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The COPD lung: Pathobiology, diagnostic advances, systemic comorbidity, and evolving therapeutic strategies — A narrative review

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Abstract
Chronic obstructive pulmonary disease (COPD) remains one of the leading causes of morbidity and mortality worldwide, with its defining lesion, the COPD lung, shaped by a convergence of chronic inhalational injury, dysregulated repair, and persistent inflammation. This narrative review synthesizes contemporary evidence on the structural and cellular pathology of the COPD lung, including emphysematous alveolar destruction, small-airway fibrosis, and vascular remodeling, alongside the innate and adaptive immune circuits, oxidative stress pathways, and cellular senescence programs that sustain disease progression. Genetic susceptibility, notably alpha-1 antitrypsin deficiency, and environmental exposures such as tobacco and household biomass smoke are discussed as complementary drivers of phenotypic heterogeneity. The review further examines diagnostic advances, including quantitative computed tomography phenotyping and circulating and airway biomarkers, the growing recognition of COPD as a systemic disease with cardiovascular, musculoskeletal, and metabolic comorbidities, and the expanding pharmacological armamentarium spanning bronchodilators, inhaled corticosteroids, triple combination therapy, and the newly approved biologic agents dupilumab and mepolizumab for eosinophilic COPD. Non-pharmacological interventions, particularly pulmonary rehabilitation, are considered within a treatable-traits framework. Collectively, the evidence points toward a precision-medicine paradigm in which endotype-directed therapy, earlier detection through imaging and biomarker panels, and integrated management of comorbidities may finally begin to alter the historically relentless trajectory of the COPD lung.

Keywords: Chronic obstructive pulmonary disease, emphysema, airway remodelling, pulmonary inflammation, biomarkers, Comorbidities Pulmonary Rehabilitation

Introduction

Chronic obstructive pulmonary disease is not a single disease but a heterogeneous clinical syndrome unified by persistent, largely irreversible airflow limitation arising from a mixture of small-airway disease and alveolar destruction. The lung of a person living with COPD is best understood as an organ shaped by decades of low-grade injury, incomplete repair, and an immune response that never fully resolves (Christenson *et al*., 2022; Agustí & Hogg, 2019) [3, 27]. Long before spirometric abnormality becomes apparent, structural remodeling of the terminal and respiratory bronchioles is already underway, a fact established in classic pathological work and repeatedly confirmed with modern imaging (Hogg *et al*., 2004; Fletcher & Peto, 1977) [34, 42].

Over the past decade, the conceptual model of COPD has shifted substantially. Rather than viewing the disease purely as a consequence of cigarette smoking culminating in emphysema, contemporary frameworks emphasize lifetime trajectories of lung function, early-life determinants, non-smoking risk factors such as household air pollution, and genetic susceptibility, together with recognition that COPD behaves as a systemic disorder with far-reaching comorbidity (Agustí *et al*., 2023; Rennard & Drummond, 2015; Stolz *et al*., 2022) [5, 64, 78]. This review draws together current evidence on the pathobiology of the COPD lung, the mechanisms sustaining chronic inflammation and tissue destruction, diagnostic and imaging advances, the burden of systemic comorbidity, and the therapeutic landscape, including the recent arrival of biologic agents for eosinophilic COPD.

Epidemiology and Global Burden

COPD affects more than 400 million people worldwide and remains the third leading cause of death globally, with pronounced regional variation in prevalence, risk factor profile, and temporal trend (Montes de Oca *et al*., 2025) [54]. Pooled prevalence estimates derived from systematic reviews and meta-analyses place the global burden of spirometrically defined COPD at roughly 10% among adults, although figures vary considerably depending on diagnostic criteria, population age structure, and smoking prevalence (Al Wachami *et al*., 2024; Adeloye *et al*., 2022) [2, 6]. The Global Burden of Disease framework confirms that low- and middle-income countries contribute disproportionately to COPD mortality and disability-adjusted life-years, a pattern attributable in part to indoor biomass fuel combustion, occupational dust exposure, and comparatively limited access to spirometry-based diagnosis (GBD Chronic Respiratory Disease Collaborators, 2024) [38]. Poverty itself appears to compound risk independently of smoking, as shown in multinational cohort data linking socioeconomic deprivation with a higher prevalence of chronic airflow obstruction (Townend *et al*., 2017; Burney *et al*., 2014) [20, 82]. Sex-based differences in COPD burden are also narrowing in many regions, a trend partly explained by a slower decline in female smoking rates relative to men and by the disproportionate exposure of women to biomass

smoke in domestic cooking environments (Montes de Oca *et al*., 2025) [54]. Table 1 summarizes the widely used GOLD spirometric grading system, which continues to anchor disease classification despite growing calls for biomarker- and imaging-based refinement.

Table 1: GOLD Spirometric Classification and Refined ABE Symptom/Risk Assessment (Agustí *et al*., 2023; Vestbo *et al*., 2013) [5, 85]

Category	Criterion	Description
GOLD 1	FEV1 ≥ 80% predicted	Mild airflow limitation; often minimally symptomatic
GOLD 2	50% ≤ FEV1 < 80% predicted	Moderate airflow limitation; breathlessness on exertion typical
GOLD 3	30% ≤ FEV1 < 50% predicted	Severe airflow limitation; marked dyspnea, reduced exercise tolerance
GOLD 4	FEV1 < 30% predicted	Very severe airflow limitation; risk of respiratory failure
Group A	0–1 moderate exacerbation, low symptom burden	mMRC 0–1 or CAT < 10; bronchodilator therapy
Group B	0–1 moderate exacerbation, high symptom burden	mMRC ≥ 2 or CAT ≥ 10; dual bronchodilation favored
Group E	≥ 2 moderate exacerbations or ≥ 1 hospitalization	Highest risk irrespective of symptoms; early escalation warranted

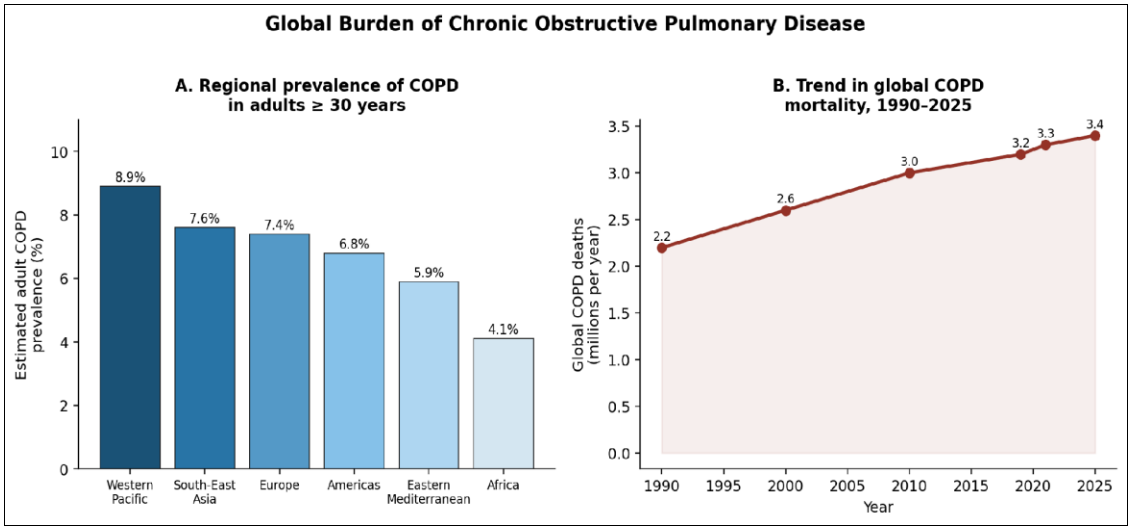

Fig 1: Regional prevalence and global mortality trend of chronic obstructive pulmonary disease. Panel A depicts illustrative regional prevalence estimates in adults aged 30 years and older; Panel B depicts the approximate global mortality trend from 1990 to the present (data synthesized from Montes de Oca *et al*., 2025; GBD Chronic Respiratory Disease Collaborators, 2024; Adeloye *et al*., 2022; Al Wachami *et al*., 2024) [2, 6, 38].

Pathophysiology of the COPD Lung

The structural hallmark of the COPD lung is the coexistence, in variable proportion, of emphysematous destruction of alveolar walls and remodeling of the small conducting airways. Early morphometric studies demonstrated that narrowing and loss of terminal and respiratory bronchioles precedes the alveolar destruction that defines emphysema, occurring years before clinically detectable airflow obstruction (Hogg *et al*., 2004) [42]. Two distinct but converging mechanisms drive airflow limitation: loss of elastic recoil secondary to alveolar wall destruction, which predisposes small airways to collapse during expiration, and intrinsic narrowing of the small airway lumen from peribronchial fibrosis, smooth muscle hypertrophy, and mucus hypersecretion (Barnes, 2019; Zhang *et al*., 2024) [11, 96].

Airway remodeling reflects a sustained imbalance between tissue destruction and aberrant repair. Fibroblasts within the COPD airway proliferate and deposit excess extracellular matrix components, including collagen and fibronectin, contributing to wall thickening even as elastin and alveolar attachments are lost elsewhere in the lung (Zhang *et al*., 2024) [96]. Epithelial–mesenchymal transition, goblet cell hyperplasia, squamous metaplasia, and impaired mucociliary clearance further compromise the epithelial barrier, exposing the submucosa to ongoing antigenic and oxidative insult (Zhao *et al*., 2024) [97]. Concurrently, capillary rarefaction and endothelial dysfunction within the pulmonary microvasculature amplify local inflammation through upregulated adhesion molecule expression and reactive oxygen species generation, closing a self-sustaining cycle of injury (Zhang *et al*., 2024) [96].

At the level of the terminal respiratory unit, disruption of alveolar attachments to the airway wall — a direct consequence of emphysematous destruction — predisposes small airways to expiratory collapse, while chronic inflammation independently thickens the airway wall and encroaches upon the lumen; both processes act synergistically rather than in isolation to produce the progressive, largely fixed airflow obstruction that defines the disease (Agustí & Hogg, 2019) [3]. This dual pathway helps explain why patients with radiologically similar degrees of emphysema can have markedly different physiological trajectories, and why quantitative imaging that separately captures emphysema and airway remodeling has become central to modern phenotyping efforts (Chen *et al*., 2024; Kirby *et al*., 2025) [25, 45].

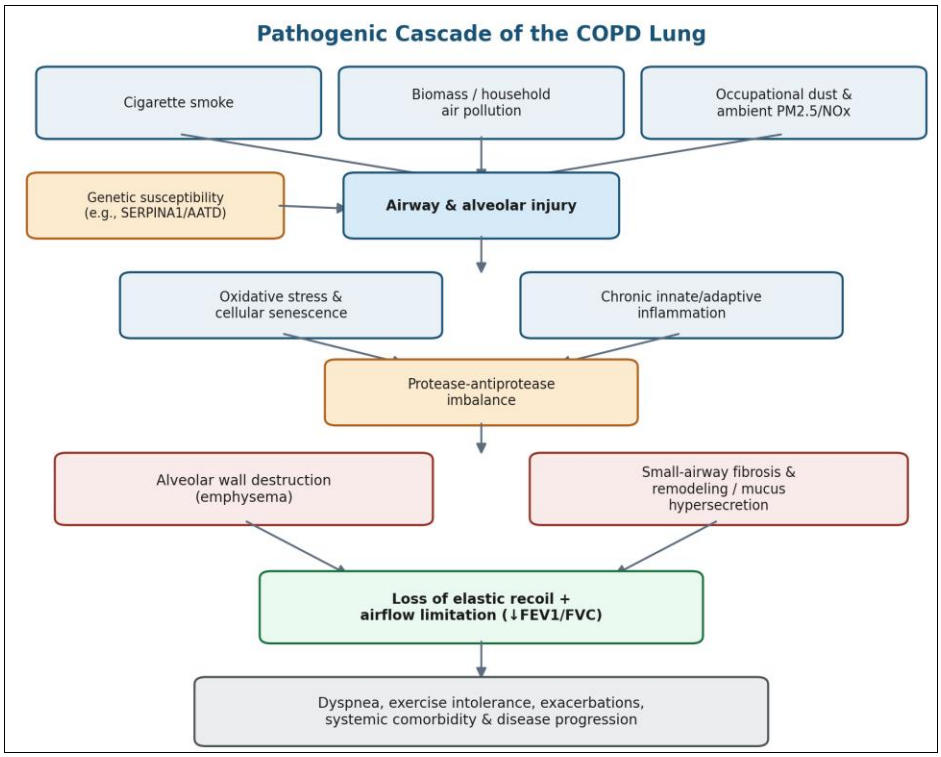

Fig 2: Schematic overview of the pathogenic cascade linking inhalational exposure and genetic susceptibility to alveolar destruction, small-airway remodeling, and progressive airflow limitation in the COPD lung (adapted from mechanistic evidence in Hogg *et al*., 2004; Barnes, 2019; Agustí & Hogg, 2019; Zhang *et al*., 2024) [19, 11, 42, 96]

Inflammatory and Immune Mechanisms

Persistent airway and parenchymal inflammation is central to COPD pathogenesis, involving both innate cells — neutrophils, macrophages, eosinophils, mast cells, and natural killer cells — and adaptive lymphocyte populations, particularly CD8+ cytotoxic T cells and, in more advanced disease, organized lymphoid follicles containing B cells (Qi *et al*., 2024; Zhao *et al*., 2024) [62, 83, 97]. Neutrophils are recruited in large numbers to the COPD airway, where they release elastase, myeloperoxidase, and reactive oxygen species, and increasingly form neutrophil extracellular traps that amplify tissue injury and contribute to airway microbial dysbiosis (Fricker & Lokwani, 2025) [36].

Alveolar macrophages in COPD display a distinctive, partially defective phenotype, with impaired phagocytic clearance of bacteria and apoptotic cells alongside an exaggerated release of proteases and pro-inflammatory cytokines such as tumor necrosis factor-alpha and interleukin-1 beta (Zhu *et al*., 2025) [99]. Immune senescence further compounds this dysfunction, diminishing host defense against recurrent respiratory infection while simultaneously sustaining a low-grade inflammatory state, a phenomenon sometimes termed inflammaging (Bafadhel *et al*., 2025). Autoimmune features have also been described, with expansion of autoreactive T- and B-cell populations and contraction of regulatory subsets, suggesting that in a subset of patients the chronic inflammatory response may become at least partly self-directed (Qi *et al*., 2024) [62].

Not all COPD inflammation is neutrophilic. Approximately 15% to 40% of patients demonstrate a type 2, eosinophil-predominant inflammatory signature, characterized by elevated blood and airway eosinophils, increased interleukin-4, interleukin-5, and interleukin-13 signaling, and a more corticosteroid-responsive phenotype (Sethi & Suki, 2025; Vitenberga-Verza & Pilmane, 2025) [71, 86]. This biological heterogeneity has direct clinical implications, as discussed further in the sections on biomarkers and biologic therapy, and underlies the increasing use of endotype-based rather than purely spirometric classification (Malinovschi & Stockley, 2026) [50].

Oxidative Stress and Cellular Senescence

Oxidative stress arises in the COPD lung from both exogenous sources — cigarette smoke and biomass smoke contain extraordinarily high concentrations of free radicals — and endogenous sources, principally reactive oxygen species generated by activated neutrophils and macrophages (Barnes, 2020; Ganesan *et al*., 2023) [12, 37]. The resulting oxidant burden overwhelms endogenous antioxidant defenses, damaging lipids, proteins, and DNA, and directly impairs histone deacetylase-2 activity, a mechanism proposed to underlie the relative corticosteroid resistance observed in many COPD patients (Barnes, 2020) [12].

A growing body of evidence implicates cellular senescence as a pathogenic driver rather than a mere epiphenomenon of aging in COPD. Senescent epithelial cells, fibroblasts, and endothelial cells accumulate in COPD lung tissue, adopting a senescence-associated secretory phenotype that releases pro-inflammatory cytokines, matrix metalloproteinases, and chemokines capable of perpetuating tissue injury and further inducing senescence in neighboring cells — a paracrine amplification loop (Birch *et al*., 2022) [15]. Telomere attrition, DNA damage responses, mitochondrial dysfunction, and epigenetic alterations all converge on this senescence program, and each has been proposed as a therapeutic target for so-called senotherapeutic or senolytic strategies (Cardoso *et al*., 2024) [22].

Genetic and Environmental Risk Factors

Cigarette smoking remains the dominant risk factor for COPD in high-income countries, yet only a minority of heavy smokers develop clinically significant airflow

obstruction, implicating individual susceptibility (Barnes, 2020) [12]. Alpha-1 antitrypsin deficiency, caused by mutations in the SERPINA1 gene, represents the best-characterized monogenic risk factor, disrupting the protease–antiprotease balance that normally protects the lung from unchecked neutrophil elastase activity (Palummo *et al*., 2026; Silverman, 2020) [58, 72]. The severe PI*ZZ genotype is associated with markedly reduced life expectancy and early-onset panacinar emphysema, and augmentation therapy with intravenous alpha-1 antitrypsin remains the only disease-modifying treatment specific to this genotype, despite decades of accumulated trial evidence of only modest effect on lung function decline (Brantly *et al*., 1988; Edgar *et al*., 2017; Sandhaus *et al*., 2026) [19, 30].

Beyond this monogenic cause, genome-wide association studies have identified numerous common variants of modest individual effect that collectively shape susceptibility to airflow obstruction, spanning genes involved in lung development, extracellular matrix biology, and protease regulation (Silverman, 2020) [72]. Household air pollution from biomass fuel combustion is now recognized as a globally significant, non-smoking pathway to COPD, particularly among women in low- and middle-income countries, producing a phenotype characterized by greater airway-predominant disease, bronchial hyperresponsiveness, and comparatively less emphysema than tobacco-associated COPD (Ortiz-Quintero *et al*., 2023; Amaral *et al*., 2018) [8, 57]. Occupational exposures to mineral dusts, vapors, and fumes, together with ambient particulate matter and nitrogen oxides, represent additional, often under-recognized contributors to the global COPD burden (MacNee, 2021) [49].

Airway Microbiome and Acute Exacerbations

Acute exacerbations of COPD (AECOPD) are pivotal events that accelerate lung function decline, increase mortality risk, and impose substantial healthcare costs; bacterial and viral respiratory infection precipitates the majority of these episodes (Wedzicha & Seemungal, 2007) [89]. The healthy lower airway microbiome, previously assumed to be sterile, is now understood to undergo dysbiosis during exacerbation, typically marked by reduced microbial diversity and relative expansion of Proteobacteria, including Haemophilus influenzae, while protective taxa such as Veillonella tend to diminish (Yan *et al*., 2024; Wang *et al*., 2022) [88, 93].

Microbiome–host crosstalk during exacerbation appears to operate through innate immune signaling pathways, including type I interferon and Toll-like receptor cascades, and metabolite-mediated mechanisms; for example, indole-3-acetic acid produced by airway lactobacilli has been shown experimentally to mitigate neutrophilic inflammation and lung function decline (Yan *et al*., 2024) [93]. In critically ill patients requiring intensive care for AECOPD, the pulmonary microbiome shows even more pronounced disruption, with implications for antimicrobial stewardship and ventilator-associated infection risk (van der Bie *et al*., 2024) [43]. Host genomic variation may further modulate susceptibility to microbial dysbiosis and exacerbation frequency, an area of active investigation (Zuo *et al*., 2022) [100].

Table 2: Principal Circulating and Imaging Biomarkers Relevant to COPD Lung Disease (Vitenberga-Verza & Pilmane, 2025; Stockley *et al*., 2019; Ellingsen *et al*., 2024) [31, 76, 86]

Biomarker	Biological compartment	Principal clinical utility
Blood eosinophil count	Peripheral blood	Predicts ICS/biologic response; prognostic for exacerbations
C-reactive protein	Peripheral blood	Predicts exacerbation risk; may guide antibiotic use
Fibrinogen	Peripheral blood	FDA-qualified prognostic marker for mortality and exacerbations
Fraction of exhaled nitric oxide (FeNO)	Exhaled breath	Marker of eosinophilic/type 2 airway inflammation
Interleukin-6, interleukin-8	Sputum / serum	Reflects neutrophilic inflammatory burden
sRAGE	Peripheral blood	Associated with emphysema severity
Quantitative CT emphysema index (%LAA-950)	Chest imaging	Quantifies alveolar destruction extent
Functional small-airway disease (CT parametric mapping)	Chest imaging	Detects early small-airway pathology, predicts FEV1 decline

Diagnostic Advances: Imaging and Biomarkers

Spirometry remains the diagnostic reference standard, defined by a post-bronchodilator FEV1/FVC ratio below 0.70, yet this threshold is increasingly recognized as a relatively late-stage marker that may miss substantial structural disease (Thawanaphong *et al*., 2025) [81]. Quantitative computed tomography has emerged as the leading tool for earlier and more granular phenotyping, allowing separate quantification of emphysema extent, air trapping, and functional small-airway disease within the same scan (Chen *et al*., 2024; Choi *et al*., 2017) [25, 26]. Parametric response mapping and airway fractal dimension analysis have been shown to predict respiratory morbidity and mortality independently of spirometric stage, while airway surface area-to-volume ratio offers a non-invasive window onto airway remodeling that closely parallels histological findings (Bodduluri *et al*., 2018; Bodduluri *et al*., 2021) [16, 17].

Emerging artificial intelligence approaches applied to single inspiratory CT scans can now estimate functional small-airway disease without the need for paired inspiratory–expiratory acquisitions, with output significantly associated with subsequent FEV1 decline (Thawanaphong *et al*., 2025; Kirby *et al*., 2025) [45, 81]. Alongside imaging, a panel of circulating and airway biomarkers now informs both diagnosis and treatment selection. Blood eosinophil count has become the most clinically actionable biomarker, guiding decisions about inhaled corticosteroid use and eligibility for biologic therapy, while also carrying prognostic value for exacerbation frequency and lung function trajectory (Vitenberga-Verza & Pilmane, 2025; Stockley *et al*., 2019) [76, 86].

Systemic inflammatory markers, particularly C-reactive protein and fibrinogen, retain value as prognostic indicators of future exacerbation risk, with fibrinogen holding the distinction of being the first FDA-qualified prognostic biomarker in COPD (Ellingsen *et al*., 2024; Malinovschi & Stockley, 2026) [31, 50]. Composite blood-cell indices such as the neutrophil-to-lymphocyte ratio and systemic immune-inflammation index have shown more limited incremental

value once adjusted for established clinical predictors (Ellingsen *et al*., 2024) [31]. Table 2 summarizes the principal biomarker categories currently under clinical and investigational use.

Systemic Comorbidities of the COPD Lung

COPD is now firmly established as a multisystem disease in which the localized pulmonary lesion is accompanied by, and mechanistically linked to, a range of extrapulmonary comorbidities that materially influence prognosis (Santos *et al*., 2022; Divo *et al*., 2023) [29, 69]. Systemic inflammation, often described as an overspill of pulmonary inflammatory mediators into the circulation, is implicated as a shared pathogenic pathway across most of these comorbid conditions (Sin & Man, 2003) [73].

Cardiovascular disease is the most consequential comorbidity, with COPD independently increasing risk of ischemic heart disease, heart failure, and arrhythmia; overlapping symptoms such as dyspnea frequently delay diagnosis of either condition, and physicians often under-treat cardiovascular disease in COPD patients out of unfounded concern regarding beta-blocker safety (Roversi *et al*., 2019) [67]. Skeletal muscle dysfunction, sarcopenia, and cachexia are similarly prevalent, reflecting a combination of physical inactivity, systemic inflammation, corticosteroid exposure, and nutritional deficits, and are associated with reduced exercise capacity and higher mortality independent of FEV1 (Bon & Zhang, 2016; Papadopoulos *et al*., 2025) [18].

Osteoporosis affects a substantial proportion of COPD patients, with pooled prevalence estimates around 38%, driven by shared risk factors including advanced age, low body mass index, physical inactivity, systemic inflammation, and glucocorticoid exposure (Kim *et al*., 2022) [43]. Metabolic syndrome, anemia, obstructive sleep apnea, depression, and anxiety round out the comorbidity spectrum, each contributing independently to symptom burden, exacerbation risk, and reduced quality of life (Divo *et al*., 2023) [29]. Notably, distinct comorbidity clusters appear to associate with different structural phenotypes: cardiometabolic disease is more frequent in airway-predominant COPD, whereas sarcopenia and osteoporosis are more closely linked to the emphysema-predominant phenotype (Roversi *et al*., 2019) [67]. Table 3 summarizes key comorbidities and approximate prevalence figures.

Table 3: Common Systemic Comorbidities Associated with COPD and Approximate Reported Prevalence (Santos *et al*., 2022; Divo *et al*., 2023; Kim *et al*., 2022; Roversi *et al*., 2019) [29, 43, 67, 69]

Comorbidity	Approximate prevalence in COPD	Predominant associated phenotype
Cardiovascular disease (any)	30–60%	Airway-predominant / cardiometabolic
Osteoporosis	~38%	Emphysema-predominant, glucocorticoid use
Sarcopenia / cachexia	15–55%	Emphysema-predominant, low BMI
Metabolic syndrome / diabetes	15–30%	Airway-predominant / cardiometabolic
Anxiety and depression	20–50%	All phenotypes; higher with severe dyspnea
Obstructive sleep apnea (overlap syndrome)	10–30%	Variable; worsens nocturnal hypoxemia
Anemia of chronic disease	10–25%	Advanced disease, systemic inflammation

Pharmacological Management

Long-acting bronchodilators — long-acting muscarinic antagonists (LAMA) and long-acting beta-2 agonists (LABA) — form the pharmacological foundation of stable COPD management, improving airflow, reducing hyperinflation, and lowering exacerbation frequency (Vestbo *et al*., 2013) [85]. Landmark trials such as UPLIFT demonstrated sustained benefit of tiotropium on lung function and exacerbation risk over four years, establishing long-acting muscarinic blockade as a cornerstone therapy (Tashkin *et al*., 2008) [80].

The role of inhaled corticosteroids (ICS) in COPD has been substantially clarified over the past decade. While ICS monotherapy is no longer recommended, combination ICS/LABA/LAMA triple therapy has demonstrated reductions in exacerbation frequency and, in the landmark TORCH, IMPACT, and ETHOS trials, measurable effects on mortality and lung function decline, particularly among patients with elevated blood eosinophil counts and frequent exacerbations (Calverley *et al*., 2007; Lipson *et al*., 2018; Rabe *et al*., 2020) [21, 46, 63]. Network meta-analyses confirm that higher ICS doses within triple therapy regimens further reduce exacerbation risk in appropriately selected patients, though this benefit must be weighed against a well-documented, dose-dependent increase in pneumonia risk (Suzuki *et al*., 2022; Cazzola *et al*., 2021) [23, 79].

Despite optimized triple inhaled therapy, exacerbation rates are reduced by only around half in trial populations, leaving considerable residual risk that has motivated the search for additional therapeutic targets, including phosphodiesterase-4 inhibition with roflumilast and prophylactic macrolide therapy in selected frequent exacerbators with a non-eosinophilic phenotype (Sethi & Suki, 2025) [71]. Figure 3 depicts a stepwise pharmacological approach consistent with current guideline recommendations, integrating symptom burden, exacerbation history, and blood eosinophil count.

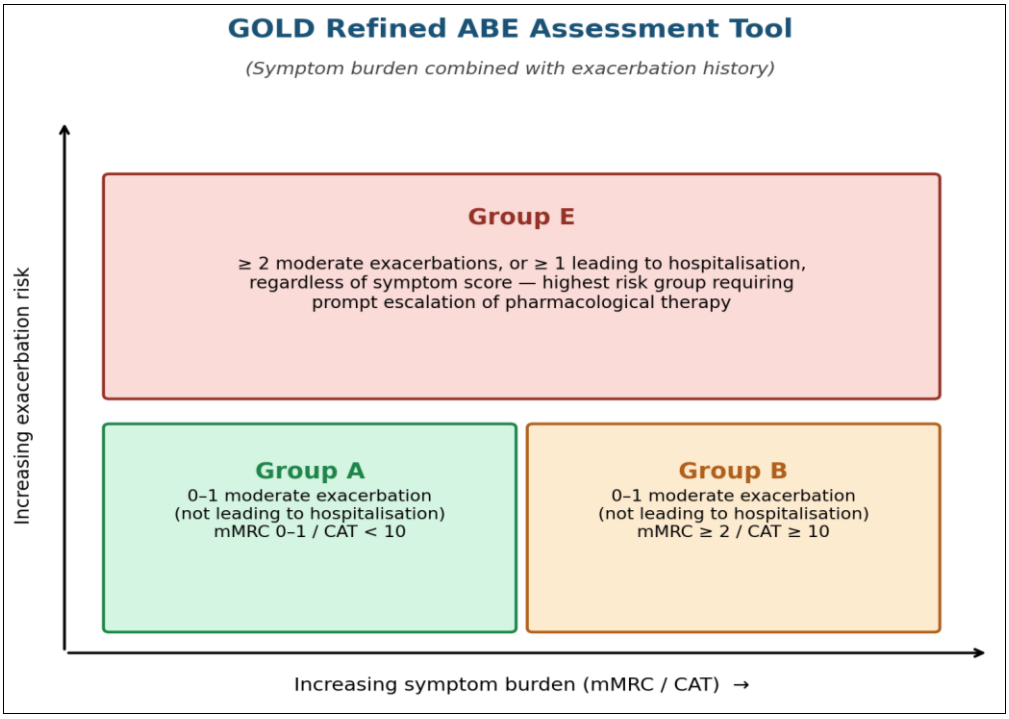

Fig 3: The GOLD refined ABE assessment tool, combining symptom burden (modified Medical Research Council [mMRC] dyspnea scale or COPD Assessment Test [CAT] score) with prior exacerbation history to guide initial and follow-up pharmacological therapy (adapted from Agustí *et al*., 2023; Vestbo *et al*., 2013) [5, 85].

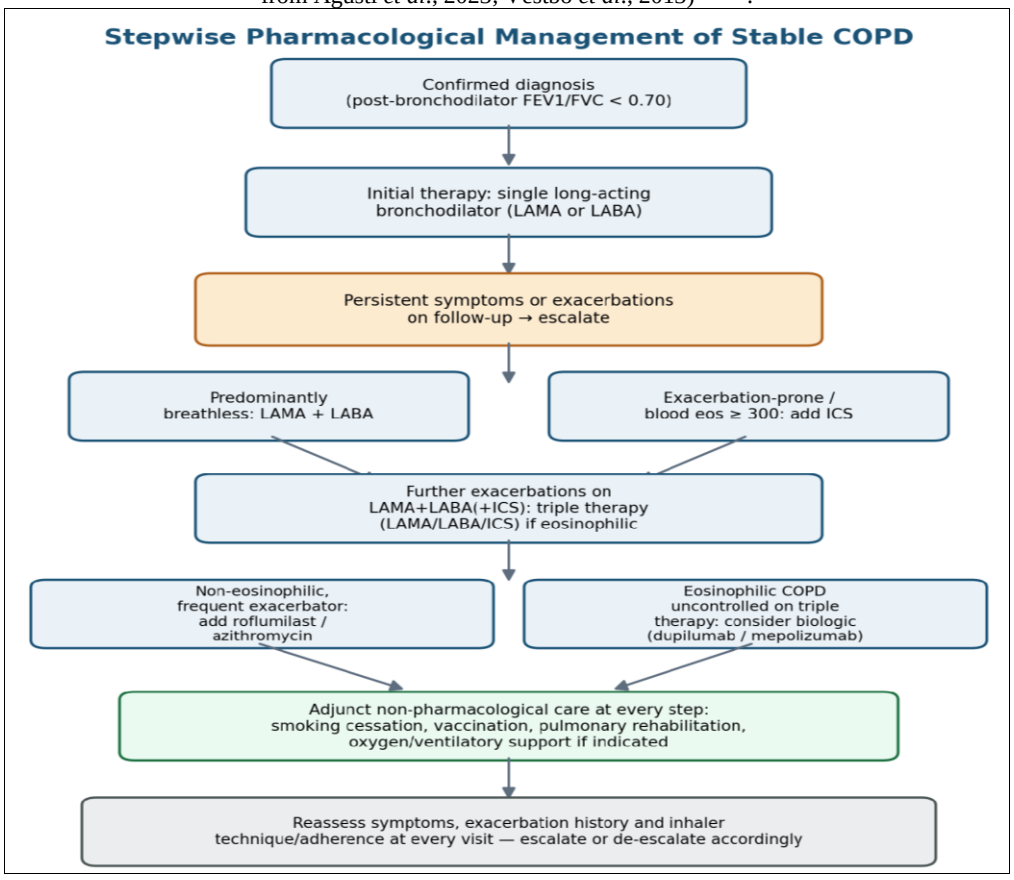

Fig 4: Stepwise pharmacological and non-pharmacological management algorithm for stable COPD, incorporating bronchodilator escalation, biomarker-guided anti-inflammatory therapy, and biologic add-on therapy for eosinophilic, exacerbation-prone disease (adapted from Agustí *et al*., 2023; Lipson *et al*., 2018; Rabe *et al*., 2020; Sethi & Suki, 2025) [5, 46, 63, 71].

Biologic and Emerging Precision Therapies

The most significant recent development in COPD pharmacotherapy has been the arrival of biologic agents targeting type 2 inflammation in patients with eosinophilic COPD who remain symptomatic despite optimized triple inhaled therapy. The BOREAS and NOTUS trials established that dupilumab, an anti-interleukin-4 receptor alpha monoclonal antibody, reduces moderate-to-severe exacerbations by approximately 30% to 34% and produces clinically meaningful improvements in FEV1 among

patients with blood eosinophil counts of 300 cells/μL or greater, leading to regulatory approval as the first biologic indicated for COPD (Bhatt *et al*., 2023; Bhatt *et al*., 2024) [13, 14].

Mepolizumab, an anti-interleukin-5 monoclonal antibody previously established in severe eosinophilic asthma, subsequently demonstrated a significant, though comparatively more modest, reduction in exacerbation frequency in the MATINEE trial among patients with an eosinophilic, exacerbation-prone phenotype, without the same magnitude of lung function benefit observed with dupilumab (Sciurba *et al*., 2025; Yılmaz & Bahçecioğlu, 2026) [70, 94]. Mechanistically, this differential efficacy has been attributed to inflammatory redundancy within the interleukin-5 axis and the persistence of tissue-resident eosinophils maintained through interleukin-5-independent survival pathways, whereas interleukin-4/13 blockade addresses a broader upstream signaling node (Yılmaz & Bahçecioğlu, 2026) [94].

In contrast, trials of benralizumab, an anti-interleukin-5 receptor antibody, and tezepelumab, an anti-thymic stromal lymphopoietin antibody, have not demonstrated consistent clinical benefit in COPD populations, underscoring that not every therapy effective in asthma translates directly to COPD despite overlapping type 2 inflammatory features (Halpin, 2025; Rossi *et al*., 2026) [40, 66]. Multi-criteria decision analyses synthesizing the available phase 2 and 3 biologic trials in COPD currently rank dupilumab as offering the most robust and consistent efficacy signal, with mepolizumab positioned as a reasonable alternative in appropriately selected, biomarker-enriched patients (Riha *et al*., 2025) [65]. These developments mark a genuine inflection point, establishing eosinophilic COPD as a treatable, biologically defined minority phenotype within the broader COPD population (Halpin, 2025) [40].

Pulmonary Rehabilitation and Non-Pharmacological Management

Pulmonary rehabilitation is among the most effective interventions available for COPD, consistently improving exercise capacity, dyspnea, and health-related quality of life across the spectrum of disease severity, and is recommended by essentially all major clinical guidelines (Spruit *et al*., 2013) [75]. Component network meta-analyses indicate that supervised, higher-intensity aerobic and resistance exercise training delivers the greatest functional benefit, though the optimal combination of program duration, supervision intensity, and adjunctive components remains an active area of investigation (Nolan *et al*., 2025) [55].

Inspiratory muscle training as an adjunct to standard pulmonary rehabilitation produces measurable improvements in inspiratory muscle strength, although its incremental effect on six-minute walk distance and health-related quality of life beyond standard rehabilitation remains inconsistent across trials (Xie *et al*., 2025; Lötters *et al*., 2002) [48, 92]. Programs employing minimal equipment have been shown to achieve outcomes broadly comparable to equipment-intensive models, an important finding for expanding access in resource-limited settings (Alison *et al*., 2023) [7]. Combined aerobic and respiratory training protocols similarly demonstrate consistent benefit on functional capacity and symptom burden in stable COPD (Wang *et al*., 2025; Ferreira *et al*., 2022) [33, 87].

Beyond structured exercise, smoking cessation remains the single intervention most clearly demonstrated to slow the rate of lung function decline, and vaccination against influenza, pneumococcus, and respiratory syncytial virus reduces exacerbation-associated morbidity (Fletcher & Peto, 1977; Thawanaphong *et al*., 2025) [34, 81]. Nutritional optimization, management of comorbid sarcopenia and osteoporosis, and, in advanced hypoxemic disease, long-term oxygen therapy or non-invasive ventilatory support round out a comprehensive, multimodal approach consistent with the treatable-traits paradigm increasingly advocated in precision respiratory medicine (McDonald & Holland, 2024; Agusti *et al*., 2016) [51]. Table 4 summarizes the principal drug and non-drug intervention classes discussed in this review alongside their primary mechanism and evidence base.

Table 4: Principal Therapeutic Classes for COPD, Mechanism of Action, and Representative Evidence (Vestbo *et al*., 2013; Lipson *et al*., 2018; Rabe *et al*., 2020; Bhatt *et al*., 2024; Sciurba *et al*., 2025; Spruit *et al*., 2013) [14, 46, 63, 70, 75, 85]

Therapeutic class	Mechanism / target	Representative evidence
Long-acting muscarinic antagonist (LAMA)	Blocks M3 muscarinic receptor-mediated bronchoconstriction	Tashkin *et al*. (2008) [80], UPLIFT trial
Long-acting beta-2 agonist (LABA)	Beta-2 adrenoceptor-mediated bronchodilation	Calverley *et al*. (2007) [21], TORCH trial
Inhaled corticosteroid (as part of triple therapy)	Suppresses eosinophilic airway inflammation	Lipson *et al*. (2018) [46]; Rabe *et al*. (2020)
Phosphodiesterase-4 inhibitor (roflumilast)	Reduces neutrophilic inflammation via cAMP pathway	Sethi & Suki (2025) [71]
Anti-IL-4Rα biologic (dupilumab)	Blocks IL-4/IL-13 signaling (type 2 inflammation)	Bhatt *et al*. (2023, 2024) [13, 14], BOREAS/NOTUS
Anti-IL-5 biologic (mepolizumab)	Depletes eosinophils via IL-5 blockade	Sciurba *et al*. (2025) [70], MATINEE
Pulmonary rehabilitation	Multimodal exercise, education, and self-management	Spruit *et al*. (2013); Nolan *et al*. (2025) [55, 75]
Long-term oxygen / non-invasive ventilation	Corrects hypoxemia; reduces work of breathing	Thawanaphong *et al*. (2025) [81]

Future Directions

Several converging lines of investigation are likely to reshape the management of the COPD lung over the coming decade. Multi-omic profiling — integrating transcriptomic, proteomic, and lipidomic data — is beginning to reveal molecularly distinct endotypes that cut across traditional spirometric staging, suggesting that future classification systems may rely as much on biological signature as on airflow measurement (Thawanaphong *et al*., 2025) [81]. Artificial intelligence applied to quantitative CT is progressively lowering the barrier to early structural phenotyping, potentially enabling intervention before irreversible small-airway loss occurs (Kirby *et al*., 2025; Thawanaphong *et al*., 2025) [45, 81].

Senolytic and senotherapeutic strategies targeting the senescence-associated secretory phenotype represent a conceptually novel avenue, aiming to interrupt the paracrine amplification of inflammation and tissue injury rather than merely suppressing downstream inflammatory mediators (Birch *et al*., 2022; Cardoso *et al*., 2024) [15, 22]. In parallel, the expanding biologic pipeline, together with more refined biomarker-based patient selection, points toward an increasingly stratified, endotype-directed therapeutic model in which eosinophilic, neutrophilic, and non-inflammatory COPD phenotypes may ultimately warrant substantially different treatment pathways (Riha *et al*., 2025; Malinovschi & Stockley, 2026) [50, 65].

Conclusion

The COPD lung is the product of a lifelong interplay between inhaled injury, genetic susceptibility, and a chronic inflammatory response that ultimately fails to resolve. What was once viewed largely through the narrow lens of spirometric airflow limitation is now understood as a structurally heterogeneous, biologically diverse, and systemically consequential disease. Advances in quantitative imaging and circulating biomarkers are making it possible to detect and characterize disease earlier and with greater precision than ever before, while the recognition of distinct inflammatory endotypes has, for the first time, translated into genuinely differentiated pharmacological pathways, exemplified by the arrival of dupilumab and mepolizumab for eosinophilic COPD. At the same time, the persistently high burden of cardiovascular, musculoskeletal, and metabolic comorbidity underscores that meaningful improvement in outcomes will depend on integrated, whole-person management rather than lung-directed therapy alone. Pulmonary rehabilitation, smoking and biomass smoke cessation, vaccination, and comorbidity management remain indispensable complements to pharmacotherapy and should not be regarded as secondary considerations. As multi-omic phenotyping, artificial intelligence-assisted imaging, and senescence-targeted therapeutics mature, the field appears to be moving, cautiously but genuinely, toward a precision-medicine model capable of altering what has historically been a relentless and progressive disease trajectory. Continued investment in early detection, mechanistic research, and equitable access to both diagnosis and therapy — particularly in the low- and middle-income settings that bear the greatest burden — will determine how quickly this promise is realized in practice.

References

1. Adam R, Bianchi L, De Vitis C. Alpha-1 antitrypsin deficiency in bronchiectasis: Evidence for an overlooked entity beyond COPD — a retrospective observational study. ERJ Open Research,2025:11(5):00512–2025.
2. Adeloye D, Song P, Zhu Y, Campbell H, Sheikh A, Rudan I, *et al*. Global, regional, and national prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: A systematic review and modelling analysis. The Lancet Respiratory Medicine,2022:10(5):447–458.
3. Agustí A, Hogg JC. Update on the pathogenesis of chronic obstructive pulmonary disease. New England Journal of Medicine,2019:381(13):1248–1256.
4. Agustí A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, *et al*. Treatable traits: Toward precision medicine of chronic airway diseases. European Respiratory Journal,2016:47(2):410–419.
5. Agustí A, Celli BR, Criner GJ, Halpin D, Anzueto A, Barnes P, *et al*. Global Initiative for Chronic Obstructive Lung Disease 2023 report: GOLD executive summary. European Respiratory Journal,2023:61(4):2300239.
6. Al Wachami N, Guennouni M, Iderdar Y, Boumendil K, Arraji M, Mourajid Y, *et al*. Estimating the global prevalence of chronic obstructive pulmonary disease (COPD): A systematic review and meta-analysis. BMC Public Health,2024:24:297.
7. Alison JA, McKeough ZJ, Johnston K. Pulmonary rehabilitation using minimal equipment for people with chronic obstructive pulmonary disease: A systematic review and meta-analysis. Archives of Physical Medicine and Rehabilitation,2023:104(9):1500–1516.
8. Amaral AFS, Patel J, Kato BS, Obaseki DO, Lawin H, Tan WC, *et al*. Airflow obstruction and use of solid fuels for cooking or heating: BOLD results. American Journal of Respiratory and Critical Care Medicine,2018:197(5):588–597.
9. Bafadhel M, Rabe KF, Martinez FJ, *et al*. Immune cell regulatory networks in chronic obstructive pulmonary disease: Mechanistic analysis from innate to adaptive immunity. Frontiers in Immunology,2016:16:1651808.
10. Barnes PJ. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. Journal of Allergy and Clinical Immunology,2016:138(1):16–27.
11. Barnes PJ. Small airway fibrosis in COPD. The International Journal of Biochemistry & Cell Biology,2019:116:105598.
12. Barnes PJ. Oxidative stress in chronic obstructive pulmonary disease. Antioxidants,2020:11(5):965.
13. Bhatt SP, Rabe KF, Hanania NA, Vogelmeier CF, Bafadhel M, Christenson SA, *et al*. Dupilumab for COPD with type 2 inflammation indicated by eosinophil counts. New England Journal of Medicine,2023:389(3):205–214.
14. Bhatt SP, Rabe KF, Hanania NA, Vogelmeier CF, Cole J, Bafadhel M, *et al*. Dupilumab for COPD with blood eosinophil evidence of type 2 inflammation. New England Journal of Medicine,2024:390(24):2274–2283.
15. Birch J, Barnes PJ, Passos JF. Senescence: Pathogenic driver in chronic obstructive pulmonary disease. Medicina,2022:58(6):817.
16. Bodduluri S, Newell JD, Hoffman EA, Reinhardt JM. Airway fractal dimension predicts respiratory morbidity and mortality in COPD. Journal of Clinical Investigation,2018:128(12):5374–5382.
17. Bodduluri S, Puliyakote ASK, Gerard SE, Reinhardt JM, Bhatt SP, Newell JD, *et al*. Computed tomography-based airway surface area-to-volume ratio for phenotyping airway remodeling in chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine,2021:203(2):185–191.
18. Bon J, Zhang Y. COPD: Osteoporosis and sarcopenia. COPD Research and Practice,2016:2:4.
19. Brantly ML, Paul LD, Miller BH, Falk RT, Wu M, Crystal RG. Clinical features and history of the destructive lung disease associated with alpha-1-antitrypsin deficiency of adults with pulmonary

symptoms. American Review of Respiratory Disease,1988:138(2):327–336.
20. Burney P, Jithoo A, Kato B, Janson C, Mannino D, Nizankowska-Mogilnicka E, *et al*. Chronic obstructive pulmonary disease mortality and prevalence: The associations with smoking and poverty — a BOLD analysis. Thorax,2014:69(5):465–473.
21. Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, *et al*. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. New England Journal of Medicine,2007:356(8):775–789.
22. Cardoso AL, Fernandes A, Aguilar-Pimentel JA, de Angelis MH, Guedes JR, Brito MA, *et al*. Aging lung: Molecular drivers and impact on respiratory diseases — a narrative clinical review. Antioxidants,2024:13(12):1480.
23. Cazzola M, Rogliani P, Matera MG. Triple versus LAMA/LABA combination therapy for patients with COPD: A systematic review and meta-analysis. Respiratory Research,2021:22:171.
24. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, *et al*. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. New England Journal of Medicine,2004:350(10):1005–1012.
25. Chen H, Li W, Zhou Q. Computed tomography-identified phenotypes of small airway obstructions in chronic obstructive pulmonary disease. Chinese Medical Journal,2024:137(9):1027–1036.
26. Choi S, Hoffman EA, Wenzel SE, Castro M, Lin CL. Differentiation of quantitative CT imaging phenotypes in asthma versus COPD. BMJ Open Respiratory Research,2017:4(1): e000252.
27. Christenson SA, Smith BM, Bafadhel M, Putcha N. Chronic obstructive pulmonary disease. The Lancet,2022:399(10342):2227–2242.
28. Diagnostic Challenges and Pathogenetic Differences in Biomass-Smoke-Induced versus Tobacco-Smoke-Induced COPD Study Group. Diagnostic challenges and pathogenetic differences in biomass-smoke-induced versus tobacco-smoke-induced COPD: A comparative review. Journal of Clinical Medicine,2024:13(19):5730.
29. Divo MJ, Casanova C, Marin JM, Pinto-Plata VM, de-Torres JP, Zulueta JJ, *et al*. Comorbidities of COPD: Mechanisms and treatment. Update 2023. Medical Research Archives,2023:11(6):1–19.
30. Edgar RG, Patel M, Bayliss S, Crossley D, Sapey E, Turner AM. Treatment of lung disease in alpha-1 antitrypsin deficiency: A systematic review. International Journal of Chronic Obstructive Pulmonary Disease,2017:12:1295–1308.
31. Ellingsen J, Janson C, Bröms K, Hårdstedt M, Högman M, Lisspers K, *et al*. CRP, fibrinogen, white blood cells, and blood cell indices as prognostic biomarkers of future COPD exacerbation frequency: The TIE cohort study. Journal of Clinical Medicine,2024:13(13):3855.
32. Ferrante di Ruffano L, Alonso-Coello P, Marušić A. Retrospective study for correlation analysis of nutritional status with osteoporosis, sarcopenia and cognitive impairment in elderly patients with coronary heart disease. Frontiers in Nutrition,2024:11:1349732.
33. Ferreira G, Feuerstein N, Pereira J. Effectiveness of pulmonary rehabilitation performed through exercise training for patients with stable COPD: A meta-analysis of randomized controlled trials. Fisioterapia em Movimento,2022:35:e35125.
34. Fletcher C, Peto R. The natural history of chronic airflow obstruction. British Medical Journal,1977:1(6077):1645–1648.
35. Franciosi AN, Fraughen D, Carroll TP, McElvaney NG. Alpha-1 antitrypsin deficiency: Genetics, clinical manifestations, AI prognostics, and advanced imaging in liver disease. World Journal of Hepatology,2025:17(9):1–18.
36. Fricker M, Lokwani R. COPD: The role of neutrophils in inflammation, pathophysiology, and as drug targets. Clinical Science,2025:139(20):1199–1214.
37. Ganesan S, Comstock AT, Sajjan US. Cigarette smoke-induced respiratory response: Insights into cellular processes and biomarkers. Antioxidants,2023:12(6):1263.
38. GBD Chronic Respiratory Disease Collaborators. Prevalence and attributable health burden of chronic respiratory diseases, 1990–2021: Findings from the Global Burden of Disease Study 2021. The Lancet Respiratory Medicine,2024:12(11):891–908.
39. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2024 report. Global Initiative for Chronic Obstructive Lung Disease,2024.
40. Halpin DMG. COPD drug development in 2025: Trouble ahead? Apria Clinical Education Hub,2025.
41. Han MK, Kazerooni EA, Lynch DA, Liu LX, Murray S, Curtis JL, *et al*. Chronic obstructive pulmonary disease exacerbations in the COPDGene study: Associated radiologic phenotypes. Radiology,2011:261(1):274–282.
42. Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, Buzatu L, *et al*. The nature of small-airway obstruction in chronic obstructive pulmonary disease. New England Journal of Medicine,2004:350(26):2645–2653.
43. Kim SW, Lee JH, Oh YM. Editorial: Osteoporosis, sarcopenia and muscle-bone crosstalk in COPD. Frontiers in Physiology,2022:13:1005826.
44. Kim YH, Kim JH, Kim YS. Fibrinogen as a potential biomarker for clinical phenotype in patients with chronic obstructive pulmonary disease. Journal of Thoracic Disease,2018:10(11):6317–6328.
45. Kirby M, Tanabe N, Vasilescu DM, Cooper JD, McDonough JE, Verleden SE, *et al*. Seeing is believing — on the utility of CT in phenotyping chronic obstructive pulmonary disease. British Journal of Radiology,2025:98(1171):812–823.
46. Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, *et al*. Once-daily single-inhaler triple versus dual therapy in patients with COPD. New England Journal of Medicine,2018:378(18):1671–1680.
47. Liu X, Zhao Y, Sun H. Quantitative CT analysis of small airway remodeling in patients with chronic obstructive pulmonary disease. International Journal of Chronic Obstructive Pulmonary Disease,2021:16:3405–3415.
48. Lötters F, van Tol B, Kwakkel G, Gosselink R. Effects of controlled inspiratory muscle training in patients with COPD: A meta-analysis. European Respiratory Journal,2002:20(3):570–576.

49. MacNee W. Environmental exposures and lung aging: Molecular mechanisms and implications for improving respiratory health. Current Environmental Health Reports,2021:8(4):314–325.
50. Malinovschi A, Stockley RA. The next frontier for biomarkers in COPD precision medicine. Expert Review of Precision Medicine and Drug Development,2026:11(1):1–14.
51. McDonald VM, Holland AE. Treatable traits models of care. Respirology,2024:29(1):24–35.
52. Micheletto C, Bagnasco D, Milanese M. Short-term effects of dupilumab in eosinophilic COPD. Journal of Clinical Medicine,2025:14(24):8677.
53. Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ,2021:372: n71.
54. Montes de Oca M, Perez-Padilla R, Celli B, Aaron SD, Wehrmeister FC, Amaral AFS, *et al*. The global burden of COPD: Epidemiology and effect of prevention strategies. The Lancet Respiratory Medicine,2025:13(8):709–724.
55. Nolan CM, Kon SSC, Man WD-C. Impact of pulmonary rehabilitation programme design on effectiveness in COPD: A systematic review and component network meta-analysis. eClinicalMedicine,2025:87:103433.
56. O'Brien K, Geddes EL, Reid WD, Brooks D, Crowe J. Inspiratory muscle training compared with other rehabilitation interventions in chronic obstructive pulmonary disease: A systematic review update. Journal of Cardiopulmonary Rehabilitation and Prevention,2008:28(2):128–141.
57. Ortiz-Quintero B, Martínez-Espinosa I, Pérez-Padilla R. Mechanisms of lung damage and development of COPD due to household biomass-smoke exposure: Inflammation, oxidative stress, microRNAs, and gene polymorphisms. Cells,2023:12(1):67.
58. Palummo F, Pisano G, Terrenato I. Alpha-1 antitrypsin deficiency-associated chronic obstructive pulmonary disease. Medicina,2026:62(4):639.
59. Papadopoulos A, Kontogianni K, Anagnostopoulos N. Multimodal therapeutic strategies for the management of sarcopenia and frailty in chronic obstructive pulmonary disease: A narrative review. Journal of Clinical Medicine,2024:14(20):7215.
60. Papi A, Faner R, Torres A. Applications of artificial intelligence in alpha-1 antitrypsin deficiency: A systematic review from a respiratory medicine perspective. Diagnostics,2025:15(20):2612.
61. Porszasz J, Emtner M, Goto S, Somfay A, Whipp BJ, Casaburi R. Exercise training decreases ventilatory requirements and exercise-induced hyperinflation at submaximal intensities in patients with COPD. Chest,2005:128(4):2025–2034.
62. Qi Y, Zhang X, Wang L. Inflammatory and immune mechanisms in COPD: Current status and therapeutic prospects. Journal of Inflammation Research,2024:17:6603–6618.
63. Rabe KF, Martinez FJ, Ferguson GT, Wang C, Singh D, Wedzicha JA, *et al*. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. New England Journal of Medicine,2020:383(1):35–48.
64. Rennard SI, Drummond MB. Early chronic obstructive pulmonary disease: Definition, assessment, and prevention. The Lancet,2015:385(9979):1778–1788.
65. Riha C, Papadopoulos NG, Brightling CE. Multi-criteria decision analysis of biologics in chronic obstructive pulmonary disease. Therapeutic Advances in Respiratory Disease,2025:19:1–15.
66. Rossi A, Vitacca M, Blasi F. Beyond triple therapy: Anti-type 2 biologic therapies for eosinophilic COPD and respiratory comorbidities — a review of clinical evidence. Current Allergy and Asthma Reports,2026:26:12.
67. Roversi S, Fabbri LM, Sin DD, Hawkins NM, Agustí A. Cardiovascular comorbidities in chronic obstructive pulmonary disease (COPD) — current considerations for clinical practice. Journal of Clinical Medicine,2019:8(1):69.
68. Sandhaus RA, Turner AM, Stocks J. Pulmonary function decline in alpha-1 antitrypsin deficiency: A systematic review. International Journal of Chronic Obstructive Pulmonary Disease,2021:21:15–32.
69. Santos NCD, Miravitlles M, Camelier AA, Almeida Vde C, Maciel RRBT, Camelier FWR. Prevalence and impact of comorbidities in individuals with chronic obstructive pulmonary disease: A systematic review. Tuberculosis and Respiratory Diseases,2022:85(3):205–220.
70. Sciurba FC, Bhatt SP, Criner GJ, Christenson SA, Boen K, Bhattacharya I, *et al*. Mepolizumab for exacerbation-prone COPD with an eosinophilic phenotype. New England Journal of Medicine,2025:392(11):1059–1071.
71. Sethi S, Suki B. The COURSE trial and beyond: Rethinking chronic obstructive pulmonary disease exacerbation management with biologics. Journal of Thoracic Disease,2025:17(9):6120–6131.
72. Silverman EK. Genetics of COPD. Annual Review of Physiology,2020:82:413–431.
73. Sin DD, Man SFP. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. Circulation,2003:107(11):1514–1519.
74. Souto-Miranda S, Saraiva I, Spruit MA, Marques A. Core outcome set for pulmonary rehabilitation of patients with COPD: Results of a modified Delphi survey. Thorax,2023:78(12):1240–1247.
75. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, *et al*. An official American Thoracic Society/European Respiratory Society statement: Key concepts and advances in pulmonary rehabilitation. American Journal of Respiratory and Critical Care Medicine,2013:188(8):e13–e64.
76. Stockley RA, Halpin DMG, Celli BR, Singh D. Chronic obstructive pulmonary disease biomarkers and their interpretation. American Journal of Respiratory and Critical Care Medicine,2019:199(10):1195–1204.
77. Stoller JK, Aboussouan LS. A review of alpha-1 antitrypsin deficiency. American Journal of Respiratory and Critical Care Medicine,2012:185(3):246–259.
78. Stolz D, Mkorombindo T, Schumann DM, Agusti A, Ash SY, Bafadhel M, *et al*. Towards the elimination of chronic obstructive pulmonary disease: A Lancet Commission. The Lancet,2022(10356):921–972.
79. Suzuki M, Makita H, Konno S. Different inhaled corticosteroid doses in triple therapy for chronic obstructive pulmonary disease: Systematic review and

Bayesian network meta-analysis. Scientific Reports,2022:12:15612.
80. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, *et al*. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. New England Journal of Medicine,2008:359(15):1543–1554.
81. Thawanaphong S, Bhatt SP, Hansel NN. Contemporary concise review 2024: Chronic obstructive pulmonary disease. Respirology,2025:30(7):553–567.
82. Townend J, Minelli C, Mortimer K, Obaseki DO, Al Ghobain M, Cherkaski H, *et al*. The association between chronic airflow obstruction and poverty in 12 sites of the multinational BOLD study. European Respiratory Journal,2017:49(6):1601880.
83. van der Bie S, Haaksma ME, Vermin B, van Assema H, van Gorp ECM, Langerak T, *et al*. A systematic review of the pulmonary microbiome in patients with acute exacerbation COPD requiring ICU admission. Journal of Clinical Medicine,2024:13(2):472.
84. Vestbo J, Anderson JA, Brook RD, Calverley PMA, Celli BR, Crim C, *et al*. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): A double-blind randomised controlled trial. The Lancet,2016:387(10030):1817–1826.
85. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, *et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. American Journal of Respiratory and Critical Care Medicine,2013:187(4):347–365.
86. Vitenberga-Verza Z, Pilmane M. The emerging biomarkers in chronic obstructive pulmonary disease: A narrative review. Journal of Clinical Medicine,2025:14(10):3412.
87. Wang Y, Li T, Zhao X. Meta-analysis of the effect of aerobic exercise combined with respiratory training on stable chronic obstructive pulmonary disease. Journal of Cardiothoracic Surgery,2025:20:2519598.
88. Wang Z, Bafadhel M, Haldar K, Spivak A, Mayhew D, Miller BE, *et al*. Characteristics of the sputum microbiome in COPD exacerbations and correlations between clinical indices. Journal of Translational Medicine,2022:20:39.
89. Wedzicha JA, Seemungal TAR. COPD exacerbations: Defining their cause and prevention. The Lancet,2007:370(9589):786–796.
90. World Health Organization. Chronic obstructive pulmonary disease (COPD) fact sheet. World Health Organization,2024.
91. Xia X, Liu S, Tan Q. Sarcopenia and cardiovascular diseases: A systematic review and meta-analysis. Journal of Cachexia, Sarcopenia and Muscle,2023:14(3):1183–1198.
92. Xie J, Zhu Y, Wang Y, Mo Y, Shi X, Liang W-M, *et al*. Effects of pulmonary rehabilitation combined with inspiratory muscle training on lung function and exercise capacity in older patients with COPD: A systematic review and meta-analysis. Frontiers in Medicine,2025:12:1621375.
93. Yan Z, Chen B, Yang F. Microbiome-host interactions in the pathogenesis of acute exacerbation of chronic obstructive pulmonary disease. Frontiers in Cellular and Infection Microbiology,2024:14:1386201.
94. Yılmaz İ, Bahçecioğlu SN. GOLD 2026: Transforming COPD management with early intervention, multi-dimensional assessment, and personalized care. Journal of Clinical Medicine,2026:(6):1980.
95. Zhang R, Liu Y. A meta-analysis of the effects of pulmonary rehabilitation on exercise tolerance and quality of life in patients with chronic obstructive pulmonary diseases. New Medicine,2025:29(2):88–97.
96. Zhang Y, Liu H, Chen S. Airway remodeling in chronic obstructive pulmonary disease: Characteristics and opportunities. Frontiers in Physiology,2024:16:1620112.
97. Zhao Q, Wang T, Li F. Inflammation mechanism and research progress of COPD. Frontiers in Immunology,2024:15:1404615.
98. Zhou J, Xu D, Feng Y. Peribronchial inflammatory cell assessment in COPD lung tissues. Journal of Cellular and Molecular Medicine,2025:29(1):e70229.
99. Zhu X, Yin S, Xu L. Unraveling the immune landscape of chronic obstructive pulmonary disease: Insights into inflammatory cell subtypes, pathogenesis, and treatment strategies. International Journal of Chronic Obstructive Pulmonary Disease,2025:20:1091–1108.
100. Zuo Y, Li C, Sun J. Exome and sputum microbiota as predictive markers of frequent exacerbations in chronic obstructive pulmonary disease. International Journal of Molecular Sciences,2022:23(19):11305.