genetically susceptible individuals. Hepatology. 1999;29(4):1078–1084.
4. World Health Organization. Chronic obstructive pulmonary disease (COPD). [cited 2016 Nov 16]. Available from: http://www.who.int/mediacentre/factsheets/fs315/en/
5. Minino AM, Murphy SL, Xu J, et al. Deaths: final data for 2008. National Vital Stat Rep. 2011;59(10):1–126.
6. World Health Organization. Global Health Observatory (GHO) data - Top 10 causes of death. [cited 2017 Feb 2]. Available from: http://www.who.int/gho/mortality_burden_disease/causes_death/top_10/en/
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. 2014;2(1):54–62.
8. Tan WC, Ng TP. COPD in Asia: where east meets west. Chest. 2008;133(2):517–527.
9. To T, Zhu J, Larsen K, et al. Progression from asthma to chronic obstructive pulmonary disease. Is air pollution a risk factor? Am J Respir Crit Care Med. 2016;194(4):429–438.
10. Oxman AD, Muir DC, Shannon HS, et al. Occupational dust exposure and chronic obstructive pulmonary disease. A systematic overview of the evidence. Am Rev Respir Dis. 1993;148(1):38–48.
11. Global Initiative for Chronic Obstructive Lung Disease. GOLD 2017 global strategy for the diagnosis, management and prevention of

COPD. [cited 2017 Feb 2]. Available from: http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/

12. Global Initiative for Asthma. 2016 GINA report, global strategy for asthma management and prevention. [cited 2016 Nov 19]. Available from: http://ginasthma.org/2016-gina-report-global-strategy-for-asthma-management-and-prevention/

13. Postma DS, Rabe KF. The asthma-COPD overlap syndrome. N Engl J Med. 2015;373(13):1241–1249.
•• State-of-the-art review describing the clinical management of ACOS.

14. Orie NGM SH, De Vries K, Tammeling GJ, et al. The host factor in bronchitis. Bronchitis. Assen (Ed. The Netherlands: Royal Van Gorcum; 1961. p. 43–59.

15. Vermeire PA, Pride NB. A "splitting" look at chronic nonspecific lung disease (CNSLD): common features but diverse pathogenesis. Eur Respir J. 1991;4(4):490–496.

16. Barnes PJ. Against the Dutch hypothesis: asthma and chronic obstructive pulmonary disease are distinct diseases. Am J Respir Crit Care Med. 2006;174(3):240–243;discussion 243–244.

17. Postma DS, Weiss ST, van den Berge M, et al. Revisiting the Dutch hypothesis. J Allergy Clin Immunol. 2015;136(3):521–529.

18. Sluiter HJ, Koeter GH, de Monchy JG, et al. The Dutch hypothesis (chronic non-specific lung disease) revisited. Eur Respir J. 1991;4(4):479–489.

19. Sin DD, Miravitlles M, Mannino DM, et al. What is asthma-COPD overlap syndrome? Towards a consensus definition from a round table discussion. Eur Respir J. 2016;48(3):664–673.
•• Consensus definitions for ACOS arising from round table discussions between expert clinicians.

20. Kiljander T, Helin T, Venho K, et al. Prevalence of asthma-COPD overlap syndrome among primary care asthmatics with a smoking history: a cross-sectional study. NPJ Primary Care Respir Med. 2015;25:15047.

21. Golpe R, Sanjuan Lopez P, Cano Jimenez E, et al. Distribution of clinical phenotypes in patients with chronic obstructive pulmonary disease caused by biomass and tobacco smoke. Arch Bronconeumol. 2014;50(8):318–324.

22. Hardin M, Silverman EK, Barr RG, et al. The clinical features of the overlap between COPD and asthma. Respir Res. 2011;12:127.

23. Miravitlles M, Soriano JB, Ancochea J, et al. Characterisation of the overlap COPD-asthma phenotype. Focus on physical activity and health status. Respir Med. 2013;107(7):1053–1060.

24. Miravitlles M, Soriano JB, Garcia-Rio F, et al. Prevalence of COPD in Spain: impact of undiagnosed COPD on quality of life and daily life activities. Thorax. 2009;64(10):863–868.

25. Tho NV, Park HY, Nakano Y. Asthma-COPD overlap syndrome (ACOS): a diagnostic challenge. Respirology. 2016;21(3):410–418.

26. Caillaud D, Chanez P, Escamilla R, et al. Asthma-COPD overlap syndrome (ACOS) vs 'pure' COPD: a distinct phenotype? Allergy. 2017;72(1):137–145.

27. Cosio BG, Soriano JB, López-Campos JL, et al. Defining the asthma-COPD overlap syndrome in a COPD cohort. Chest. 2016;149(1):45–52.

28. Sorino C, Pedone C, Scichilone N. Fifteen-year mortality of patients with asthma-COPD overlap syndrome. Eur J Intern Med. 2016;34:72–77.

29. Lange P, Colak Y, Ingebrigtsen TS, et al. 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. 2016;4(6):454–462.
•• Large-scale cohort study assessing ACOS prevalence.

30. McShane PJ, Naureckas ET, Tino G, et al. Non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med. 2013;188(6):647–656.

31. Pasteur MC, Bilton D, Hill AT. British Thoracic Society Non CFBGG. British Thoracic Society guideline for non-CF bronchiectasis. Thorax. 2010;65(7):577.

32. Barker AF. Bronchiectasis. N Engl J Med. 2002;346(18):1383–1393.

33. Agusti A, Calverley PM, Celli B, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res. 2010;11:122.

34. Martinez-Garcia MA, Soler-Cataluna JJ, Donat Sanz Y, et al. Factors associated with bronchiectasis in patients with COPD. Chest. 2011;140(5):1130–1137.

35. Patel IS, Vlahos I, Wilkinson TM, et al. Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2004;170(4):400–407.

36. O'Brien C, Guest PJ, Hill SL, et al. Physiological and radiological characterisation of patients diagnosed with chronic obstructive pulmonary disease in primary care. Thorax. 2000;55(8):635–642.

37. Bafadhel M, Umar I, Gupta S, et al. The role of CT scanning in multidimensional phenotyping of COPD. Chest. 2011;140(3):634–642.

38. Gursel G. Does coexistence with bronchiectasis influence intensive care unit outcome in patients with chronic obstructive pulmonary disease? Heart Lung. 2006;35(1):58–65.

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;1-29. doi:10.1016/j.chest.2016.12.024.
•• 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. 2005;26(4):586–593.
• One of the earliest descriptions of FCOS.

41. Ryerson CJ, Hartman T, Elicker BM, et al. Clinical features and outcomes in combined pulmonary fibrosis and emphysema in idiopathic pulmonary fibrosis. Chest. 2013;144(1):234–240.

42. Chilosi M, Poletti V, Rossi A. The pathogenesis of COPD and IPF: distinct horns of the same devil? Respir Res. 2012;13:3.

43. Epstein LJ, Kristo D, Strollo PJ Jr., et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med. 2009;5(3):263–276.

44. Calverley PM, Brezinova V, Douglas NJ, et al. The effect of oxygenation on sleep quality in chronic bronchitis and emphysema. Am Rev Respir Dis. 1982;126(2):206–210.

45. Flenley DC. Sleep in chronic obstructive lung disease. Clin Chest Med. 1985;6(4):651–661.

46. Sanders MH, Newman AB, Haggerty CL, et al. Sleep and sleep-disordered breathing in adults with predominantly mild obstructive airway disease. Am J Respir Crit Care Med. 2003;167(1):7–14.

47. Mermigkis C, Kopanakis A, Foldvary-Schaefer N, et al. Health-related quality of life in patients with obstructive sleep apnoea and chronic obstructive pulmonary disease (overlap syndrome). Int J Clin Pract. 2007;61(2):207–211.

48. He B-T, Lu G, Xiao S-C, et al. Coexistence of OSA may compensate for sleep related reduction in neural respiratory drive in patients with COPD. Thorax. 2017;72(3):256–262.

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

50. Machado MC, Vollmer WM, Togeiro SM, et al. CPAP and survival in moderate-to-severe obstructive sleep apnoea syndrome and hypoxaemic COPD. Eur Respir J. 2010;35(1):132–137.

51. Hawrylkiewicz I, Sliwinski P, Gorecka D, et al. Pulmonary haemodynamics in patients with OSAS or an overlap syndrome. Monaldi Arch Chest Dis. 2004;61(3):148–152.

52. Sharma B, Neilan TG, Kwong RY, et al. Evaluation of right ventricular remodeling using cardiac magnetic resonance imaging in coexistent chronic obstructive pulmonary disease and obstructive sleep apnea. COPD. 2013;10(1):4–10.

53. Hurst JR, Elborn JS, De Soyza A, et al. COPD-bronchiectasis overlap syndrome. Eur Respir J. 2015;45(2):310–313.
•• International position on BCOS.

54. King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2083–2092.

55. Martinez-Garcia MA, Soler-Cataluna JJ, Catalan-Serra P, et al. Clinical efficacy and safety of budesonide-formoterol in non-cystic fibrosis bronchiectasis. Chest. 2012;141(2):461–468.

56. Cazzola M, Rogliani P. Do we really need asthma-chronic obstructive pulmonary disease overlap syndrome? J Allergy Clin Immunol. 2016;138(4):977–983.

57. Cameron SJ, Lewis KE, Huws SA et al. Metagenomic Sequencing of the Chronic Obstructive Pulmonary Disease Upper Bronchial Tract Microbiome Reveals Functional Changes Associated with Disease Severity. PLoS One. 2016;1-16. doi:10.1371/journal.pone.0149095.

58. Rogers GB, Zain NM, Bruce KD, et al. A novel microbiota stratification system predicts future exacerbations in bronchiectasis. Ann Am Thorac Soc. 2014;11(4):496–503.

59. Cameron SJ, Lewis KE, Huws SA, et al. Metagenomic sequencing of the chronic obstructive pulmonary disease upper bronchial tract microbiome reveals functional changes associated with disease severity. PLoS One. 2016;11(2):e0149095.

60. Budden KF, Gellatly SL, Wood DLA et al. Emerging pathogenic links between microbiota and the gut-lung axis. Nat Rev Micro. 201715 (1):55-63.

61. Han MK, Zhou Y, Murray S, et al. Lung microbiome and disease progression in idiopathic pulmonary fibrosis: an analysis of the COMET study. Lancet Respir Med. 2014;2(7):548–556.

62. Yii AC, Koh MS, Lapperre TS, et al. The emergence of Aspergillus species in chronic respiratory disease. Front Biosci (Schol Ed). 2017;9:127–138.

63. Miravitlles M, Huerta A, Fernandez-Villar JA, et al. Generic utilities in chronic obstructive pulmonary disease patients stratified according to different staging systems. Health Qual Life Outcomes. 2014;12:120.

64. Hardin M, Silverman EK, Barr RG, et al. The clinical features of the overlap between COPD and asthma. Respir Res. 2011;12 (1):127–127.

65. Gatheral T, Kumar N, Sansom B, et al. COPD-related bronchiectasis; independent impact on disease course and outcomes. COPD. 2014;11(6):605–614.

66. Mao B, Lu HW, Li MH, et al. The existence of bronchiectasis predicts worse prognosis in patients with COPD. Sci Rep. 2015;5:10961.

67. Jin J, Yu W, Li S, et al. Factors associated with bronchiectasis in patients with moderate-severe chronic obstructive pulmonary disease. Medicine (Baltimore). 2016;95(29):e4219.

68. Akagi T, Matsumoto T, Harada T, et al. Coexistent emphysema delays the decrease of vital capacity in idiopathic pulmonary fibrosis. Respir Med. 2009;103(8):1209–1215.

69. Schmidt SL, Nambiar AM, Tayob N, et al. Pulmonary function measures predict mortality differently in IPF versus combined pulmonary fibrosis and emphysema. Eur Respir J. 2011;38(1):176–183.

70. Kim YJ, Shin SH, Park JW, et al. Annual change in pulmonary function and clinical characteristics of combined pulmonary fibrosis and emphysema and idiopathic pulmonary fibrosis: over a 3-year follow-up. Tuberc Respir Dis (Seoul). 2014;77(1):18–23.

71. Wurst KE, Laurent SS, Hinds D, et al. Disease Burden of Patients with Asthma/COPD Overlap in a US Claims Database: Impact of ICD-9 Coding-based Definitions. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2017;1-10. doi:10.1080/15412555.2016.1257598.

72. Fu JJ, Gibson PG, Simpson JL, et al. Longitudinal changes in clinical outcomes in older patients with asthma, COPD and asthma-COPD overlap syndrome. Respiration. 2014;87(1):63–74.

73. Izquierdo-Alonso JL, Rodriguez-Gonzalezmoro JM, De Lucas-Ramos P, et al. Prevalence and characteristics of three clinical phenotypes of chronic obstructive pulmonary disease (COPD). Respir Med. 2013;107(5):724–731.

74. Kessler R, Chaouat A, Schinkewitch P, et al. The obesity-hypoventilation syndrome revisited: a prospective study of 34 consecutive cases. Chest. 2001;120(2):369–376.

75. Chalmers JD, Goeminne P, Aliberti S, et al. The bronchiectasis severity index. An international derivation and validation study. Am J Respir Crit Care Med. 2014;189(5):576–585.

76. Martinez-Garcia MA, de Gracia J, Vendrell Relat M, et al. Multidimensional approach to non-cystic fibrosis bronchiectasis: the FACED score. Eur Respir J. 2014;43(5):1357–1367.

77. Du Q, Jin J, Liu X, et al. Bronchiectasis as a comorbidity of chronic obstructive pulmonary disease: a systematic review and meta-analysis. PLoS One. 2016;11(3):e0150532.

78. Mannino DM. Coexisting asthma and COPD: confused clinicians or poor prognosticator? Chest. 2008;134(1):1–2.

79. Andersen H, Lampela P, Nevanlinna A, et al. High hospital burden in overlap syndrome of asthma and COPD. Clin Respir J. 2013;7 (4):342–346.

80. Milanese M, Di Marco F, Corsico AG, et al. Asthma control in elderly asthmatics. An Italian observational study. Respir Med. 2014;108 (8):1091–1099.

81. Kumbhare S, Pleasants R, Ohar JA, et al. Characteristics and prevalence of asthma/chronic obstructive pulmonary disease overlap in the United States. Ann Am Thorac Soc. 2016;13(6):803–810.

82. Ding B, DiBonaventura M, Karlsson N, et al. Asthma-chronic obstructive pulmonary disease overlap syndrome in the urban Chinese population: prevalence and disease burden using the 2010, 2012, and 2013 China National Health and Wellness Surveys. Int J Chron Obstruct Pulmon Dis. 2016;11:1139–1150.

83. Kim MA, Noh CS, Chang YJ, et al. Asthma and COPD overlap syndrome is associated with increased risk of hospitalisation. Int J Tuberculosis Lung Dis. 2015;19(7):864–869.

84. Gerhardsson de Verdier M, Andersson M, Kern DM, et al. Asthma and chronic obstructive pulmonary disease overlap syndrome: doubled costs compared with patients with asthma alone. Value Health. 2015;18(6):759–766.

85. Yeh JJ, Wang YC, Kao CH. Asthma-chronic obstructive pulmonary disease overlap syndrome associated with risk of pulmonary embolism. PLoS One. 2016;11(9):e0162483.

86. Yeh JJ, Wang YC, Kao CH. Asthma-chronic obstructive pulmonary diseases overlap syndrome increases the risk of incident tuberculosis: a national cohort study. PLoS One. 2016;11(7):e0159012.

87. Chaouat A, Weitzenblum E, Krieger J, et al. Association of chronic obstructive pulmonary disease and sleep apnea syndrome. Am J Respir Crit Care Med. 1995;151(1):82–86.

88. Doyle TJ, Washko GR, Fernandez IE, et al. Interstitial lung abnormalities and reduced exercise capacity. Am J Respir Crit Care Med. 2012;185(7):756–762.

89. Menezes AM, Montes de Oca M, Perez-Padilla R, et al. Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype: COPD-asthma. Chest. 2014;145(2):297–304.

90. Cottin V, Nunes H, Mouthon L, et al. Combined pulmonary fibrosis and emphysema syndrome in connective tissue disease. Arthritis Rheum. 2011;63(1):295–304.

91. Ravensberg AJ, Slats AM, van Wetering S, et al. CD8(+) T cells characterize early smoking-related airway pathology in patients with asthma. Respir Med. 2013;107(7):959–966.

92. Wenzel SE, Szefler SJ, Leung DY, et al. Bronchoscopic evaluation of severe asthma. Persistent inflammation associated with high dose glucocorticoids. Am J Respir Crit Care Med. 1997;156(3 Pt 1):737–743.

93. Yii ACA, Tan GL, Tan KL, et al. Fixed airways obstruction among patients with severe asthma: findings from the Singapore General Hospital-Severe Asthma Phenotype Study. BMC Pulm Med. 2014;14(1):191.

94. Brightling CE, Monteiro W, Ward R, et al. Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomised controlled trial. Lancet. 2000;356 (9240):1480–1485.

95. Christenson SA, Steiling K, van den Berge M, et al. Asthma-COPD overlap. Clinical relevance of genomic signatures of type 2 inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2015;191(7):758–766.

96. Tashkin DP, Altose MD, Connett JE, et al. Methacholine reactivity predicts changes in lung function over time in smokers with early chronic obstructive pulmonary disease. The Lung Health Study

Research Group. Am J Respir Crit Care Med. 1996;153(6 Pt 1):1802–1811.

97. Gelb AF, Yamamoto A, Verbeken EK, et al. Unraveling the pathophysiology of the asthma-COPD overlap syndrome: unsuspected mild centrilobular emphysema is responsible for loss of lung elastic recoil in never smokers with asthma with persistent expiratory airflow limitation. Chest. 2015;148(2):313–320.

98. Chinn S, Jarvis D, Luczynska CM, et al. An increase in bronchial responsiveness is associated with continuing or restarting smoking. Am J Respir Crit Care Med. 2005;172(8):956–961.

99. Chaudhuri R, Livingston E, McMahon AD, et al. Cigarette smoking impairs the therapeutic response to oral corticosteroids in chronic asthma. Am J Respir Crit Care Med. 2003;168(11):1308–1311.

100. Anthonisen NR, Connett JE, Murray RP. Smoking and lung function of Lung Health Study participants after 11 years. Am J Respir Crit Care Med. 2002;166(5):675–679.

101. To T, Zhu J, Larsen K, et al. Progression from asthma to chronic obstructive pulmonary disease. Is air pollution a risk factor? Am J Respir Crit Care Med. 2016;194(4):429–438.

102. Jamieson DB, Matsui EC, Belli A, et al. Effects of allergic phenotype on respiratory symptoms and exacerbations in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2013;188(2):187–192.

103. Fattahi F, ten Hacken NH, Lofdahl CG, et al. Atopy is a risk factor for respiratory symptoms in COPD patients: results from the EUROSCOP study. Respir Res. 2013;14:10.

104. King PT. The pathophysiology of bronchiectasis. Int J Chron Obstruct Pulmon Dis. 2009;4:411–419.

105. Cole PJ. Inflammation: a two-edged sword–the model of bronchiectasis. Eur J Respir Dis Suppl. 1986;147:6–15.

106. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. Lancet. 2009;374(9691):733–743.

107. Whiteley M, Bangera MG, Bumgarner RE, et al. Gene expression in Pseudomonas aeruginosa biofilms. Nature. 2001;413(6858):860–864.

108. Pappalettera M, Aliberti S, Castellotti P, et al. Bronchiectasis: an update. Clin Respir J. 2009;3(3):126–134.

109. Garcia-Vidal C, Almagro P, Romani V, et al. Pseudomonas aeruginosa in patients hospitalised for COPD exacerbation: a prospective study. Eur Respir J. 2009;34(5):1072–1078.

110. Almagro P, Salvado M, Garcia-Vidal C, et al. Pseudomonas aeruginosa and mortality after hospital admission for chronic obstructive pulmonary disease. Respiration. 2012;84(1):36–43.

111. Groenewegen KH, Wouters EF. Bacterial infections in patients requiring admission for an acute exacerbation of COPD; a 1-year prospective study. Respir Med. 2003;97(7):770–777.

112. Patel IS, Seemungal TAR, Wilks M, et al. Relationship between bacterial colonisation and the frequency, character, and severity of COPD exacerbations. Thorax. 2002;57(9):759–764.

113. American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med. 2003;168(7):818–900.

114. Cuvelier A, Muir JF, Hellot MF, et al. Distribution of alpha(1)-antitrypsin alleles in patients with bronchiectasis. Chest. 2000;117(2):415–419.

115. Shin MS, Ho KJ. Bronchiectasis in patients with alpha 1-antitrypsin deficiency. A rare occurrence? Chest. 1993;104(5):1384–1386.

116. Parr DG, Guest PG, Reynolds JH, et al. Prevalence and impact of bronchiectasis in alpha1-antitrypsin deficiency. Am J Respir Crit Care Med. 2007;176(12):1215–1221.

117. Chotirmall SH, Al-Alawi M, McEnery T, et al. Alpha-1 proteinase inhibitors for the treatment of alpha-1 antitrypsin deficiency: safety, tolerability, and patient outcomes. Ther Clin Risk Manag. 2015;11:143–151.

118. Dawkins PA, Dawkins CL, Wood AM, et al. Rate of progression of lung function impairment in alpha1-antitrypsin deficiency. Eur Respir J. 2009;33(6):1338–1344.

119. Morse D, Rosas IO. Tobacco smoke-induced lung fibrosis and emphysema. Annu Rev Physiol. 2014;76:493–513.

120. Navaratnam V, Fleming KM, West J, et al. The rising incidence of idiopathic pulmonary fibrosis in the U.K. Thorax. 2011;66(6):462–467.

121. Kohansal R, Martinez-Camblor P, Agusti A, et al. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort. Am J Respir Crit Care Med. 2009;180(1):3–10.

122. Murray MA, Chotirmall SH. The impact of immunosenescence on pulmonary disease. Mediators Inflamm. 2015;692546:2015.

123. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010;363(12):1128–1138.

124. Kim S, Clark S, Camargo CA Jr. Mortality after an emergency department visit for exacerbation of chronic obstructive pulmonary disease. COPD. 2006;3(2):75–81.

125. Faner R, Rojas M, Macnee W, et al. Abnormal lung aging in chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2012;186(4):306–313.

126. MacNee W. Pulmonary and systemic oxidant/antioxidant imbalance in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2005;2(1):50–60.

127. Rahman I, Skwarska E, Henry M, et al. Systemic and pulmonary oxidative stress in idiopathic pulmonary fibrosis. Free Radic Biol Med. 1999;27(1–2):60–68.

128. Rode L, Bojesen SE, Weischer M, et al. Short telomere length, lung function and chronic obstructive pulmonary disease in 46,396 individuals. Thorax. 2013;68(5):429–435.

129. Dai J, Cai H, Zhuang Y, et al. Telomerase gene mutations and telomere length shortening in patients with idiopathic pulmonary fibrosis in a Chinese population. Respirology. 2015;20(1):122–128.

130. Diaz de Leon A, Cronkhite JT, Katzenstein AL, et al. Telomere lengths, pulmonary fibrosis and telomerase (TERT) mutations. PLoS One. 2010;5(5):e10680.

131. Liu T, Ullenbruch M, Young Choi Y, et al. Telomerase and telomere length in pulmonary fibrosis. Am J Respir Cell Mol Biol. 2013;49(2):260–268.

132. Naikawadi RP, Disayabutr S, Mallavia B, et al. Telomere dysfunction in alveolar epithelial cells causes lung remodeling and fibrosis. JCI Insight. 2016;1(14):e86704.

133. Alder JK, Guo N, Kembou F, et al. Telomere length is a determinant of emphysema susceptibility. Am J Respir Crit Care Med. 2011;184(8):904–912.

134. Armanios MY, Chen JJ, Cogan JD, et al. Telomerase mutations in families with idiopathic pulmonary fibrosis. N Engl J Med. 2007;356(13):1317–1326.

135. Tsakiri KD, Cronkhite JT, Kuan PJ, et al. Adult-onset pulmonary fibrosis caused by mutations in telomerase. Proc Natl Acad Sci USA. 2007;104(18):7552–7557.

136. Mieczkowski B, Ezzie ME. Update on obstructive sleep apnea and its relation to COPD. Int J Chron Obstruct Pulmon Dis. 2014;9:349–362.

137. Poulain M, Doucet M, Major GC, et al. The effect of obesity on chronic respiratory diseases: pathophysiology and therapeutic strategies. CMAJ. 2006;174(9):1293–1299.

138. Taranto-Montemurro L, Messineo L, Perger E, et al. Cardiac sympathetic hyperactivity in patients with chronic obstructive pulmonary disease and obstructive sleep apnea. COPD. 2016;13(6):706–711.

139. Ganga HV, Nair SU, Puppala VK, et al. Risk of new-onset atrial fibrillation in elderly patients with the overlap syndrome: a retrospective cohort study. J Geriatr Cardiol. 2013;10(2):129–134.

140. Chaouat A, Weitzenblum E, Krieger J, et al. Pulmonary hemodynamics in the obstructive sleep apnea syndrome. Results in 220 consecutive patients. Chest. 1996;109(2):380–386.

141. Hurst JR, Perera WR, Wilkinson TM, et al. Systemic and upper and lower airway inflammation at exacerbation of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2006;173(1):71–78.

142. Ryan S, Taylor CT, McNicholas WT. Predictors of elevated nuclear factor-kappaB-dependent genes in obstructive sleep apnea syndrome. Am J Respir Crit Care Med. 2006;174(7):824–830.

143. Takabatake N, Nakamura H, Abe S, et al. The relationship between chronic hypoxemia and activation of the tumor necrosis factor-alpha system in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000;161(4 Pt 1):1179–1184.

144. Yokoe T, Minoguchi K, Matsuo H, et al. Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. Circulation. 2003;107(8):1129–1134.

145. Lavie L. Obstructive sleep apnoea syndrome–an oxidative stress disorder. Sleep Med Rev. 2003;7(1):35–51.

146. Loebinger MR, Wells AU, Hansell DM, et al. Mortality in bronchiectasis: a long-term study assessing the factors influencing survival. Eur Respir J. 2009;34(4):843–849.

147. Ashley SL, Jegal Y, Moore TA, et al. gamma-Herpes virus-68, but not Pseudomonas aeruginosa or influenza A (H1N1), exacerbates established murine lung fibrosis. Am J Physiol Lung Cell Mol Physiol. 2014;307(3):L219–230.

148. Edwards MR, Bartlett NW, Hussell T, et al. The microbiology of asthma. Nat Rev Microbiol. 2012;10(7):459–471.

149. Cho I, Blaser MJ. The human microbiome: at the interface of health and disease. Nat Rev Genet. 2012;13(4):260–270.

150. Budden KF, Gellatly SL, Wood DLA et al. Emerging pathogenic links between microbiota and the gut-lung axis. Nat Rev Micro. 2017;15(1):55-63.

151. Chotirmall SH, Burke CM. Aging and the microbiome: implications for asthma in the elderly? Expert Rev Respir Med. 2015;9(2):125–128.

152. Morris A, Beck JM, Schloss PD, et al. Comparison of the respiratory microbiome in healthy nonsmokers and smokers. Am J Respir Crit Care Med. 2013;187(10):1067–1075.

153. Segal LN, Alekseyenko AV, Clemente JC, et al. Enrichment of lung microbiome with supraglottic taxa is associated with increased pulmonary inflammation. Microbiome. 2013;1(1):19.

154. Denning DW, Pashley C, Hartl D, et al. Fungal allergy in asthma-state of the art and research needs. Clin Transl Allergy. 2014;4:14.

155. Chotirmall SH, Gellatly SL, Budden KF, et al. Microbiomes in respiratory health and disease: an Asia-Pacific perspective. Respirology. 2017;22(2):240–250.

156. Al-Alawi M, Hassan T, Chotirmall SH. Advances in the diagnosis and management of asthma in older adults. Am J Med. 2014;127(5):370–378.

157. Chotirmall SH, Watts M, Branagan P, et al. Diagnosis and management of asthma in older adults. J Am Geriatr Soc. 2009;57(5):901–909.

158. Kobayashi S, Hanagama M, Yamanda S, et al. Inflammatory biomarkers in asthma-COPD overlap syndrome. Int J Chron Obstruct Pulmon Dis. 2016;11:2117–2123.

159. Goto T, Camargo CA, Hasegawa K. Fractional exhaled nitric oxide levels in asthma-COPD overlap syndrome: analysis of the National Health and Nutrition Examination Survey, 2007-2012. Int J Chron Obstruct Pulmon Dis. 2016;11:2149–2155.

160. Chen F-J, Huang X-Y, Liu Y-L, et al. Importance of fractional exhaled nitric oxide in the differentiation of asthma-COPD overlap syndrome, asthma, and COPD. Int J Chron Obstruct Pulmon Dis. 2016;11:2385–2390.

161. Altenburg J, de Graaff CS, Stienstra Y, et al. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. JAMA. 2013;309(12):1251–1259.

162. Crockett AJ, Cranston JM, Moss JR, et al. A review of long-term oxygen therapy for chronic obstructive pulmonary disease. Respir Med. 2001;95(6):437–443.

163. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071–2082.

164. McNicholas WT, Strohl KP, White D et al. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep. 1999;22(5):667-689.

165. Bateman ED, Reddel HK, van Zyl-Smit RN, et al. The asthma–COPD overlap syndrome: towards a revised taxonomy of chronic airways diseases? Lancet Respir Med. 2015;3(9):719–728.

166. Barnes PJ. Asthma-COPD overlap. Chest. 2016;149(1):7–8.

167. Jfm VB, Román-Rodríguez M, Palmer JF, et al. Comorbidome, pattern, and impact of asthma-COPD overlap syndrome in real life. Chest. 2016;149(4):1011–1020.

168. Ishiura Y, Fujimura M, Shiba Y, et al. A comparison of the efficacy of once-daily fluticasone furoate/vilanterol with twice-daily fluticasone propionate/salmeterol in asthma-COPD overlap syndrome. Pulm Pharmacol Ther. 2015;35:28–33.

169. Maltby S, Gibson PG, Powell H, et al. Omalizumab treatment response in a population with severe allergic asthma and overlapping COPD. Chest. 2017;151(1):78–89.

170. Pasteur MC, Bilton D, Hill AT. British Thoracic Society Bronchiectasis non CFGG. British Thoracic Society guideline for non-CF bronchiectasis. Thorax. 2010;65(Suppl 1):i1–58.

171. Martinez-Garcia MA, Soler-Cataluna JJ, Perpina-Tordera M, et al. Factors associated with lung function decline in adult patients with stable non-cystic fibrosis bronchiectasis. Chest. 2007;132(5):1565–1572.

172. Washko GR, Hunninghake GM, Fernandez IE, et al. Lung volumes and emphysema in smokers with interstitial lung abnormalities. N Engl J Med. 2011;364(10):897–906.

173. Cottin V, Le Pavec J, Prevot G, et al. Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome. Eur Respir J. 2010;35(1):105–111.

174. Seeger W, Adir Y, Barbera JA, et al. Pulmonary hypertension in chronic lung diseases. J Am Coll Cardiol. 2013;62(25 Suppl):D109–D116.

175. Weitzenblum E, Chaouat A, Kessler R, et al. Overlap syndrome: obstructive sleep apnea in patients with chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2008;5(2):237–241.

176. Kohnlein T, Windisch W, Kohler D, et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. Lancet Respir Med. 2014;2(9):698–705.

177. Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. Eur Respir J. 2016;47(2):410–419.

178. Lange P, Celli B, Agusti A, et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. N Engl J Med. 2015;373(2):111–122.
   •• **Early adulthood FEV1 is a key determinant of COPD in later life. Accelerated decline of FEV1 is not an obligate feature of COPD.**