Chronic obstructive pulmonary disease

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Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity, mortality, and health-care use worldwide. COPD is caused by exposure to inhaled noxious particles, notably tobacco smoke and pollutants. However, the broad range of factors that increase the risk of development and progression of COPD throughout the life course are increasingly being recognised. Innovations in omics and imaging techniques have provided greater insight into disease pathobiology, which might result in advances in COPD prevention, diagnosis, and treatment. Although few novel treatments have been approved for COPD in the past 5 years, advances have been made in targeting existing therapies to specific subpopulations using new biomarker-based strategies. Additionally, COVID-19 has undeniably affected individuals with COPD, who are not only at higher risk for severe disease manifestations than healthy individuals but also negatively affected by interruptions in health-care delivery and social isolation. This Seminar reviews COPD with an emphasis on recent advances in epidemiology, pathophysiology, imaging, diagnosis, and treatment.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of death and disability worldwide. Although COPD is heterogeneous, defining features include persistent airflow obstruction and respiratory symptoms. COPD is caused by exposure to inhaled particulate matter, such as cigarette smoke and air pollutants, in combination with genetic, developmental, and social factors.[1] Chronic exposure to particulate matter affects much of the world's ageing population;[2,3] consequently, the projected increase in COPD prevalence is unsurprising.[4] Decreasing the burden of COPD will require better treatment strategies and public health and personalised efforts to limit exposures. Many individuals diagnosed with COPD in late adulthood begin having symptoms in midlife, which might progress for years before diagnosis.[5,6] A greater knowledge of early COPD symptoms has led to an improved awareness of the early-life factors contributing to risk of COPD. Although smoking cessation is crucial to COPD prevention, recognising the entire COPD exposome (ie, all the relevant exposures an individual has in their lifetime)[7–9] could be important in decreasing risk of COPD overall. Furthermore, implementing treatments early, before progression to severe irreversible disease, could minimise disability.

Contemporary COPD guidelines emphasise management of treatable traits, particularly dyspnoea and exacerbations, and comorbidities. The prevention of exacerbations, defined as a rapid increase in COPD symptoms outside of the normal day-to-day variation, is crucial because of their substantial contribution to detrimental outcomes.[10] By addressing treatable traits, rather than providing a standardised approach to a heterogeneous disease, clinicians and researchers aim to reduce COPD morbidity and mortality.

Current mechanistic concepts in COPD could provide new avenues for therapeutic development. Studies using modern genetic and omic techniques have advanced the mechanistic understanding of COPD subgroups. Imaging innovations have informed the association between lung structure and lung function. This progress has moved the field closer to implementing a precision medicine approach to diagnosis and treatment.

In this Seminar, we summarise the current and evolving topics in COPD, with an emphasis on epidemiology, pathophysiology, imaging, diagnosis, and treatments. We also review the literature on COPD during the COVID-19 pandemic.

Epidemiology, exposures, and disparities

In 2017, the number of people living with chronic respiratory disease was estimated to be 544·9 million, with approximately 55% of cases being attributed to COPD.[11] In 2019, COPD was the third leading cause of death globally.[12] Yet, the prevalence of COPD is expected to increase, partly due to an ageing population.[4]

COPD is commonly associated with tobacco smoking. In non-smokers, second-hand smoke, occupational exposures, air pollutants, and history of previous lung infections including tuberculosis have been identified as COPD risk factors.[13,14] In low-income and middle-income countries, fuel sources such as biomass and coal are common indoor air pollutants.[14,15] These exposures also probably contribute to and speed up COPD development among individuals who smoke,[16] and interact with host susceptibility factors,[17,18] ultimately resulting in COPD pathogenesis and progression.

The use of electronic nicotine device systems (ENDS; ie, vaping) is another potential increasing exposure risk,

Search strategy and selection criteria

We searched PubMed on chronic obstructive pulmonary disease (COPD) and related topics using the following terms: "COPD", "epidemiology", "exposures", "disparities", "exacerbations", "phenotyping", "genetics", "omics", "pathophysiology", "imaging", "treatment", "non-invasive ventilation", "pulmonary rehabilitation", "inhaler therapy", "BLVR", "COVID-19", and "SARS-CoV-2". We focused on works published in English and preferentially selected those published between Jan 1, 2018, and Jan 31, 2022.

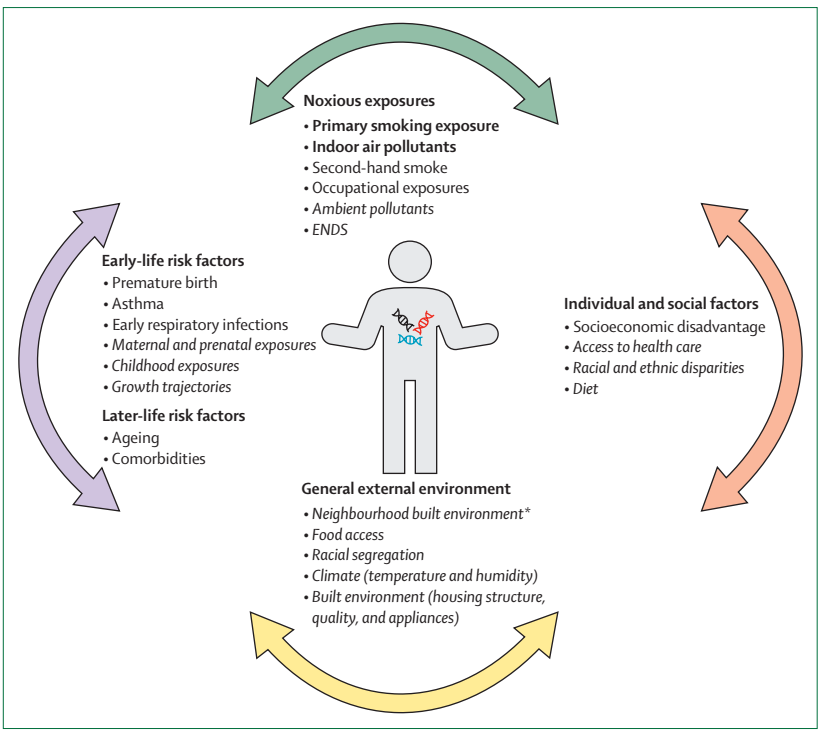

Figure 1: **Risk factors for development, progression, and morbidity of COPD**
General categories for risk factors beyond genetic factors include early-life risk factors, later-life risk factors, noxious exposures, individual and social factors, and general external environment. Bold indicates highest level of evidence for risk factor, italics indicate that the risk factor is under investigation with smaller evidence base. COPD=chronic obstructive pulmonary disease. ENDS=electronic nicotine device systems. *Neighbourhood built environment encompasses the structures, facilities, and make-up of the neighbourhood, including presence and types of business, greenspaces and recreation facilities, urbanity, cultural facilities, schools and educational institutions, and pollution.

particularly among adolescents and young adults.[19,20] Early cross-sectional studies and longitudinal analyses have shown that ENDS users have increased respiratory symptoms, incident airway disease, and lung function decline.[21–23] Furthermore, ENDS use has been associated with decreased smoking cessation,[21] and the dual use of cigarettes and ENDS might pose higher risks than those caused by the use of one of the two products alone.[24] Further studies that consider the rapidly changing constituents and delivery of ENDS products are needed to determine the risk of long-term use of ENDS with regard to the risk for developing COPD, and the harms and benefits of ENDS use for smoking cessation (figure 1).

Antenatal and early childhood exposures are also associated with COPD development.[25,26] Maternal smoking—the most studied early life exposure—leads to an increased risk for reduced lung function,[25,27–29] potentially by altering lung development. Such alteration could then heighten susceptibility to adverse effects from tobacco smoking throughout life (figure 1).[30]

Disparities by sex, country, race, and residence exist in COPD risk factors, incidence, and outcomes. Globally, 52–54% of cases of COPD among males and 19–24% of cases among females have been attributed to smoking, with large differences across countries.[31] Women might have higher susceptibility to development of and morbidity from COPD in response to exposures, and greater symptom burden than men.[1,32–34] Exposures leading to COPD development in non-smokers, such as cooking fuels and inefficient indoor ventilation, also disproportionally affect women.[15]

WHO estimates that 90% of COPD deaths are in low-income and middle-income countries.[35] This proportion might indicate the presence of disparities in extent and range of exposures, and access to health care compared with high-income countries.

Additionally, a study from the USA has shown racial disparities, with African Americans having greater risk of exacerbations and worse disease status than White individuals.[36] Individual-level and neighbourhood-level sociodemographic factors probably contribute to this disadvantage (figure 1).[36,37]

Rural residence also contributes to disparate COPD outcomes.[38] In the USA, death certificate data have shown increasing age-adjusted mortality from chronic lower respiratory disease in rural areas compared with metropolitan areas.[39] Similar disparities have also been identified in low-income and middle-income countries.[40] Distribution of exposures, availability of diagnostic testing, and access to health care might contribute to this disparity, which appears to be increasing.

The exposome is a contemporary holistic view of the environment that shapes COPD risk (figure 1).[41] Exposome models propose the contribution of exposures from multiple domains (eg, personal, social, neighbourhood, and environmental) to chronic disease risk.[7–9,42,43] Other than an association between childhood disadvantage factors (eg, parenthal history of asthma or smoking, and early respiratory infections) and COPD risk,[44] the contribution of social factors (eg, socioeconomic disadvantage and diet) and neighbourhood-level exposures (eg, climate and built environment) to COPD risk are understudied. Research is needed to identify the combinations of factors posing the greatest risks for disease development to inform prevention strategies locally and globally.

Early COPD and trajectories of disease

COPD is often not diagnosed, and therapies not implemented, until symptoms are burdensome and the disease is pathologically advanced. Current research focuses on earlier timepoints to identify when and how exposure-induced damage could be halted or reversed before progression to advanced disease. COPD research usually studies older individuals (aged >60 years) in whom progression of mild disease is unlikely if it has not yet occurred. Early COPD refers to mild COPD manifestations in middle-aged individuals (approximately aged 35–55 years). These individuals are most at risk for developing clinically significant irreversible pathology.[45]

Studies have shown that airway obstruction and chronic respiratory symptoms before age 50 years are associated with COPD onset and progression.[5,6,46–50] For example, an increased prevalence of chronic mucous hypersecretion among smokers aged 36–43 years usually precedes the development of airflow obstruction.[6]

However, the timepoints crucial to COPD development might vary between individuals. The usual trajectory leading to COPD is accelerated decline of lung function from a normal function level, in response to noxious exposures during adulthood.[51] However, analyses have shown that only half of older adults (aged 50–65 years) with COPD have this trajectory. The other half do not attain normal maximal lung function by early adulthood and then decline at an age-appropriate rate to reach spirometrically-defined COPD.[52] These differing trajectories suggest that genetic risk, early life and prenatal exposures, and exposures in adulthood contribute to COPD pathogenesis to varying degrees in each individual.[12,53–56] COPD, however, is burdensome regardless of trajectory,[57,58] suggesting that assessment of the mechanisms leading to COPD requires examination across the lifespan (figure 1).

Mild disease in mid-to-late life (age 40–80 years) might be burdensome despite near-normal lung function. Indeed, COPD diagnosis based on partly reversible airway obstruction might be too conservative to capture all clinically relevant tobacco-related airway disease. In two large US observational studies, smokers with preserved lung function had several characteristics indicative of COPD.[59–61] Furthermore, in SPIROMICS, when smokers with preserved lung function were deeply phenotyped, over 80% had evidence of lung disease.[62] Accordingly, smoking might erode lung health before the persistent airflow limitation that defines COPD is established. A study is underway to determine whether treating smokers with symptoms but preserved lung function is beneficial.[63]

Pathology: genetic and epigenetic risk

COPD pathogenesis is heterogeneous, with patients exhibiting airway disease, emphysema, inflammation, pathological mucus production, and vascular dysfunction to varying extents. Genetic risk has a crucial role in both COPD susceptibility and heterogeneity. An expanding list of genetic variants are associated with lung function, COPD, and aspects of the clinical presentation in genome-wide association studies (GWASs), including *HHIP* and *FAM13A*.[64–66]

Although the heritability of lung function and COPD are estimated to be 38–50%, each genetic variant explains a small proportion of COPD risk.[18,67,68] In one of the largest lung function GWASs, the 279 variants identified accounted for at most 13·1% of lung function heritability.[68] Missing heritability is attributed to either common variants contributing small effects that miss GWASs significance thresholds or rare variants contributing to disease risk in a small portion of the population.[69] Research combines variants from GWASs into genetic risk scores to predict larger proportions of COPD risk and heritability.[17,70,71] A recent polygenic risk score did not limit inclusion to significant GWASs variants, but included more than 2 million variants weighted on the basis of the full results of the largest lung function GWAS to date.[17] Individuals with the highest risk scores had a greatly increased risk of COPD, independent of smoking status. The score also correlated with emphysema and airway disease on CT imaging, and patterns of reduced lung growth in children with asthma. Genetic risk scores do not discriminate COPD cases and techniques that inherently incorporate both genetic and exposure-related risk (eg, CT imaging).[70] However, genetic scores could assist in disentangling the proportion of clinical, radiological, or biological findings due to genetics.

The contribution of rare genetic variants to COPD risk is another research area of interest. Rare variants are not captured in GWASs, but might have large effects on risk in a small proportion of the population.[72] For example, in SPIROMICS, rare variants in *SERPINA1* (ie, the gene causally linked to α1-antitrypsin deficiency) have cumulative effects on α1-antitrypsin concentrations, lung function, and emphysema in smokers.[73]

How exposures and genetic risk interact is an area of active research, and epigenetic mechanisms, including DNA methylation, might partly explain the interaction. Epigenetic alterations provide some of the earliest opportunities for exposures to silence or induce gene expression over the long term, and can accumulate over time in response to additional exposures. Smoking induces methylation in lung tissue and blood, probably contributing to xenobiotic metabolism, among other processes.[74] Methylation studies in COPD are scarce, and have only been conducted in small sample populations, but suggest diverse biological roles, including altered inflammatory and stress responses.[75] Epigenetic mechanisms might also partly explain the increased susceptibility of women to tobacco smoke. For example, methylation at *CYP1B1*, a gene involved in xenobiotic metabolism, in the buccal epithelium was correlated with lung function and radiographic emphysema in women but not men.[76] Importantly, differentially methylated sites in COPD are enriched adjacent to COPD-associated GWASs loci, suggesting that genetic regulation of gene expression in COPD might occur through DNA methylation.[77] These processes could partly explain why early life exposures contribute to COPD risk later in life.

Profiling of the transcriptome, metabolome, and proteome could aid in the understanding of lung-specific or systemic biology that contributes to COPD. Integrating these data with genetic data using methods such as gene expression quantitative trait locus analyses could provide a better understanding of how specific genetic variants contribute to COPD pathology. For example, alterations in lung gene expression that are regulated by lung function-associated genetic variants

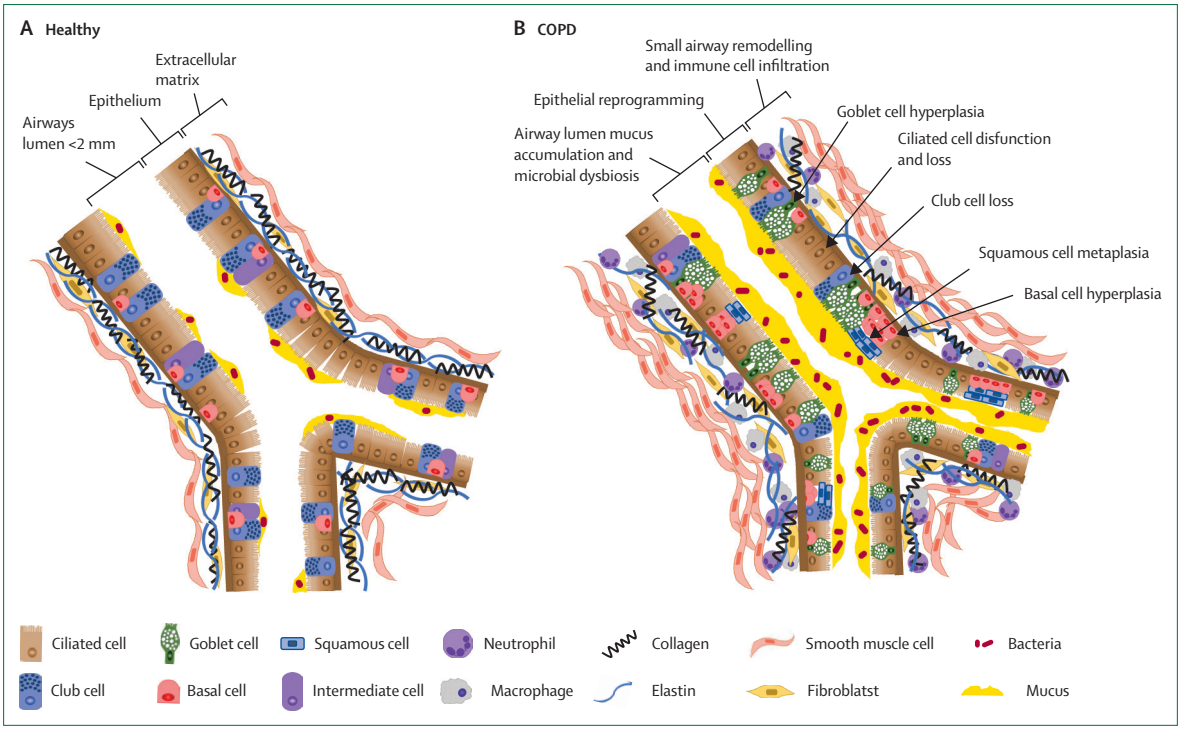

Figure 2: **Small airways in a healthy individual (A) and small airway alterations in an individual with COPD (B)**
Small airways (<2 mm) depicted at the level of the terminal and transitional respiratory bronchioles. Part A shows the healthy small (<2 mm) airway epithelium, which is predominantly composed of ciliated, club, and basal cells, and cells intermediate between differentiated cell types. Part B shows how tobacco smoke and other inhalational exposures reprogramme the epithelium, stimulating basal cell hyperplasia and differentiation into squamous cells and mucus-producing goblet cells. Ciliated and club cell proportions decrease during this reprogramming, and the remaining ciliated cells are dysfunctional. Mucus might accumulate in the airway lumen in the setting of goblet cells hyperplasia and mucociliary defects, which, in parallel with smoking-induced immunosuppression, allow for microbial dysbiosis and inflammatory cell infiltration. Proteases produced by infiltrating immune cells contribute to extracellular matrix remodelling, in which elastins are reduced and collagen organisation is disordered. Not all components of the extracellular matrix are depicted. Adapted from Hogg and colleagues.[79] COPD=chronic obstructive pulmonary disease.

were found to be enriched in lung developmental pathways.[78] Although not ready for clinical practice, omic methods hold promise for explaining COPD pathobiology, identifying functions of causal genetic variants, and developing biomarkers that predict disease progression or outcomes.

Pathological alterations: the airway epithelium, immune cells, and mesenchyme

The small (<2 mm) airways are an early site of alteration in COPD development (figure 2).[79] Small airway epithelium composition in healthy individuals provides an optimal environment for defence against pathogens and other inhaled insults.[80] The small airway epithelium is predominantly composed of secretory (club) cells, which synthesise and secrete products that line the small airway epithelium and aid in the innate immune response; ciliated cells, which aid in foreign material removal; and self-renewing basal cells, which replenish the major epithelial cell types after injury. Mucus-producing goblet cells that trap foreign materials are present to a lesser extent in the small airway epithelium than in the upper airway. Pulmonary neuroendocrine cells and ionocytes are rare throughout the airways, and their functions are only partly understood.[81,82]

Inhaled exposures cause oxidant-induced injury leading to reprogramming of the basal cells that maintain the airway epithelium (figure 2). Reprogramming induces a shift in the small airway epithelium to more closely resemble the proximal airways, which are more exposed to irritants and microbes than the small airway epithelium and thus better equipped for defence against these factors.[80] Smoking-induced upregulation of epidermal growth factor and amphiregulin (ie, the ligands of the epidermal growth factor receptor) stimulates basal cell differentiation into squamous and goblet cells, respectively.[83] This transformation causes secretory and ciliated cell loss, and squamous and goblet cell metaplasia. The result is a new small airway epithelium micro-environment in which altered innate immune defences, pathological mucus secretion, and dysfunctional cilia contribute to the onset and progression of COPD. The epithelial reprogramming occurs in the absence of inflammation in most individuals who smoke, suggesting it occurs early in COPD pathogenesis.[84] However, advancing COPD stages are associated with increasing

small airway pathology, including mucous accumulation, immune cell infiltration, and airway wall thickening.[85] Epithelial reprogramming, in combination with immune and remodelling responses, probably culminates in this progressive response and contributes to the development of emphysema.

Imaging studies based on parametric response mapping (PRM) further suggest that small airway disease precedes emphysema. PRM, a voxel-based CT imaging technique, coregisters inspiratory and expiratory scans to distinguish regions of normal lung from functional small airways disease (fsad) and emphysema (emph). These are quantified as the relative volume of normal lungs compared with PRM-detected fsad (PRM^{fsad}) and emph (PRM^{emph}).[86] PRM^{fsad} is associated with small airway epithelium pathology, including airway thickening and loss.[87] Conversely, PRM^{emph}, which closely matches emphysema as defined in Hounsfield units, is associated with emphysema pathology, including decreased alveolar surface area and alveolar attachments. In the COPDGene study, disease progression for individuals with milder COPD was typified by increases in PRM^{fsad}, whereas progression for individuals with advanced disease was typified by increases in PRM^{emph}.[88]

Altered innate immune defences are a crucial contributor to COPD development and progression and are linked to epithelial reprogramming. Smoking-induced alterations to the small airway epithelium disturb epithelial barrier function and mucociliary clearance, leading to disruption of airway microbiome homoeostasis (ie, dysbiosis).[79] Smoking stimulates an airway epithelium-specific immunosuppression that further contributes to dysbiosis and inflammatory cell infiltration. One mechanism for this immunosuppression is via a smoking-associated deficiency in intraluminal secretory IgA (sIgA), due to a loss of the polymeric immunoglobulin receptor that is required for the translocation of sIgA across the epithelium and into the lumen.[89,90] Intraluminal sIgA deficiency promotes bacterial invasion and macrophage and neutrophil accumulation.

Macrophages and neutrophils are crucial innate immune cells in COPD pathogenesis, implicated in chronic inflammation and emphysema development. Increased pathological macrophage concentrations in COPD are partly due to oxidant-induced resistance to apoptosis caused by smoking.[91] Despite an extended lifespan, COPD-associated macrophages exhibit defective phagocytosis of bacteria and apoptotic cells, leading to more inflammation to mitigate the reduced clearance. This defect might be caused by altered macrophage immunometabolism, including mitochondrial dysfunction and reduced compensatory glycolysis.[92,93] The matrix metalloproteinases (MMP), particularly MMP12 produced by macrophages, are the major proteinases implicated in emphysema; although, maybe to a lesser extent, neutrophil elastase and a disintegrin and metalloproteinase (known as ADAM) proteins also appear to contribute to the pathogenesis of COPD.[94,95] Overall, the roles of innate immune cells in COPD are complex and not fully understood.

Although protease induced-tissue degradation is central to emphysema development, small airway epithelium remodelling occurs concurrently, leaving airways deficient in the elastin that contributes to elastic recoil but rich in disordered collagen (figure 2).[96] The extracellular matrix (ECM) that maintains the basement membrane is home to multiple mediators of profibrotic signalling, tissue degradation, and angiogenesis, all of which are altered in COPD, thus contributing to airway and vascular remodelling.[97] The remodelled ECM works with immune signalling to enhance protease-based destruction of ECM components. Together with endothelial cell death and loss of the microvasculature supporting lung architecture, protease-based tissue destruction eventually leads to emphysema when these processes occur at a faster rate than the increased maintenance and repair.[97,98]

Adaptive immune responses and shifts in the microbial environment are crucial but heterogeneous in COPD. Humoral immune responses seem particularly important in emphysema-predominant severe COPD, in which lymphoid follicles containing B cells are a major feature.[99,100] Cell-mediated adaptive immune responses can have contrasting contributions to COPD, steering inflammation towards one of four major polarised responses: type 1 (T1; interferon driven, generally considered a response to viruses); type 2 (T2; IL-4, IL-5, and IL-13 driven, a response to helminths or allergens); type 17 (T17; IL-17 and IL-22 driven, a response to extracellular bacteria); and T regulatory (regulatory T cell, anti-inflammatory). Markers of T17-driven inflammation in the airway are increased in association with emphysema, neutrophilic inflammation, and absence of response to inhaled corticosteroids (ICS).[101,102] T2-associated inflammation is probably a major component of the biology underlying the ill-defined asthma-COPD overlap entity.[103] Lung microbial community alterations might drive some of this heterogeneity in host inflammation.[104]

Genomic markers of T2 inflammation are associated with an increase in eosinophils (one of the main T2 effector cells) and a better ICS response.[103] The eosinophil count was the first blood biomarker added to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, on the basis of evidence showing that it aids in determining the role of ICS in symptomatic patients prone to exacerbations.[1] However, anti-IL-5 biologics did not meet primary endpoints in COPD trials.[105,106] A lower effectiveness in the sole treatment of eosinophilic inflammation in COPD might be due to overlapping inflammatory alterations or irreversible lung damage. The ageing lung could also be more difficult to treat because of competing pathological alterations, such as stem cell exhaustion (resulting in reduced regenerative capacity) and inflammageing (as indicated by a pro-inflammatory state).[107–109]

Pathophysiology and phenotyping of exacerbations

COPD is often punctuated by periods of acute worsening, known as exacerbations. Exacerbations treated with systemic corticosteroids and antibiotic therapy are classified as moderate in the community setting, and severe in the hospital setting; yet, many unreported exacerbations go untreated.[84,110] Exacerbations are associated with substantial harm, including accelerated morbidity and mortality after severe and repeated events.[10]

Generally, the immunophysiological response during an exacerbation includes a reduction in forced expiratory volume in 1 s (FEV_1), airway neutrophilia, and peripheral blood leukocytosis.[111] Frequently, the cause is a microbial pathogen. Viruses can be found in approximately 50% of patients with severe exacerbations and 25% of patients with moderate exacerbations,[111,112] and bacteria are often found in co-culture with other pathogens;[113] however, microbial causes are probably underestimated.

Exacerbations are heterogeneous. No clinical, physiological, radiological, or biological marker can predict exacerbation onset.[114] Until the early 2010s, the heterogeneity of COPD exacerbations was classified as infectious or non-infectious. Bafadhel and colleagues[111] examined airway and systemic inflammation in moderate exacerbations and identified four exacerbation clusters, also known as exacerbation endotypes, related to (1) high concentrations of airway TNF and IL-1β (pro-inflammatory exacerbation endotype); (2) high concentrations of airway CXCL10 (IP-10) and CXCL11 (IP-9; T1 inflammatory exacerbation endotype); (3) high concentrations of airway CCL17 and IL-5 (T2 inflammatory exacerbation endotype); and (4) low concentrations of measured airway inflammatory biomarkers (pauci-inflammatory exacerbation endotype). The first three endotypes were associated with the detection of bacteria, viruses, and eosinophilic inflammation, respectively. Microbiome profiling identified microbial community differences associated with each endotype, providing further insight into the interaction of infection and innate immune cells.[115,116] Clinical trials using blood eosinophils to direct systemic corticosteroid therapy for exacerbation treatment on the basis of endotype have been promising but require validation.[117,118]

At present, few treatment options at the time of exacerbation are available and have changed little in over four decades. Predicting who is most at risk for exacerbation is also difficult. Therapeutic guidelines suggest increased preventive management for patients having two or more exacerbations in a year, or for patients requiring admission to hospital.[1] The discovery of biological exacerbation endotypes and an increased understanding of the complex interplay between inflammation and the microbiome could lead to novel therapeutics targeting biological pathways for the management and prevention of exacerbations. Treatments targeted toward exacerbations are separately discussed in the Diagnosis and treatment section.

Contributions of imaging to understanding COPD phenotypes and progression

Since the early roentgenographic descriptions of COPD in the mid-20th century,[119,120] imaging advances have contributed greatly to the understanding of COPD pathophysiology. Imaging methods such as CT and MRI permit in-vivo study of structure-function associations and are emerging as potential tools for individualised COPD management.[121]

In-vivo imaging has shown the variable extent of airway and airspace abnormalities in patients with COPD.[122–124] These observations support the long-standing hypothesis that COPD is a heterogenous syndrome resulting from various pathologies with distinct causes, prognoses, and treatments (ie, endotypes).[1] Indeed, imaging studies of parenchymal and airway abnormalities associated with COPD show distinct associations with genetic loci, environmental exposures, and clinical manifestations (eg, exacerbations).[70,123,125–127]

Multi-resolution imaging of surgically isolated lungs showed 70% fewer terminal bronchioles in patients with COPD than in controls.[128] Moreover, the lower terminal bronchiole count and associated reduction in cross-sectional airway lumen area in lungs from patients with COPD were evident in regions without airspace enlargement, suggesting that airway loss might occur early in the disease.[128] Similar imaging techniques applied to lungs from non-smoking donors revealed an association between increasing age and a reduction in terminal bronchioles across the adult lifespan.[129] This association followed established age-related declines in lung function, supporting the mechanistic hypothesis of COPD as a disorder of accelerated ageing. Advances in functional imaging, such as PRM, have provided image-based biomarkers of small airway dysfunction to facilitate detection in vivo, opening avenues for early detection of small airway pathology and treatment.[86,87,130]

Imaging of general population samples has shed light on COPD risk factors beyond exposure to tobacco smoke. Dysanapsis, a mismatch of airway tree calibre relative to lung size, was initially inferred from the variation in maximal expiratory airflows among healthy adults and hypothesised to have a role in risk of obstructive lung disease.[131,132] Smaller than predicted airway tree calibre associated with dysanapsis has repeatedly been shown to be a major risk factor for COPD, at the same level as tobacco smoking and other risk factors (eg, second-hand smoke and air pollutants).[131–133] Moreover, adults who are heavy smokers who are free of spirometry-defined COPD exhibit airway tree calibres that are larger than predicted, suggesting that dysanapsis might help to explain heterogeneity of COPD susceptibility among individuals who smoke.[132] Understanding the biological basis of dysanapsis could lead to early life interventions to promote resilient lung health across the lifespan. Imaging lung structure can also serve as an intermediate outcome measure when

investigating the potential role of common exposures with small-to-moderate effect size that have potentially large population-attributable risk. Using this approach, higher concentrations of outdoor ozone, nitrogen oxides, and particulate matter less than 2·5 µm were each associated with accelerated emphysema progression, as quantified by lung density on serial CT over 18 years of follow-up.[134] Such observations contribute to evidence that informs policy decisions related to air pollution and respiratory health.

Imaging has also advanced knowledge of comorbidities in COPD.[1] Cardiovascular disease is a common COPD comorbidity shown to affect outcomes.[1] In-vivo imaging has shown that decreased lung perfusion, increased vessel tapering, and altered large vessel and cardiac structure are evident even at early stages of COPD.[135–139] Ongoing studies might determine the contribution of these cardiovascular abnormalities to functional impairment and potential for therapeutic targeting.[140–143]

In the therapeutic context, the role of imaging as a tool for patient selection is expanding. For example, CT-assessed upper-lobe dominant emphysema is associated with survival benefit among patients undergoing lung volume reduction surgery,[144] among other factors, and is recommended for patient selection.[1] Bronchoscopic approaches to lung volume reduction have been developed, the success of which partly relies on the absence of collateral ventilation between lobes to facilitate atelectasis of the targeted lobe.[145] Clinical trials assessing bronchoscopic lung volume reduction have used imaging for patient selection (ie, identifying target lung regions and assessing fissure integrity as an indicator of collateral ventilation) and as an intermediate outcome (ie, assessing target lobe atelectasis).[145–150] Imaging-based intermediate outcome assessment has also been applied in the treatment of α1-antitrypsin deficiency. A clinical trial relied on CT-assessed lung density as the primary outcome to show that α1-antitrypsin slowed emphysema progression over 24 months.[151]

Diagnosis and treatment

Screening and diagnosis

Screening spirometry, although not universally recommended,[152,153] is appropriate among individuals with particular symptoms (eg, progressive dyspnoea, chronic cough or sputum production, recurrent pneumonia, or respiratory infections) or risk factors (eg, relevant exposures, genetic and family history, history of prematurity, or low birthweight).[1,154,155] Screening questionnaires to identify individuals needing spirometry have shown preliminary value[156] and are being tested more broadly in the primary care setting.[157] COPD diagnosis is made on the basis of the presence of risk factors, symptoms, and spirometry showing persistent airflow obstruction. GOLD recommends post-bronchodilator testing showing the ratio of FEV_1 to forced vital capacity be less than 70% to diagnose obstruction.[1]

***Panel*: Pharmacological and non-pharmacological treatments for COPD, based on stable versus exacerbated state and setting of use**

Stable COPD

Individualised non-pharmacological treatments

- Vaccinations (eg, influenza, pneumococcus, pertussis, SARS-CoV-2, and shingles)
- Smoking cessation counselling (which might include pharmacological aids)
- Pulmonary rehabilitation, exercise training, self-management, and disease education (eg, inhaler technique and adherence, breathing techniques, and written action plan)
- Long-term oxygen therapy
- Long-term non-invasive ventilation
- Surgical or bronchoscopic lung volume reduction
- Bullectomy
- Lung transplantation
- Screening for COPD-associated comorbid health conditions and diseases (eg, anxiety, depression, cardiovascular disease, lung cancer, and osteoporosis)
- Palliative care (eg, end-of-life planning)

Individualised pharmacotherapies

- β_2 agonists
- Anticholinergics
- Corticosteroids
- Antibiotic prophylaxis
- Phosphodiesterase-4 inhibitors
- Mucoregulators
- Methylxanthines
- α1-antitrypsin augmentation therapy

Acute exacerbation of COPD

Individualised non-pharmacological treatments

- Oxygen
- Ventilation (eg, non-invasive positive pressure ventilation)

Individualised pharmacotherapies

- β_2 agonists
- Anticholinergics
- Corticosteroids
- Antibiotics

COPD=chronic obstructive pulmonary disease.

Non-pharmacological interventions for COPD

Non-pharmacological treatments for COPD are a crucial part of the treatment plan (panel). Prevention strategies include vaccinations, smoking cessation, and avoidance of exposures.[1] Pulmonary rehabilitation is key for select individuals.[158–160] Supplemental oxygen and non-invasive ventilation are widely used adjunctive methods.[161–163] Lung volume reduction surgery is rarely pursued. However, bronchoscopic lung volume reduction[145,164–166] is a less invasive alternative than surgical lung volume reduction.

Pulmonary rehabilitation is particularly effective after exacerbations[159] and in individuals with exercise limitation.[158] However, barriers including programme scarcity and capacity limitations affect access to and implementation of pulmonary rehabilitation.[160] Patient-related factors including mobility, transportation access, social isolation, and cost are also barriers.[160] Medical literature on the use of virtual rehabilitation programmes is evolving, particularly as a method to reach sparsely populated areas.[167,168] Early telemedicine studies, bolstered by the COVID-19 pandemic, have been promising, showing feasibility and outcome improvement.[169,170] However, before widespread adoption, further studies, infrastructure development, and streamlined implementation of virtual programmes are needed.

Oxygen supplementation has long been indicated as a therapy for patients with COPD with severe resting hypoxaemia (oxygen saturation [SpO_2] ≤88%).[171] However, the 2016 LOTT trial suggested oxygen supplementation in moderate resting (SpO_2 89–93%) and exertional hypoxaemia (SpO_2 81–89%) might be less important than in severe resting hypoxaemia, because of absence of association with mortality, hospitalisations, and exacerbations.[172] Accordingly, American Thoracic Society clinical practice guidelines recommend against supplemental oxygen initiation for moderate resting hypoxaemia, but this recommendation is based on low-quality evidence.[173]

Non-invasive ventilation reduces intubation risk, length of hospital stay, and mortality in respiratory failure due to COPD exacerbations.[174,175] Consequently, non-invasive ventilation is recommended as the first line ventilatory support in this setting.[1] However, trials of non-invasive ventilation for severe resting hypercapnia in patients with chronic COPD have had mixed results. Some studies showed reduced mortality and hospital readmissions,[162,163] particularly in patients with resting hypercapnia and who have been admitted to hospital within the past 2–4 weeks for respiratory failure.[163] Other studies showed no clear benefit,[161] but differences in ventilatory strategy restrict the ability to draw definitive conclusions. Ultimately, chronic non-invasive ventilation might be beneficial in patient subgroups with suitable home care support.

Bronchoscopic lung volume reduction might be appropriate in a highly select patient subgroup, but benefits are largely limited to improvements in exercise capacity and symptoms.[164] Identifying the correct patients is crucial because of the relatively invasive nature of the bronchoscopic procedure and the moderate-to-high risk for adverse events such as pneumothorax. Considerations include presence of air trapping, continued exercise limitation after pulmonary rehabilitation, smoking cessation, emphysema heterogeneity, and collateral ventilation to the treated area.[145,166] Ultimately, palliative care and symptom management can be considered for patients with substantial disease burden and low quality of life despite available treatments.

Pharmacotherapies for COPD

Since 2011, GOLD has used the symptom-based and exacerbation-based classification system using letters A, B, C, and D, which emphasises symptom scores and risk for exacerbations to determine long-term pharmacotherapy. Since 2019, follow-up treatment targeting exacerbations or dyspnoea has been considered separately from initial management (figure 3).[176] Although there is substantial overlap in strategies used in both pathways, we describe these pathways separately to better align with GOLD recommendations. Pathways targeting dyspnoea prioritise long-acting bronchodilators and de-emphasise ICS. Pathways targeting exacerbations draw on evolving literature[118,177,178] to suggest ICS initiation in individuals who frequently have exacerbations and have blood eosinophil counts of 300 cells per μL or greater (>100 cells per μL if escalating treatment due to recent exacerbation).[1] The timing and frequency for assessing eosinophil counts to guide management are not clear. Although blood eosinophil measurements can be relatively stable over time in COPD,[179–181] studies show that variability increases with higher absolute counts.[179,180] Ultimately, studies are needed to better guide blood eosinophil targeted treatment in COPD and determine whether biomarkers that more accurately reflect eosinophilic inflammation in the lung could be developed.[109]

ICS withdrawal might be considered in patients with low risk for exacerbations or high risk for adverse outcomes (eg, pneumonia), but should be avoided in those with persistent elevations of eosinophil counts despite ICS.[182–184] Recent trials studied so-called triple therapy in patients with moderate-to-severe COPD, in which ICS, long-acting β_2 agonists (LABAs), and long-acting muscarinic antagonists (LAMAs) are combined into a single inhaler, compared with ICS plus LABA or LABA plus LAMA combination therapies.[185,186] These studies have largely supported the GOLD approach to preventive management. Triple therapy is associated with exacerbation reduction, particularly in individuals with elevated eosinophil counts, and a moderate mortality benefit in secondary analyses. Triple therapy might prevent exacerbations even in patients with low eosinophil counts, but further studies are needed.

Other emerging pharmacotherapies in COPD include nebulised LAMAs,[187,188] a novel delivery mechanism for a mainstay of long-acting COPD treatment. Nebulisers might be useful in individuals with low peak inspiratory flow in whom medication delivery via some inhalers could be less efficient.[189,190] However, whether peak inspiratory flow-guided therapy choices affect delivery to the extent that clinical outcomes are improved is unclear.

GOLD guidelines also recommend screening for and treating other causes of dyspnoea. The prevalence of comorbidities among individuals with COPD is high,[191–193] including cardiovascular disease, depression, and

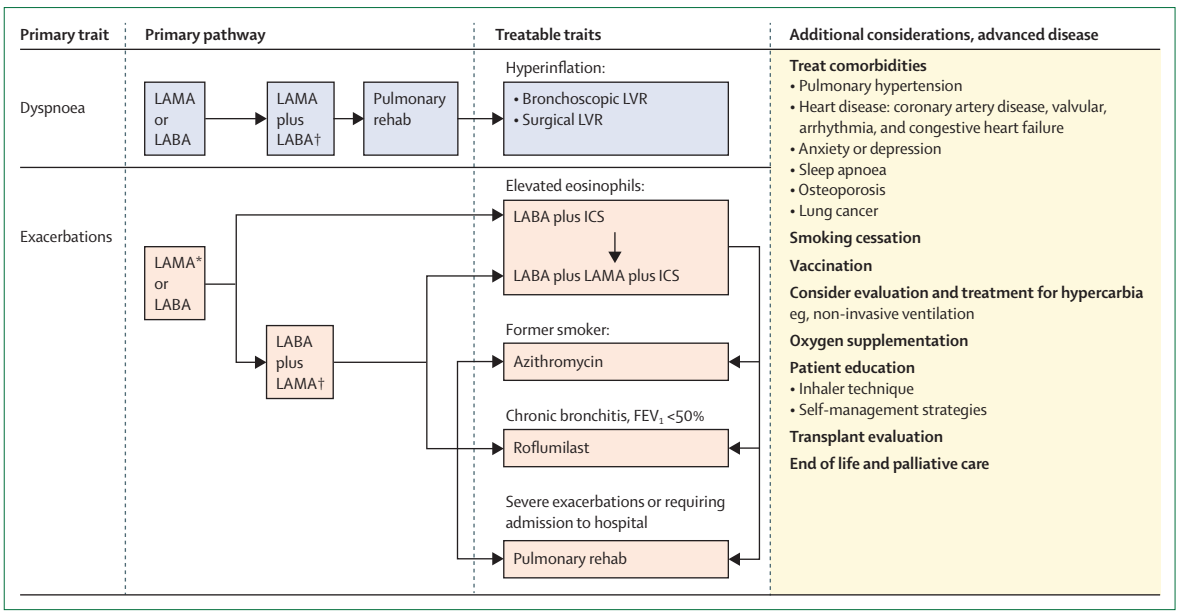

Figure 3: **Treatment pathways for COPD**
Pathways are based on primary trait, dyspnoea or exacerbations, including relevant treatable traits. Additional considerations that are important across all individuals with COPD are listed in the right column. COPD=chronic obstructive pulmonary disease. FEV_1=forced expiratory volume in 1 s. ICS=inhaled corticosteroids. LABA=long-acting β_2 agonists. LAMA=long-acting muscarinic antagonists. LVR=lung volume reduction. *LAMA is preferred initial therapy to LABA in exacerbation-prone COPD. †LAMA plus LABA therapy can be used as initial therapy in both dyspnoea and exacerbation pathways if severe dyspnoea is present.

anxiety. These comorbidities are associated with worse symptoms and exacerbations.[194–197]

Treatment targeted at exacerbations

Pharmacological treatments for the prevention of exacerbations have largely targeted patients with at least two exacerbations in the past year (or at least one resulting in admission to hospital). Therapies of value beyond inhaled bronchodilators and ICS include azithromycin and roflumilast (figure 3).[118,177,178] Azithromycin is associated with reduction of exacerbations and improved quality of life;[198] subgroup analyses have shown higher efficacy among former smokers.[199] Roflumilast reduces exacerbations in individuals with chronic bronchitis symptoms and frequent exacerbations.[200–202] A meta-analysis of studies on vitamin D has prompted a recommendation for assessing vitamin D status (and providing supplementation if deficient) among individuals admitted to hospital for COPD exacerbations.[203]

Non-pharmacological treatments that are effective in preventing exacerbations include self-management programmes and pulmonary rehabilitation. Self-management programmes have been used for decades, often in association with pulmonary rehabilitation. Evidence for the incremental value of disease-specific educational interventions, including self-efficacy training and broader educational programmes for improved outcomes, is still unclear.[204,205]

Palliative care

Palliative care strategies in COPD include treatments targeted at symptom control, both in the setting of end-of-life care and in all patients with COPD. End-of-life palliative measures are probably underused in patients with COPD,[206] possibly because of challenges involved in establishing mortality risk.[207] Regardless, even among those patients not thought to be at the end of life, symptom-oriented treatments of debilitating symptoms, such as dyspnoea, have been studied. Some strategies showing promise include use of opiates,[208] fans,[209] and oxygen.[210]

Impact of SARS-CoV-2 and the COVID-19 pandemic on COPD

The COVID-19 pandemic has had both direct and indirect effects on individuals with COPD, and the literature is evolving. Although the estimated prevalence of COPD among individuals infected with SARS-CoV-2 varies,[211,212] with a few exceptions,[213,214] most studies have shown heightened adverse effects of COVID-19 in individuals with COPD. These adverse effects include more frequent treatment in hospital, readmissions to hospital, admissions to intensive care units, necessity for mechanical ventilation, cardiovascular events, and higher mortality than among patients without COVID-19.[212,215–225] The mechanisms for such heightened adverse events are not clear. One possibility is related to the ACE2 receptor that binds SARS-CoV-2, which has been shown to be increased in the small airways of patients with COPD.[226] Individuals with COPD also appear to be at higher risk for inflammageing, a dysfunctional pro-inflammatory state associated with increasing age, which could provide a lung environment more prone to severe COVID-19 disease than in healthy individuals.[227–229]

Unlike other respiratory viruses, research has not suggested that SARS-CoV-2 is a major cause of COPD exacerbations. A recent meta-analysis of 13 studies showed that the proportion of patients admitted to hospital due to COPD exacerbations decreased by approximately 50% during the pandemic.[230] These numbers did not increase back to historical levels over time, whereas numbers for myocardial infarction did increase back to historical levels.[231] Hypothesised mechanisms for this decrease include reduction in exposure to respiratory viruses[232–234] that commonly trigger exacerbations due to social distancing[235] and enhanced respiratory precautions (eg, wearing face masks), or background ICS treatment.[236] Conversely, worse self-reported symptoms and lower physical capacity have been reported among individuals with COPD during the COVID-19 pandemic than before the pandemic.[237]

COVID-19 has also had indirect effects on individuals with COPD, who have been identified as a high risk group for COVID-19.[238,239] Concerns for increased social isolation, anxiety, and depression exist in this group,[240] in whom anxiety and depression are already common and linked to worse outcomes.[241,242] Other consequences include decreased access to in-person care.[243] Despite the negative impacts, the COVID-19 pandemic has resulted in the rapid adoption of digital health and innovation, enabling programmes such as virtual rehabilitation, which might ultimately improve overall COPD care.

Future directions and conclusions

Although tobacco smoke is the greatest COPD risk factor, there is increasing awareness of the essential roles for genetics, early-life risk factors, and exposures incurred over the life course in COPD pathogenesis. Accordingly, more recognition is being given to the importance of identifying COPD at earlier stages, with the goal of preventing progression of disease and morbidity. Concurrently, as in many chronic diseases, precision medicine approaches hold promise for finding and targeting COPD characteristics amenable to specific treatments. Future studies are required to better understand both early COPD treatment and precision medicine in the context of existing treatment and prevention approaches.

Contributors

SAC and NP contributed to conception and design of the manuscript. All authors contributed to literature search, organisation of search results, and manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

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