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REVIEW ARTICLE

Respiratory Microbiome Alterations in Chronic obstructive pulmonary disease Pathogenesis and Therapeutic Implications

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Abstract

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disorder characterized by persistent airflow limitation, chronic inflammation, and recurrent exacerbations. Recent advances in microbiome research have revealed that microbial dysbiosis plays a significant role in COPD pathogenesis and disease progression. Alterations in the lung microbiome are commonly associated with reduced microbial diversity and enrichment of pathogenic bacteria such as Haemophilus, Moraxella, and Pseudomonas. These microbial shifts contribute to chronic airway inflammation, immune dysregulation, tissue remodeling, and exacerbation frequency. Several studies have demonstrated that microbiome composition varies according to disease severity, anatomical location, and sample type, highlighting the complexity of respiratory microbial communities in COPD. In addition to the lung microbiome, growing evidence supports the importance of the gut–lung axis, where gut microbial alterations may influence pulmonary immune responses and systemic inflammation. Microbial metabolites and host–microbiome interactions have also emerged as potential biomarkers for disease prognosis and therapeutic response. Despite promising findings, inconsistencies among studies remain due to differences in sampling methods, patient populations, and analytical approaches. This review summarizes current knowledge regarding respiratory and gut microbiome dysbiosis in COPD, its immunological implications, associated clinical outcomes, and potential microbiome-targeted therapeutic strategies for future disease management.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major global health problem and remains one of the leading causes of morbidity and mortality worldwide. The disease is characterized by persistent airflow limitation, chronic respiratory symptoms, airway remodeling, and progressive decline in lung function (Adeloye et al., 2022). Cigarette smoking remains the primary risk factor. However, environmental pollutants, occupational exposure, biomass fuel inhalation, and recurrent respiratory infections also contribute significantly to disease development. COPD is now recognized as a heterogeneous disorder involving complex interactions between environmental triggers, host immunity, genetics, and microbial communities (De Nuccio et al., 2022). Traditionally, the lungs were considered sterile under healthy conditions. Advances in next-generation sequencing technologies have changed this concept. The respiratory tract contains a diverse microbial ecosystem composed of bacteria, fungi, and viruses. These microbial communities participate in immune regulation and maintenance of pulmonary homeostasis (Rastogi et al., 2022). Alterations in microbial composition, referred to as dysbiosis, have been increasingly linked to chronic respiratory diseases including asthma, cystic fibrosis, idiopathic pulmonary fibrosis, lung cancer, and COPD.

Microbial dysbiosis in COPD is commonly characterized

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by reduced microbial diversity and enrichment of pathogenic organisms. Important bacterial genera associated with COPD include Haemophilus, Moraxella, Pseudomonas, and Streptococcus. These organisms can stimulate excessive inflammatory responses and contribute to persistent airway injury. In contrast, commensal bacteria such as Prevotella and Veillonella are often depleted during disease progression (Cheng and Zhang, 2024; Liu et al., 2021). This imbalance may alter immune signaling pathways and promote chronic inflammation. The interaction between the lung microbiome and host immunity plays a critical role in COPD pathogenesis. Microbial products activate innate immune receptors and stimulate inflammatory cytokine production. Increased neutrophilic inflammation, elevated interleukin-8 levels, and TH17 immune polarization have been associated with microbiome alterations in COPD patients. Dysbiosis has also been linked to frequent exacerbations, emphysema progression, reduced lung function, and increased mortality risk (Lewicki et al., 2025; N. Li et al., 2021).

Recent evidence suggests that the gut microbiome also contributes to COPD through the gut–lung axis. Bidirectional communication between intestinal and pulmonary microbial communities may influence systemic inflammation and immune regulation. Alterations in gut microbial composition have been associated with COPD severity and disease progression (Song et al., 2024). This emerging concept broadens the understanding of COPD beyond the respiratory system alone. Although substantial progress has been made, several limitations remain. Variability in sampling techniques, disease stages, antibiotic exposure, and sequencing methodologies contribute to inconsistent findings across studies. Therefore, further longitudinal and mechanistic studies are required to establish causality and identify clinically relevant microbial biomarkers. This review discusses current evidence regarding respiratory microbiome dysbiosis in COPD, host–microbiome immune interactions, gut–lung axis involvement, clinical implications, and future microbiome-based therapeutic opportunities.

2. Lung Microbiome Composition and Immune Interactions in COPD

COPD is a chronic inflammatory airway disease characterised by progressive airflow limitation and persistent respiratory symptoms, predominantly driven by long-term exposure to noxious stimuli including cigarette smoke and environmental pollutants. Emerging evidence has begun to clarify the contribution of the lung microbiome to COPD pathogenesis and progression (Han et al., 2012). A consistent finding across multiple studies is a shift in the phylum-level composition of the COPD airway microbiome, characterised by a decrease in Bacillota (Firmicutes) and Bacteroidota and a relative increase in Pseudomonadota, most notably the genus Haemophilus, which positively correlates with sputum IL-8 concentrations z(Dickson et al., 2015; Wang et al., 2016; Xue et al., 2023a). Gram-negative pathogenic bacteria implicated in COPD, including Haemophilus spp., Moraxella, and Pseudomonas, possess substantially greater capacity to stimulate innate immune responses compared to Gram-negative commensals such as Prevotella spp (Larsen et al., 2015a). The enrichment of Pseudomonadota has been independently associated with greater extent of emphysema, heightened immune cell infiltration, sustained chronic inflammation, airway remodelling, and increased exacerbation frequency (Liu et al., 2020; Wang et al., 2018). Proteobacteria and Actinomycetes, in particular, have been correlated with infiltration of neutrophils, eosinophils, and B cells into lung tissue (Li et al., 2024)

The lung microbiome in COPD has also been significantly associated with bacterial biomass, lymphocyte proportion, TH17 immune polarisation, exacerbation frequency, and antimicrobial resistance profiles (Table 1) (Ren et al., 2018). Poor oral hygiene represents an additional modifiable risk factor; micro-aspiration of oral commensals, particularly Veillonella and Prevotella, has been associated with TH17 lymphocyte expansion within the lung, potentially amplifying local inflammatory responses (Ren et al., 2018; Wang et al., 2018). In clinically stable COPD, pathogenic bacteria including Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, Staphylococcus aureus, Pseudomonas aeruginosa, and Enterobacterales have been consistently identified in airway samples (Ren et al., 2018). In moderate-to-severe COPD (GOLD stages 2–4), enrichment of Gammaproteobacteria, particularly Haemophilus and Moraxella spp., has been demonstrated in bronchoalveolar lavage (BAL) fluid and lung tissue (Pragman et al., 2019a; Von et al., 2012). Erb-Downward et al. reported significantly lower bacterial diversity scores in moderate-to-severe COPD compared to both healthy

smokers and non-smokers, and delineated a core COPD lung microbiome comprising Pseudomonas, Streptococcus, Prevotella, Fusobacterium, Haemophilus, Veillonella, and Porphyromonas (Erb-Downward et al., 2011). The same group also demonstrated that microbiome composition varies regionally within the same lung, suggesting that local microenvironmental factors exert significant influence over microbial dominance patterns.

In a landmark tissue-based study, Sze et al characterised the lung microbiome of GOLD 4 patients at the time of transplantation and reported an unexpected increase in bacterial diversity compared to non-smokers, smokers, and CF patients, driven by enrichment of Bacillota (Firmicutes) specifically Lactobacillus alongside elevated Burkholderia (O'Shaughnessy et al., 2023; Sze et al., 2012). In a separate analysis comparing GOLD 4 tissue to healthy donor samples, the same group identified increased Proteobacteria and Actinobacteria and decreased Firmicutes and Bacteroidetes, and described ten microbial species capable of distinguishing GOLD 4 microbiomes from controls: Prevotella oralis, Streptococcus spp., Prevotella oris, Porphyromonas spp., Flavobacterium succinicans, Haemophilus influenzae, Bacteroidales, Elizabethkingia meningoseptica, Dialister spp., and Flavobacterium gelidilacus (Wang et al., 2019). These findings underscore the stage-dependent and anatomically variable nature of the COPD lung microbiome.

Table 1. Summary of key studies on lung microbiome composition in COPD.

Reference	Sample Type	Population / GOLD Stage	Diversity Trend	Key Taxa Identified	Main Finding / Limitation
(Erb-Downward et al., 2011)	BAL, lung tissue	2–4 vs. healthy smokers and non-smokers	↓ vs. healthy smokers and non-smokers	*Pseudomonas, Streptococcus, Prevotella, Fusobacterium, Haemophilus, Veillonella, Porphyromonas* (core microbiome)	Lower bacterial diversity in moderate-severe COPD; defined a core COPD lung microbiome; demonstrated intra-lung regional microbiome variation
(Sze et al., 2012)	Lung tissue (at	4 (very severe) vs. non-smokers, smokers, CF	↑ vs. all	↑ Firmicutes (particularly *Lactobacillus); ↑ Burkholderia*	Paradoxical increase in diversity at GOLD 4; Firmicutes enrichment driven by Lactobacillus; contrasts with moderate-severe COPD findings
(Wang et al., 2019)	Airway (sputum/ BAL)	Mixed (stable and exacerbating)	↓ in	10 taxa distinguishing COPD from controls: *Prevotella oralis, Streptococcus spp., Prevotella oris, Porphyromonas spp., Flavobacterium succinicans, H. influenzae, Bacteroidales, Elizabethkingia meningoseptica, Dialister spp., Flavobacterium gelidilacus*	Airway host-microbiome interactions characterised; 10 microbial species identified as discriminating COPD GOLD 4 from controls; positive correlation of neutrophil counts with Moraxella, Haemophilus, Neisseria; negative correlation with Streptococcus, Megasphaera, Veillonella
(Pragman et al., 2018)	BAL	Moderate–severe (GOLD 2–3)	↑ with increasing severity	↑ Firmicutes (severe COPD); ↓ Actinobacteria and Proteobacteria (severe vs. moderate)	Diversity increased with COPD severity — directly contradicts Erb-Downward [16,25]; limited by small sample size and confounding medication burden
(Pragman et al., 2018)	Lung tissue (mild–moderate COPD)	Mild–moderate (GOLD 1–2)	Lower bronchial tree more diverse than upper	*Streptococcus* (most abundant), *Corynebacterium, Alloiococcus, Prevotella, Veillonella, Rothia, Neisseria, Staphylococcus*	Streptococcus most common genus in COPD lung tissue; upper bronchial tree richer but less diverse than lower bronchial tree

(Pragman et al., 2019b)	Upper airway (nasal, bronchial, oral)	Mixed; exacerbation phenotype subgroups	Upper airway α-diversity associated with	*Haemophilus* (exacerbation-prone); diverse commensal profile (non-exacerbation)	Upper airway microbiota α-diversity associated with exacerbation phenotype in COPD; case-control design
(Dicker et al., 2021)	Sputum (clinically stable COPD)	Mixed (stable)	↓ in low-eosinophil /	Low diversity: ↑ Proteobacteria, ↑ *Haemophilus*; High diversity: ↑ Firmicutes, ↑ *Streptococcus*	Low microbiome diversity and Haemophilus dominance inversely correlated with blood eosinophil count; low diversity independently associated with ↑ mortality; eosinophil count guides ICS prescribing
(Wu et al., 2014)	Sputum	Mixed	↑ vs. healthy controls	*S. pneumoniae, K. pneumoniae, P. aeruginosa*	Greater sputum diversity in COPD than healthy controls; enrichment of three key respiratory pathogens; small sample limits generalisability
(Cabrera-Rubio et al., 2012)	BAL, sputum, bronchial tissue	Mixed	Lower bronchial tree > upper bronchial tree	Actinobacteria: predominant in BAL, underrepresented in sputum; shared phylum-level core across BAL and sputum	Upper and lower bronchial microbiomes are distinct; BAL and sputum share core phyla but differ significantly in Actinobacteria abundance; sample type is a major confound in COPD microbiome studies
(Zakharkina et al., 2013)	Airway microbiota (T-RFLP and clone sequencing)	Mixed COPD vs. healthy	Altered community	Actinobacteria, Firmicutes, Proteobacteria, Nitrospira, Fusobacteria, Bacteroidetes (BALF phylum ranking)	Characterised airway microbiota by T-RFLP; identified BALF phylum prevalence ranking; provides phylum-level reference data for COPD vs. healthy
(Xue et al., 2023b)	Sputum (longitudinal cohort)	Mixed disease states	↓ in AECOPD-associated cluster	*Pseudomonas and Haemophilus* (AECOPD cluster); *Veillonella and Prevotella* (diverse/ stable cluster)	Four microbiome-based COPD clusters identified: AECOPD cluster (↑ TNF-α, ↑ Pseudomonas/Haemophilus); stable diverse cluster (↑ IL-17A, Veillonella/Prevotella); cytokine profiles differed between clusters

Abbreviations: BAL, bronchoalveolar lavage; BALF, BAL fluid; CF, cystic fibrosis; AECOPD, acute exacerbation of COPD; ICS, inhaled corticosteroids; GOLD, Global Initiative for Chronic Obstructive Lung Disease; n, sample size (— = not stated); T-RFLP, terminal restriction fragment length polymorphism. ↑ increased; ↓ decreased.

3. Sample-Type Variability and Discrepancies Across Studies

The composition of the COPD microbiome is substantially influenced by sample type. Cabrera et al. demonstrated that the upper and lower bronchial trees harbour distinct microbial communities, with the lower bronchial tree exhibiting greater diversity (Cabrera-Rubio et al., 2012b). While BAL and sputum samples share a common core microbiome at the phylum level, Actinobacteria predominates in BAL and is markedly underrepresented in sputum. Consistent with this, Pragman et al examining lung tissue alongside nasal, bronchial, and oral samples from nine COPD patients identified *Streptococcus* as the most abundant genus, with *Corynebacterium, Alloiococcus, Prevotella, Veillonella, Rothia, Neisseria*, and *Staphylococcus* also commonly represented (Pragman et al., 2018b)

The most prevalent phyla in BALF from COPD patients are *Actinobacteria*, followed by *Firmicutes, Proteobacteria, Nitrospira, Fusobacteria, and Bacteroidetes* (Cabrera-Rubio et al., 2012b; Pragman et al., 2018b), while *predominant genera include Prevotella, Pseudomonas, Fusobacterium, Veillonella, Streptococcus, Haemophilus, Lactobacillus*, and *Bacillus* (Erb-Downward et al., 2011b; Seixas et al., 2021). Apparent contradictions across studies warrant careful interpretation. Pragman et al. found more Firmicutes and fewer Actinobacteria and Proteobacteria in severe versus

moderate COPD BAL, and associated disease development with increased microbial diversity (Pragman et al., 2012) a finding at odds with Erb-Downward et al. (Erb-Downward et al., 2011a), who linked impaired lung function and COPD progression to reduced diversity and *Pseudomonas* dominance. Both studies are constrained by small sample sizes and are likely confounded by the heavier medication burden in advanced disease, which in itself may perturb microbiome composition. Similarly, Wu et al. observed greater microbial diversity in COPD sputum compared to healthy controls, alongside enrichment of *Streptococcus pneumoniae, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* (Wu et al., 2014), while Dicker et al. in a larger cohort of 253 stable COPD patients demonstrated an inverse relationship between microbiome diversity and *Pseudomonadota/Haemophilus* abundance, both correlating with low peripheral blood eosinophil counts (Dicker et al., 2021a). This latter finding is clinically significant, as eosinophil counts guide inhaled corticosteroid prescribing in current practice.

4. Microbiome Profiles, Disease Severity, and Clinical Outcomes

Across studies, decreased microbiome diversity alongside increased abundance of Proteobacteria, *Pseudomonas spp*., and *Haemophilus*, and decreased representation of *Actinobacteria, Prevotella*, and *Veillonella* have been consistently associated with greater disease severity (Abate et al., 2022; Natalini et al., 2023). At the cellular level, sputum neutrophil counts positively correlate with *Moraxella, Haemophilus,* and *Neisseria*, and negatively correlate with *Streptococcus, Megasphaera*, and *Veillonella* (Wang et al., 2019), suggesting that the neutrophilic inflammatory milieu in advanced disease selectively enriches pathogenic genera (Taucher et al., 2022) (Table 2).

In a longitudinal observational study of clinically stable COPD patients, reduced microbiome diversity dominated by *Pseudomonadota* predominantly *Haemophilus* was associated with neutrophil-related proteomic signatures and significantly increased mortality risk (Dicker et al., 2021b). Microbiome-based clustering identified four distinct COPD endotypes; the exacerbation-prone cluster was characterised by *Pseudomonas* and *Haemophilus* enrichment and elevated TNF-α levels (Xue et al., 2023c). In contrast, patients harbouring a more diverse microbiome including *Veillonella* and *Prevotella* demonstrated elevated sputum and serum IL-17A, a more temporally dynamic microbiome, and a distinct immunological profile (Zhu et al., 2020). This emerging stratification of COPD by microbiome composition may offer novel avenues for personalised therapeutic intervention.

Beyond bacterial community structure, specific bacterial metabolites including adenosine, 5'-methylthioadenosine, sialic acid, tyrosine, and glutathione have been associated with improved COPD prognosis, suggesting that metabolomic profiling of the microbiome may provide complementary prognostic information (Madapoosi et al., 2022; Segal et al., 2016). The lung mycobiome has been shown to promote sensitisation in COPD-associated bronchiectasis (Everaerts et al., 2017), although the precise contribution of the pulmonary virome to disease pathogenesis remains to be elucidated.

Table 2. Bacterial taxa positively and negatively associated with COPD (lung microbiome).

Taxon		Sample Type	Reference	Direction	Notes
Positively associated and enriched in COPD vs healthy controls					
Haemophilus spp. (esp. H. influenzae)	Genus / Species	Sputum, BAL, lung tissue	(Dicker et al., 2021; Erb-Downward et al., 2011; Wang et al., 2016; Xue et al., 2023a)	↑ Enriched	Most consistently enriched genus in COPD across multiple sample types; correlates with sputum IL-8, neutrophil counts, ↑ exacerbation risk, and ↑ mortality; dominant in low-diversity endotype
Moraxella catarrhalis	Species	BAL, sputum	(Wang et al., 2019, 2018)	↑ Enriched	Enriched in GOLD 2–4 BAL and sputum; positively correlates with sputum neutrophil count per Wang et al.; Gram-negative pathogen with high innate immune stimulation capacity

Pseudomonas aeruginosa	Species	Sputum, BAL	(Erb-Downward et al., 2011; Wang et al., 2018)	↑ Enriched	Dominant in AECOPD cluster and severe disease; Pseudomonas dominance associated with reduced diversity and impaired lung function; implicated in antimicrobial resistance
Streptococcus pneumoniae	Species	Sputum, lung tissue	(Pragman et al., 2018; Ren et al., 2018)	↑ Enriched	Consistently identified in stable and exacerbating COPD; most abundant genus overall in lung tissue of mild-moderate COPD per Pragman
Staphylococcus aureus	Species	Airway samples (stable COPD)	(Ren et al., 2018)	↑ Enriched	Identified in stable COPD alongside other pathogens; associated with bacterial biomass and host inflammatory status
Klebsiella pneumoniae	Species	Sputum	(Wu et al., 2014)	↑ Enriched	Enriched in COPD sputum vs. healthy controls; small study (n=10)
Enterobacterales	Order	Airway samples (stable COPD)	(Ren et al., 2018)	↑ Enriched	Consistently identified in stable COPD; associated with transcriptionally active lung microbiome
Pseudomonadota (Proteobacteria)	Phylum	Sputum, BAL, lung tissue	(Dickson et al., 2015; Liu et al., 2020; Wang et al., 2016; Xue et al., 2023a)	↑ Enriched	↑ across moderate-severe COPD; associated with emphysema, neutrophil/eosinophil/B cell infiltration, airway remodelling, and exacerbation frequency
Actinobacteria	Phylum	Lung tissue (GOLD 4), BAL	(Li et al., 2024; Wang et al., 2019)	↑ Enriched	↑ in GOLD 4 lung tissue alongside Proteobacteria; correlated with immune cell infiltration (neutrophils, eosinophils, B cells); paradoxically ↓ in severe COPD BAL
Burkholderia spp.	Genus	Lung tissue (GOLD 4)	(O'Shaughnessy et al., 2023; Sze et al., 2012)	↑ Enriched	Elevated in very severe COPD (GOLD 4) lung tissue per Sze et al.; co-occurs with Lactobacillus enrichment
Neisseria spp.	Genus	Sputum	(Wang et al., 2019)	↑ Enriched	Positively correlates with sputum neutrophil count per Wang; contributes to neutrophilic airway inflammation profile
Flavobacterium succinicans	Species	Lung tissue / airway	(Wang et al., 2019)	↑ Enriched	One of 10 taxa identified by Wang as distinguishing COPD GOLD 4 microbiomes from healthy controls
Elizabethkingia meningoseptica	Species	Lung tissue / airway	(Wang et al., 2019)	↑ Enriched	One of 10 taxa distinguishing COPD GOLD 4 from controls; opportunistic pathogen
Flavobacterium gelidilacus	Species	Lung tissue / airway	(Wang et al., 2019)	↑ Enriched	One of 10 taxa distinguishing COPD GOLD 4 from controls
Porphyromonas spp.	Genus	BAL, lung tissue	(Erb-Downward et al., 2011)	↑ Enriched	Part of the core COPD lung microbiome; also among 10 GOLD 4-distinguishing taxa
Bacteroidales	Order	Lung tissue / airway	(Wang et al., 2019)	↑ Enriched	One of 10 taxa distinguishing COPD GOLD 4 microbiomes from healthy controls per
Negatively associated and depleted in COPD vs healthy controls					
Prevotella spp. (esp. P. oralis, P. oris)	Genus / Species	BAL, sputum, lung tissue	(Erb-Downward et al., 2011; Larsen et al., 2015b; Wang et al., 2019)	↓ Depleted	Gram-negative commensal with low TLR2-stimulatory capacity vs. pathogenic Proteobacteria; ↓ in COPD vs. healthy; marker of diverse/stable microbiome endotype; oral microaspiration of Prevotella associated with TH17 expansion

Veillonella spp.	Genus	Sputum, lung tissue	(Dicker et al., 2021; Erb-Downward et al., 2011; Wang et al., 2019)	↓ Depleted	↓ in low-diversity/high-severity COPD; oral commensal; microaspiration into lungs associated with TH17 response and IL-17A elevation; negatively correlates with sputum neutrophil count
Bacteroidota (Bacteroidetes)	Phylum	Sputum, BAL, lung tissue	(Dickson et al., 2015; Sze et al., 2012; Wang et al., 2019, 2016)	↓ Depleted	Consistently ↓ with increasing COPD severity across multiple studies and sample types; ↓ in GOLD 4 tissue vs. donors
Bacillota (Firmicutes)	Phylum	Sputum, BAL, lung tissue	(Dickson et al., 2015; Wang et al., 2019, 2016)	↓ Depleted	↓ in moderate-severe COPD; exception: paradoxically ↑ at GOLD 4 driven by Lactobacillus enrichment; ↑ Firmicutes (sputum) associated with higher blood eosinophil count
Lactobacillus spp.	Genus	Lung tissue	(Sze et al., 2012)	↓ Depleted	Generally, a marker of diverse/healthier lung microbiome; paradoxically ↑ in very severe COPD (GOLD 4) lung tissue at transplantation; context-dependent interpretation required
Actinobacteria (in BAL)	Phylum	BAL	(Erb-Downward et al., 2011; Pragman et al., 2012)	↓ Depleted	↓ in severe vs. moderate COPD BAL; underrepresented in sputum vs. BAL; note: ↑ in GOLD 4 lung tissue — sample-type dependent
Megasphaera spp.	Genus	Sputum	(Wang et al., 2019)	↓ Depleted	Negatively correlates with sputum neutrophil count per; depletion associated with more severe neutrophilic inflammatory profile
Streptococcus spp. (commensal)	Genus	Sputum	(Dicker et al., 2021; Wang et al., 2019)	↓ Depleted	↑ Firmicutes/Streptococcus associated with higher blood eosinophils (diverse microbiome group); negatively correlates with sputum neutrophil count; distinct from pathogenic S. pneumoniae
Dialister spp.	Genus	Lung tissue / airway	(Wang et al., 2019)	↓ Depleted	One of 10 taxa distinguishing COPD GOLD 4 from controls; Veillonellaceae family member; reduced in standard COPD vs. control comparison

Abbreviations: BAL, bronchoalveolar lavage; TLR2, Toll-like receptor 2; TH17, T helper 17 lymphocytes; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ↑ increased; ↓ decreased.

5. Gut–Lung Axis and Gut Microbiome Dysbiosis in COPD

The gut–lung axis hypothesis posits bidirectional immunological cross-talk between gut and pulmonary microbiomes, and is supported by the high prevalence of gastrointestinal comorbidities in patients with chronic lung disease (Karakasidis et al., 2023). Experimental evidence from Sze et al. demonstrated that lipopolysaccharide-induced acute lung injury in murine models increased bacterial load in both the caecum and systemic circulation, suggesting active translocation of bacteria from the lungs to the bloodstream as a plausible mechanism linking compartments (Bowerman et al., 2020; Sze et al., 2014). In human studies, Chiu et al. found that while overall gut microbiome composition was not significantly associated with COPD severity, stage-specific differences were evident with the Ruminococcaceae NK4A214 group, Lachnoclostridium, and Bacteroidetes more abundant in mild COPD (GOLD 1). Bowerman et al. characterised the faecal microbiome of COPD patients and identified positive associations with Bifidobacteriaceae, Eubacteriaceae, Lactobacillaceae, Micrococcaceae, Streptococcaceae, and Veillonellaceae, while Desulfovibrionaceae, Bacteroidaceae, Gastranaerophilaceae, and Selenomonadaceae were negatively associated with disease (Bowerman et al., 2020). More broadly, Bacteroidetes, Proteobacteria, Lactobacillus, Oscillospira, Allobaculum, Treponema, and three Streptococcus species have been implicated in COPD development (Chiu et al., 2021; X. Li et al., 2021). Taken together, these findings highlight the gut microbiome as an important, and likely underappreciated, contributor to COPD pathogenesis. Longitudinal studies tracking concurrent gut

and lung microbiome dynamics, alongside interventional studies testing the therapeutic potential of microbiota-targeted strategies, are needed to establish causality and to define the clinical utility of microbiome profiling in COPD management.

6. Future Perspectives

Future research on COPD microbiome dysbiosis should focus on establishing causal relationships between microbial alterations and disease progression. Most currently available studies are observational. Longitudinal investigations involving large patient cohorts are necessary to determine whether dysbiosis initiates inflammation or develops as a consequence of disease severity and treatment exposure. Standardization of sampling procedures and sequencing methodologies is also essential. Variability in sputum, bronchoalveolar lavage, and lung tissue sampling contributes to conflicting microbiome findings across studies. Uniform protocols may improve reproducibility and facilitate cross-study comparisons.

Integration of multi-omics approaches represents another promising direction. Combining metagenomics, transcriptomics, metabolomics, and proteomics may provide a more comprehensive understanding of host–microbiome interactions in COPD. Microbial metabolites such as glutathione, adenosine, and sialic acid may serve as biomarkers for disease prognosis and therapeutic response. Artificial intelligence and machine learning technologies may improve microbiome analysis and patient stratification. Predictive computational models could identify COPD endotypes associated with specific microbial signatures. This approach may support personalized medicine and targeted therapeutic interventions.

Microbiome-directed therapies also hold significant clinical potential. Probiotics, prebiotics, synbiotics, bacteriophage therapy, and fecal microbiota transplantation are emerging areas of interest. Strategies aimed at restoring beneficial microbial communities may help reduce inflammation and exacerbation frequency. Further clinical trials are needed to evaluate their safety and efficacy. The gut–lung axis should also receive greater attention in future investigations. Understanding how gut microbial dysbiosis influences pulmonary immunity may open new therapeutic avenues for systemic disease management. Future studies examining simultaneous lung and gut microbiome dynamics may provide deeper insight into COPD pathophysiology. Overall, microbiome research may transform future COPD diagnosis, prognosis, and treatment strategies. Continued advances in sequencing technologies and computational biology are expected to accelerate the development of precision medicine approaches in respiratory care.

7. Conclusion

Microbiome dysbiosis has emerged as an important contributor to COPD pathogenesis, disease progression, and exacerbation susceptibility. Reduced microbial diversity and enrichment of pathogenic bacteria are consistently associated with chronic airway inflammation, immune dysregulation, and poor clinical outcomes. Both lung and gut microbial communities appear to influence disease severity through complex host–microbiome interactions and immune signaling pathways. Although current findings are promising, inconsistencies among studies highlight the need for standardized methodologies and large longitudinal investigations. Advances in multi-omics technologies, artificial intelligence, and microbiome-targeted therapies may provide new opportunities for precision medicine in COPD. A deeper understanding of microbial dynamics and the gut–lung axis may ultimately improve early diagnosis, prognostic assessment, and personalized therapeutic interventions for COPD patients.

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Author Contributions

S.J written and revised the whole manuscript.

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Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this manuscript.

Ethical Approval

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Data Availability Statement

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