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Definition, Causes, Pathogenesis, and Consequences of Chronic Obstructive Pulmonary Disease Exacerbations



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KEYWORDS

• Chronic obstructive pulmonary disease • Exacerbations • Pathogenesis

KEY POINTS

- Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are episodes of symptom worsening which have significant adverse consequences for patients.
- Highly heterogeneous events associated with increased airway and systemic inflammation and physiological changes.
- They are triggered predominantly by respiratory viruses and bacteria, which infect the lower airway and increase airway inflammation.
- A proportion of patients appear to be more susceptible to exacerbations, with poorer quality of life and more aggressive disease progression.
- Prevention and mitigation of exacerbations are therefore key goals of COPD management.

INTRODUCTION

Acute exacerbations of chronic obstructive pulmonary disease (AECOPDs) are episodes of symptom worsening¹ that have significant adverse consequences for patients.² The important causes of exacerbations include airway bacteria, viruses, and pollution; however, the interplay of these triggers must also be considered. It is recognized that defects in immunity and host defense lead to more frequent AECOPDs. Greater frequency of exacerbations is associated with accelerated lung function decline,³ quality-of-life impairment,⁴ and increased mortality.⁵ Furthermore, as the incidence of chronic obstructive pulmonary disease

(COPD) increases, exacerbations place a greater burden on health care systems, accounting for more than 10 million unscheduled attendances per year in the United States.⁶ The direct costs of COPD treatment in the United States are greater than \$32 billion per year,^{7,8} with exacerbations estimated to account for 50% to 75% of these health care costs.⁹ Exacerbations are also important outcome measures in COPD, with acute treatment targeting accelerated recovery, whereas long-term maintenance therapy is designed to prevent and reduce their frequency and severity.

Although half of the patients treated in the community recover to their baseline symptoms by

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7 days, a study of the time course found that, despite treatment, 14% had still not fully recovered by 5 weeks. Moreover, in a small proportion of exacerbations, symptoms never returned to the baseline level.¹⁰ Consequently, a substantial number of COPD exacerbations can be prolonged, which culminates in greater morbidity associated with such an event. A key audit examining hospital admissions showed that more than one-quarter of patients experience another event during the following 8 weeks.¹¹ In a cohort of patients with moderate to severe COPD followed up after exacerbation, 22% had a recurrent event within 50 days of the first (index) exacerbation. Such events are therefore complex, and an initial exacerbation seems to increase the susceptibility to a subsequent exacerbation.¹² These recurrent events are associated with substantially increased mortality¹³ and this has driven financial incentives for health care services aiming to avoid hospital readmission.^{14,15}

Exacerbations Definition

AECOPDs are transient periods of increased symptoms of dyspnea, sputum purulence, and sputum volume, but they may also encompass minor symptoms of nasal blockage/discharge, wheeze, sore throat, cough, fever, chest tightness or discomfort, fatigue/reduced energy, sleep disturbance, or limited physical activity.¹⁶ COPD exacerbations are associated with several features, including increased airway inflammation, mucus hypersecretion, and gas trapping. There is a degree of controversy over the precise definition of exacerbation events. The 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) document AECOPD definition slightly differs from this as “an acute worsening of respiratory symptoms that results in additional therapy.” This definition requires the patient to seek or use treatment and is an example of a health care use (HCU) exacerbation in which the patient or clinician decides whether treatment is warranted. The disadvantage with only considering this definition is that it risks not accounting for important events in certain key scenarios; for example, those of lesser severity that do not trigger increased treatment use, where respiratory deterioration with an alternative cause is misdiagnosed, or events in resource-poor areas with a lack of access to treatment or clinicians.

The alternative to an HCU definition is to measure the increase in symptoms and to classify an exacerbation when this change crosses a threshold (regardless of whether the patient receives treatment). This approach has been widely

accepted in research, using several validated patient-reported outcome (PRO) tools such as symptom/treatment diary cards and questionnaire tools such as the EXACT (Exacerbations of Chronic Obstructive Pulmonary Disease Tool) and CAT (The COPD Assessment Test). When implemented, it was discovered that a large number of events are unreported and untreated.⁴ Studies using symptom-based definitions typically report an incidence of exacerbations that is approximately twice as high as with HCU definitions. One reason for this is that the method captures additional milder events that the HCU definition does not.¹⁷ Although unreported exacerbations are milder than reported events, they do not seem to be inconsequential. However, the science of measuring symptoms is challenging, both in the collection of (daily) data and in their analysis. Analysis challenges include defining the threshold for exacerbation, ceiling effects, and how and when to reset the baseline symptom level in the event of incomplete exacerbation recovery.¹⁸ Two of the most extensively validated PROs in exacerbation studies are the EXACT¹⁷ and CAT,¹⁹ which seem to be valuable in the assessment of exacerbation frequency, duration, and severity and have been qualified as an exploratory end point by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).²⁰ A particular strength of the EXACT is its ability to detect unreported events, and, in the ATTAIN (Acclidinium to Treat Airway Obstruction in COPD Patients),²¹ comparing a long-acting muscarinic antagonist with placebo, unreported (untreated) symptom (EXACT)-defined events had the same medium-term health consequences as reported (treated) HCU exacerbations. Moreover, the trial intervention reduced the rate of both symptom (EXACT)-defined and HCU events. However, a challenge with interpreting PROs such as the EXACT tool is the discordance between HCU exacerbations and symptom (EXACT)-defined events, with discrepancies found in both observational studies¹⁷ and clinical trials.²¹

A major challenge is the heterogeneous nature of the clinical presentation, and alternative causes for acute deterioration, such as heart failure, pneumothorax, pulmonary emboli, or anxiety, must be considered. Traditionally, infective exacerbations are thought to be driven by infection of the airway lumen (bronchi/bronchioles), whereas pneumonia represents alveolar infection. However, it is likely that these distinct processes overlap. A chest radiograph is not routinely performed during a COPD exacerbation,¹ and consolidation may be missed if it is early in the infective process, or through the insensitivity of the test.

Exacerbation Severity

The latest GOLD guidelines define exacerbation severity by the treatment that is required.¹

- Mild: treatment with short-acting bronchodilators only
- Moderate: treated with short-acting bronchodilators plus antibiotics and/or oral corticosteroids
- Severe: requires either hospitalization or a visit to the emergency department and may also be associated with respiratory failure.

Exacerbation Cause

Exacerbations are airway inflammatory events that are triggered by infection in most cases. Respiratory viral infections are the predominant cause, although bacterial infections and environmental factors such as air pollution and ambient temperature trigger or worsen these events.^{22,23} Although early studies focused on bacteria as the primary cause of exacerbations, the development of highly specific molecular diagnostic techniques has highlighted the importance of viruses as key triggers for exacerbations.^{24–26} The primary role of different exacerbation triggers and important aspects of their interplay, including viral-bacterial

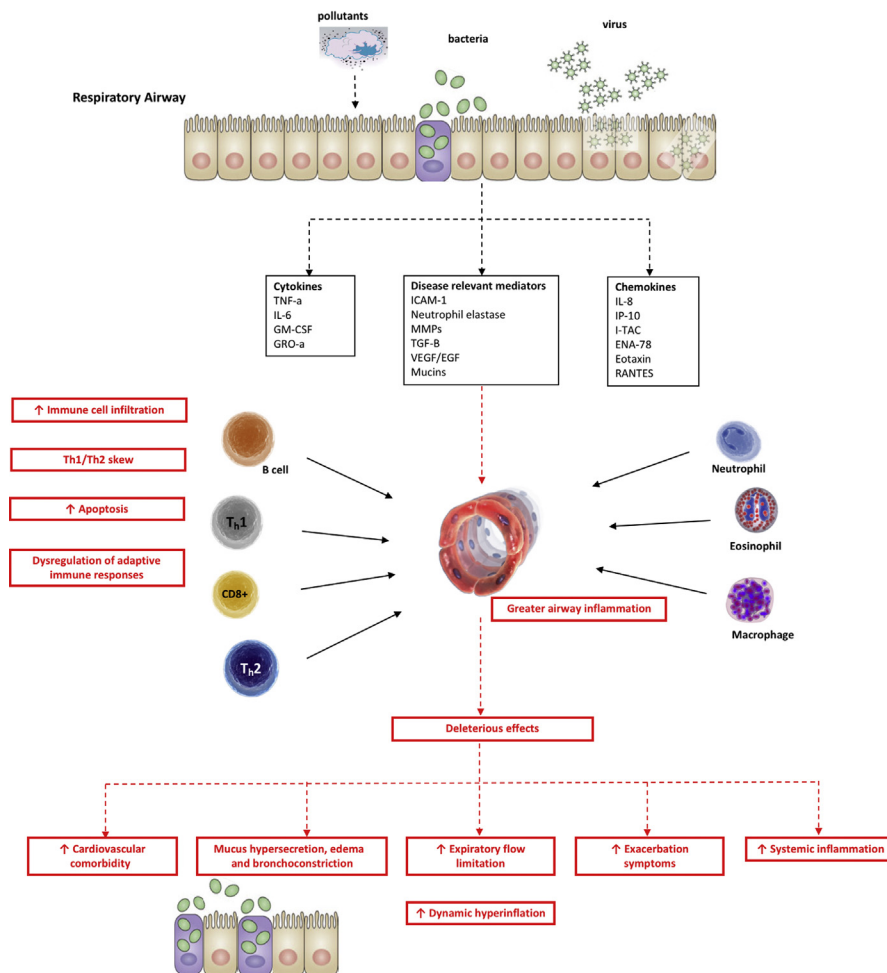


Fig. 1. Overview of AECOPD. EGF, endothelial growth factor; ENA, epithelial-derived neutrophil-activating peptide; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; IP, interferon γ -induced protein; I-TAC, interferon-inducible T-cell alpha chemoattractant; GM-CSF, granulocyte-macrophage colony-stimulating factor; GRO, growth-regulated oncogene; MMP, matrix metalloproteinase; RANTES, regulated upon activation, normal T Cell expressed and presumably secreted; TGF, transforming growth factor; Th, T helper; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

coinfection, deficient host response to bacteria, and the lung microbiome in exacerbation are described here (Fig. 1). It has long been observed that the frequency of AECOPD doubles in winter months,^{27,28} with more than 50% of exacerbations preceded by coryzal symptoms (Table 1).^{10,29,30}

Viruses

Earlier studies using culture-based methods underestimated the prevalence of respiratory viruses during COPD exacerbations. However, with the advent of polymerase chain reaction (PCR) methods, the detection of viruses in COPD exacerbations increased to 22% to 64%.^{30–52} The wide variations in virus detection are likely to be the consequence of whether patients were sampled at true onset of symptoms or sampling was delayed. Additional factors could include variation in the range of viruses tested for, sensitivity of the assays, the study period (eg, winter vs year-long, variation in virus epidemics; eg, respiratory syncytial virus [RSV]), population (eg, community vs inpatient, uptake of the influenza vaccine), and sampling method (eg, nasopharyngeal swabs, sputum). In studies where patients reported exacerbation symptoms at onset, there is a greater prevalence of viral infection, because viral load is higher at exacerbation onset^{53,54} and may therefore be undetectable by the time patients present to hospital.^{29,30,34,41,50,55}

Rhinoviruses are the most prevalent in most of these studies, accounting for up to 60% of all exacerbations.⁵³ Influenza viruses and RSVs are also commonly detected, being identified in up to 36%⁵² and 28%⁵⁵ of AECOPDs respectively. Parainfluenza viruses, human metapneumoviruses,

coronaviruses, and adenoviruses are detected, but less frequently. Importantly, viral AECOPDs are associated with more severe symptoms, greater airflow limitation, and delayed recovery compared with exacerbations where no virus is detected.^{47,56} The greater incidence of rhinovirus in induced sputum, as opposed to nasal aspirates at exacerbation,⁵⁷ further supports the theory that naturally occurring rhinovirus drive most exacerbations. Although these studies have shown an association between respiratory virus infection and exacerbations, they do not prove causation because PCR detects viral nucleic acid but it cannot prove the presence of live, replicating virus. Consequently, secondary causes cannot be excluded. However, in 2011, Mallia and colleagues⁵⁴ provided novel evidence of a causal relationship between respiratory virus infection and exacerbations in patients with COPD through their experimental rhinovirus infection in patients with mild COPD. In their human model, they showed clearly that respiratory viruses produce symptoms that are typical of an exacerbation, confirming that respiratory viruses can infect the lower airway and contribute to inflammatory changes.⁵⁴

Chronic viral infection is another key aspect to examine when considering the role played by viruses such as RSV. Although RSV infection has been seen at exacerbation,⁵⁵ whether it alone drives the event is not entirely clear, because this virus is found incidentally within the airways of patients with COPD at stable state where it is associated with increased airway inflammation.⁵⁸ Latent expression of adenoviral E1A protein in alveolar epithelial cells can potentiate the effects of lung

Table 1

Noteworthy studies showing the winter/summer seasonality incidence of acute exacerbations of chronic obstructive pulmonary disease

Study Name	Study Findings
TORCH ²⁷	80% winter/summer excess (9% of patients exacerbating in December-February compared with 5% in June to August) in the northern hemisphere and a 71% excess (12% vs 7% of patients) in the southern hemisphere
POET ²⁸	7.63 vs 3.63 exacerbations (per 100 patient months)
Donaldson et al, ¹⁴⁰ 2012	1052 exacerbations in winter vs 652 in summer. Winter exacerbations lasted longer and were more severe: 8.4% of exacerbations resulted in patients who were hospitalized, compared with 4.6% of exacerbations in the warm seasons
TIOSPIR ¹⁴¹	6646 exacerbations in winter compared with 3198 in summer

Abbreviations: TORCH, Towards a Revolution in COPD Health; POET, prevention of exacerbations with Tiotropium; TIOSPR; The Tiotropium Safety and Performance in Respiat.

Data from Refs.^{27,28,140,141}

inflammation induced by cigarette smoke.⁵⁹ It is therefore plausible that chronic viral infection could contribute to disease severity in COPD, and further work is required to understand how viruses detected in the stable state relate to exacerbations.

Impaired Antiviral Immunity in Chronic Obstructive Pulmonary Disease

It is not fully understood why patients develop an exacerbation following respiratory virus infection but never smokers do not often go on to develop significant lower respiratory symptoms. Furthermore, there is a subgroup of COPD that seems to be more susceptible to infection, irrespective of disease severity (the frequent-exacerbator phenotype).⁶⁰ COPD is associated with substantial changes in innate immunity that are likely to be relevant in the pathogenesis of exacerbations. Tobacco smoking impairs mucociliary clearance,⁶¹ and the rhinovirus binding receptor intercellular adhesion molecule 1 (ICAM-1) is upregulated by bronchial epithelial cells in COPD.⁶² Alveolar macrophages, which are numerous and form a first line of defense in the respiratory tract, are defective in COPD, with impairments in their ability to phagocytose bacteria^{63,64} and clear dead and dying cells⁶⁵ compared with alveolar macrophages from healthy smoking and nonsmoking controls.

In the human experimental rhinovirus infection model, Mallia and colleagues⁵⁴ found nasal lavage viral load was significantly higher in patients with COPD following rhinovirus infection compared with age-matched healthy controls. Because all subjects were inoculated with the same virus dose, this suggests impairment in the immune response that controls viral replication in COPD. This finding supports the work by Hurst and colleagues,²⁹ who earlier showed that exacerbation frequency was related to cold acquisition rather than the propensity to develop an exacerbation following a cold.

The most abundant cells in the airway are bronchial epithelial cells (BECs) and alveolar macrophages. Interferon (IFN) deficiency has been observed in these important cells and, therefore, proposed as a potential mechanism of increased susceptibility to rhinovirus infection. Respiratory viruses such as human rhinovirus (HRV) replicate within the respiratory epithelium triggering the production of type I (FN- α , IFN- β) and type III IFNs (IFN- λ), which limit viral replication, protein synthesis, and protein trafficking (Table 2).⁶⁶ However, IFN deficiency remains controversial in COPD. Mallia and colleagues⁵⁴ found that

bronchoalveolar lavage (BAL) cells of subjects with COPD had a deficient IFN- β response to ex vivo infection with HRV-16, but did not identify any deficiency in BEC responses. In contrast, Hsu and colleagues⁶⁷ recently showed impaired IFN responses to influenza virus in BECs from COPD. These findings are supported by a study that showed a decrease in expression of IFN stimulated genes in the induced sputum of COPD participants compared with healthy controls.⁶⁸ However, Schneider and colleagues⁶⁹ and Baines and colleagues⁷⁰ showed increased IFN- λ responses to HRV-39 and HRV-1B infection of COPD BECs respectively compared with healthy controls.⁶⁹ Further studies of IFN induction in response to viral infection in epithelial and BAL cells in COPD are clearly needed because this is a potential therapeutic target.

Viral infection in COPD also leads to the production of disease-relevant proinflammatory cytokines such as interleukin (IL)-8 (CXCL8), IL-6, chemokine ligand 5 (CCL5/RANTES), tumor necrosis factor alpha (TNF- α), and IFN- γ -induced protein (IP-10/CXCL10) via the nuclear factor κ B pathway leading to the recruitment of neutrophils, macrophages, natural killer cells, T cells, and dendritic cells at the site of infection enhancing viral clearance. Importantly, the magnitude of this response is greater in patients with COPD compared with healthy controls^{37,38,71} and may explain how increased airway inflammation contributes to lower airway symptoms in COPD exacerbations.

In general, exacerbations become both more frequent and more severe as the severity of the underlying COPD increases,^{72,73} although the reason some patients with COPD experience more frequent exacerbations than others remains unclear. The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort study identified a distinct frequent-exacerbator phenotype. This group, irrespective of disease severity, was more susceptible to exacerbations and could be identified by a previous history of 2 or more exacerbations in a preceding year.⁶⁰ There is some indirect evidence that an increased susceptibility to virus infection may be a characteristic of frequent exacerbators. In studies of naturally acquired virus-induced COPD exacerbations, virus infection was detected more commonly in exacerbation-prone patients.^{30,53} Alveolar macrophages taken from such patients (defined as having had an exacerbation during a 1-year period) and exposed to bacteria or toll-like receptor ligands ex vivo showed impaired induction of CXCL8/IL-8 and TNF- α , compared with macrophages from patients who were

Table 2
Inflammatory changes in viral infections in chronic obstructive pulmonary disease exacerbations

Mediator	Naturally Occurring Infection ¹	Experimental Infection in Humans
Chemokines		
CXCL10/IP-10	↑ Serum + sputum ³⁸	↑ BAL ¹⁰⁶
CXCL8/IL-8	↔ Serum ^{36,142} + sputum ^{37,57}	↑ Sputum ↔ BAL ^{54,106} ↑ Nasal lavage ¹⁴³
CCL5/RANTES	↑ Sputum ³⁸ ↔ Serum ³⁶	—
CCL2/MCP1	↑ Sputum ³⁸ ↔ Serum ³⁶	—
CXCL11	↑ Serum + sputum ³⁸	—
Inflammatory Cells		
Neutrophils	↔ Sputum ³⁷	↑ BAL, sputum, blood ^{54,106}
Lymphocytes	—	↑ BAL ^{54,144}
Eosinophils	↑ Sputum ⁴⁷	—
Cytokines		
IL-6	↑ Sputum ^{57,71} ↔ Serum ^{36,142}	↑ BAL ↔ Sputum ⁵⁴ ↑ Nasal lavage ¹⁴³
TNF- α	↔ Serum ³⁶ or sputum ³⁷	↔ BAL, sputum ⁵⁴ ↑ Sputum ¹⁰⁶
IL-1 β	↔ Serum ³⁶	↑ Sputum ¹⁰⁶
IL-10	↑ Serum ³⁶	—
IL-13	↔ Serum ³⁶	—
Type II IFN (γ)	↑ Serum ³⁸ ↔ Serum ³⁶	—
Selected Others		
Neutrophil elastase	—	↑ Sputum ↔ BAL ^{54,92,106}
MMP-9	—	↑ Sputum ¹⁰⁶
Antimicrobial peptides (secretory leukoprotease inhibitor, elafin)	—	↓ Sputum ⁹²
Markers of oxidative stress (8-hydroxy-2'-deoxyguanosine, 3-nitrotyrosine)	—	↑ Sputum ¹⁰⁶

Abbreviations: BAL, bronchoalveolar lavage; IL, interleukin; MMP, matrix metalloproteinase; TNF, tumor necrosis factor.
 Data from Refs.^{36–38,47,54,57,71,92,106,142–144}

exacerbation free for a year.⁷³ Nevertheless, the description of frequent exacerbators remains essentially clinical and further studies are warranted to elucidate differences in the immune responses and conclusively provide an underlying mechanism to explain this phenotype.

Bacteria

Bacteria are also extremely important in the pathogenesis of COPD exacerbations. Studies using

traditional sputum culturing techniques have isolated bacteria in 40% to 60% of exacerbations of COPD.^{25,74} The most frequently identified species are nontypeable *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and *Pseudomonas aeruginosa*.^{44,47,75} Atypical bacteria are infrequently isolated, with *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* implicated in only 4% to 5% of episodes.⁷⁴ Studies have also shown that bacterial colonization is

common in COPD and is associated with greater airway inflammation and increased risk of exacerbation.^{12,56,75} However, it remains unclear from these studies whether exacerbations occur because of the acquisition of new bacterial strains or an outgrowth of preexisting bacteria.²⁶

The Microbiome Changes During Chronic Obstructive Pulmonary Disease Exacerbations

In up to 50% of AECOPDs showing the hallmarks of a bacterial cause, the causative pathogens are not recovered from respiratory samples by traditional culture methods. The application of microbiome techniques, which are culture independent, is giving rise to a new understanding

of the interaction between the host and the millions of microorganisms that are present on bodily surfaces. Studies identifying bacteria based on 16S ribosomal RNA gene sequences have shown that the lungs of healthy people and patients with COPD are colonized by rich, complex bacterial communities.^{76–78} Recently, researchers have begun to highlight the shifts in microbial communities during COPD exacerbations (Table 3).

One of the first longitudinal studies, by Huang and colleagues,⁷⁹ found that the sputum microbiome did not show any significant changes in the key characteristics of community richness, evenness, and diversity. However, substantial taxonomic composition variation was seen during exacerbations, with an increase in Proteobacteria

Table 3
Summary of studies examining microbiome changes at chronic obstructive pulmonary disease exacerbation

Study	Subjects and Samples	Lung Sample/Site	Key Finding
Huang et al, ⁷⁶ 2010	8 intubated patients with COPD 8 tracheal aspirates	Tracheal aspirates	Individuals have distinct airway bacterial communities Intubation duration ↓ α diversity
Huang et al, ⁷⁹ 2014	12 subjects with COPD	Sputum	↑ Proteobacteria at exacerbation onset In recovery: ↓ Proteobacteria with antibiotic treatment ↑ Proteobacteria, Bacteroidetes, and Firmicutes with oral corticosteroids
Millares et al, ¹⁵⁸ 2014	16 subjects with COPD 5 <i>Pseudomonas</i> colonized, 11 uncolonized	Paired baseline and exacerbation sputum samples	No significant difference in microbiome at exacerbation between <i>Pseudomonas</i> colonized and uncolonized
Molyneux et al, ⁸² 2014	14 patients with COPD 17 Healthy subjects	RV Interventional study; sputum preinfection, 5, 15, and 52 d postinfection	Rhinovirus infection led to an outgrowth of preexisting <i>Haemophilus</i> and <i>Neisseria</i> at day 15
Wang et al, ⁸⁴ 2016 BEAT-COPD	87 patients with COPD 476 sputum samples	Sputum at baseline, exacerbation onset, recovery	Distinct bacterial and eosinophilic exacerbation microbiome Biomarkers relate to diversity
Mayhew et al, ⁸¹ 2018 AERIS cohort	101 patients with COPD	Sputum	↑ Proteobacteria with ↑ disease severity ↑ <i>Haemophilus</i> with bronchiectasis ↑ Dysbiosis in frequent exacerbations
Wang et al, ⁸⁰ 2018 COPD-MAP	281 patients with COPD	Sputum	Distinct microbiome for eosinophilic and bacterial exacerbations Similar taxa at baseline and exacerbation

but a decrease in Actinobacteria, Clostridia, and Bacteroidia. Furthermore, when levels of important pathogens such as *H influenzae* increase at AECOPD, closely related bacterial taxa were also enriched, whereas the phylogenetically distant taxa declined.⁷⁹ The larger COPD-MAP and AERIS longitudinal studies found no significant change in Shannon diversity or core taxa abundancies at exacerbation. However, both studies suggested that exacerbations result from dysbiosis caused by changes in preexisting bacteria in the lung rather than complete removal or appearance of a novel species.^{80,81} Overall, these findings suggest that, although the bacteria cultured at exacerbation undoubtedly drive events, enrichment of taxa closely related to a dominant pathogen could also contribute to pathogenesis. Therefore, exacerbations can be considered polymicrobial infections.

A study of the microbiome following experimental rhinovirus infection also showed an outgrowth in *Haemophilus* and *Neisseria* that were present in lower numbers before rhinovirus infection.⁸² These changes were correlated with increased neutrophil concentration and neutrophil elastase levels, and were not observed in the healthy control group.⁸² These findings support the hypothesis that the bacteria identified at exacerbation are not newly acquired but are caused by an outgrowth of preexisting bacteria that have experienced newly favored conditions.⁸²

Both the BEAT-COPD cohort and COPD-MAP cohorts identified distinct microbiome compositions between bacterial and eosinophilic exacerbations, suggesting that these are stable exacerbation phenotypes. The AERIS study found that individuals with concomitant bronchiectasis had a greater abundance of *Haemophilus*. It suggested that frequent exacerbators may have greater dysbiosis compared with infrequent exacerbators, thus providing a potential mechanism by which AECOPDs arise.

Treatment Effects on the Lung Microbiome

Events treated by antibiotics alone led to a reduction in the relative abundance of Proteobacteria, whereas treatment with corticosteroids alone led to an enrichment of multiple taxa, including members of Bacteroidetes, Firmicutes, and Proteobacteria.^{83,84} This finding was supported by an earlier study of tracheal aspirates from intubated patients in whom the investigators observed that bacterial communities became less diverse as the duration of intubation and antibiotic administration increased, suggesting that microbial communities are influenced by therapeutic interventions.⁷⁶

When both steroids and antibiotics were used to treat an exacerbation, a mixed effect on the airway microbiome was seen.⁷⁹

Host Response to Bacteria and Bacterial Susceptibility

A current hypothesis is that bacteria enter the lower respiratory tract by microaspiration during sleep or inhalation.⁸⁵ In healthy lungs, pathogens either fill an ecological niche or are eradicated with minimal inflammation by the innate immune response. However, in patients with COPD, a combination of defective innate immunity including impaired mucociliary clearance and variation in antigenic structure among strains allow these bacteria to persist and proliferate.⁸⁵

A complex host-pathogen interaction in the lower airway determines this outcome. In a mouse model, *H influenzae* strains associated with COPD exacerbations induced greater airway neutrophil recruitment compared with colonization-associated strains.⁸⁶ Exacerbation-associated *M catarrhalis* strains interact differently with primary human airway epithelial cells, showing greater adherence and eliciting more IL-8.⁸⁷ Sputum immunoglobulin (Ig)A levels, representing the mucosal host response to the infecting strain, were greater with colonization, whereas the systemic serum IgG host response was larger during exacerbations.⁸⁸ It is thought that a robust mucosal immune response diminishes bacterial interaction with the airway epithelium, resulting in less airway inflammation, thus favoring colonization.

Recent studies focusing on the immune response to bacterial infection have shown the development of specific antibodies to important species, including *H influenzae*, *M catarrhalis*, *S pneumoniae*, and *P aeruginosa* following exacerbations. Some of these show bactericidal and opsonophagocytic function, thereby aiding bacterial clearance.^{88–90} However, the multitude of strains may result in recurrent exacerbations with the same species and also creates a challenge for effective vaccine development.

Viral-Bacterial Coinfection

Coinfection with bacteria and viruses is common, occurring in 6% to 27% of exacerbations.^{44,47,91} The dynamics of viral and bacterial infection have been examined by Hutchinson and colleagues,³² who collected respiratory samples from patients with COPD at exacerbation onset, and also 5 to 7 days later: 36% of patients who had a virus detected at exacerbation onset went on to have a bacterial infection. George and colleagues⁵³

reported that, when HRV was detected at exacerbation onset, 60% of patients developed a bacterial infection at 14 days. Mallia and colleagues⁹² found comparable results in experimental rhinovirus infection in COPD, with 60% of patients with COPD showing bacterial infection in their sputum at day 15 compared with only 10% in healthy volunteers. Those who developed a bacterial infection had prolonged respiratory symptoms and delayed recovery compared with those in whom bacteria were not detected.⁹²

Exacerbations with coinfection with viruses and bacteria are associated with greater airflow limitation, increased airway inflammation, and delayed exacerbation recovery.^{47,56} However, mechanisms underpinning how HRV infection leads to a secondary bacterial infection have not been fully elucidated. Possible mechanisms include viral impairment of macrophage response to bacteria^{93–95} leading to a reduction in neutrophil recruitment and bacterial clearance⁹⁶ or, alternatively, an upregulation of adhesion molecules in the bronchial epithelium.⁹⁷ However, further work is needed to understand the complex pathogen-host interactions to direct further therapeutics.

Airway Inflammation and Cells of Interest

COPD is characterized by aberrant airway inflammation.¹ A further increase in airway inflammation is seen in most exacerbations, but this process is not uniform and inflammation is related to exacerbation cause. Frequent exacerbators also show greater inflammation, and exacerbation nonrecovery is associated with persistent inflammation and a shorter time to the next exacerbation.¹²

Eosinophils

Traditionally, airway eosinophilia and T-helper cell type 2 (Th2) inflammation has been considered associated with allergic airway disorders such as asthma, and airway neutrophilia with COPD. However recent studies have reported that 20% to 40% of patients with COPD show sputum eosinophilia in the stable state.^{98–100} The SPIROMICS (SubPopulations and Intermediate Outcome Measures In COPD Study) cohort has found that sputum eosinophilia at stable state is associated with more severe disease and increased exacerbation frequency.¹⁰¹ Interventional studies additionally suggest that high blood eosinophilia level at stable state might predict a better treatment response to inhaled corticosteroid use and could therefore be used to guide therapy.^{102,103}

Acute exacerbations may be associated with further enhancement of eosinophilic airway inflammation, with up to 30% of COPD exacerbations being associated with sputum eosinophilia.^{38,99} Although there is biological plausibility for viral infection leading to sputum eosinophilia,¹⁰⁴ studies of exacerbations to date have been conflicting.^{38,47,105} As a result, despite the considerable interest in the role of sputum and blood eosinophilia at stable state as biomarkers for disease outcome and steroid responsiveness, further work is needed to evaluate the significance of increased Th2 inflammation during COPD exacerbations.

Neutrophils

COPD exacerbations associated with bacterial pathogens show significantly more airway neutrophilic inflammation compared with nonbacterial episodes.⁸⁸ Furthermore, the exacerbation severity and degree of airway bacterial concentration are related to the degree of neutrophilic inflammation.^{88,89} Important mediators of this airway neutrophilia in bacterial exacerbations include IL-8, leukotriene B₄, and TNF- α .^{44,90} Studies examining bacterial exacerbations have identified an IL-1 β signature comprising TNF- α , granulocyte colony-stimulating factor (Growth-regulated oncogene- α), IL-6, cluster of differentiation (CD) 40 ligand, and macrophage inflammatory protein 1 (MIP-1).⁹² IL-17A has been associated specifically with *H influenzae* exacerbations.⁵⁴ Neutrophil degranulation and necrosis can cause significant damage related to the release of neutrophil elastase and matrix metalloproteinases.⁶⁹ Clinical resolution of the symptoms of exacerbation is associated with a consistent decrease in mediators of neutrophilic airway inflammation, whereas nonresolving exacerbations show a sustained level of exaggerated airway inflammation.⁸⁸ Studies from experimental infections also indicate that viral infection induces airway neutrophilic inflammation and innate inflammatory mediators such as IL-1 β , granulocyte colony-stimulating factor (GM-CSF), CXCL8/IL-8, and TNF- α .^{54,106,107}

Macrophages

Alveolar macrophages play a key role in the host defense against invasive pathogens by removing bacteria from the lung by phagocytosis, mediating inflammatory responses. There is increasing evidence of macrophage dysfunction in COPD.¹⁰⁸ Alveolar macrophages and monocyte-derived macrophages show impaired phagocytosis of *H influenzae*, *S pneumoniae*, and *Escherichia coli*

compared with healthy controls.^{63,64,109} Bewley and colleagues¹¹⁰ also found that phagocytosis of *H influenzae* was impaired in subjects with COPD with a history of exacerbations. Alveolar macrophages of exacerbation-prone subjects with COPD also showed impaired production of inflammatory cytokines CXCL8 and TNF- α in response to *H influenzae* compared with non-exacerbation-prone subjects with COPD, implicating macrophage dysfunction as a potential mechanism responsible for increased exacerbation frequency in COPD.⁶⁴

Macrophages from patients with COPD stimulated ex vivo with respiratory virus produce less IFN compared with healthy subjects.⁵⁴ However, in vitro studies have not necessarily supported this, with similar⁷⁰ and even increased⁶⁹ IFN released by cells taken from patients with COPD. In a murine model of COPD, IFN- α and IFN- β responses as a result of virus infection were reported as deficient in 1 study and viral clearance was impaired¹¹¹; conversely, another study reported reduced IFN- λ (but not in IFN- β) and no difference in virus load. Therefore, it remains unclear whether production of IFN in response to virus infection is impaired in patients with COPD.

Biomarkers of Acute Exacerbations of Chronic Obstructive Pulmonary Disease

A reliable and objective biomarker of an AECOPD would be invaluable to aid in reliable diagnosis and guide appropriate treatment. The patient samples most investigated are serum or plasma, although sputum, urine, or exhaled breath may also contain useful biomarkers. Several studies have shown that the levels of a variety of immunoinflammatory cells and molecules are increased during exacerbations in respiratory samples, including exhaled breath, sputum, bronchoalveolar lavage, and bronchial biopsy (Table 4).

Biomarkers of Viral Exacerbations

A viral exacerbation is suggested with a history of coryzal symptoms and can subsequently be confirmed by PCR from a respiratory sample. However, a reliable biomarker would be invaluable for guiding therapy and antibiotic stewardship (see Tables 2 and 4). To date, serum CXCL10 (IP-10) seems the most promising,¹¹² with Bafadhel and colleagues³⁸ reporting a cutoff of 56 pg/mL to distinguish viral from nonviral exacerbations, giving a specificity of 65% and sensitivity of 75%. Quint and colleagues¹⁴² reported an area under the curve for serum IP-10 alone of 0.78 (95% confidence interval, 0.65–0.91) for detecting a human rhinovirus infection at exacerbation. Other biomarkers have

been investigated, with levels of IL-6, monocyte chemoattractant protein-1 (MCP-1), and TNF- α all being increased in viral-associated AECOPD compared with viral-negative subjects and controls.¹¹³ Procalcitonin has also been used to try to detect viral-associated AECOPD, but the evidence so far is equivocal.¹¹⁴

Biomarkers of Bacterial Exacerbations

Bafadhel and colleagues³⁸ suggested that a useful biomarker for determining bacterial-associated AECOPD was sputum IL-1 β , with a cutoff of 125 pg/mL having a specificity of 80% and sensitivity of 90%. The serum biomarker best suited for distinguishing a bacterial cause in this study was C-reactive protein (CRP) at a cutoff of 10 mg/L, having a specificity of 70% and sensitivity of 60%.³⁸ Dal Negro and colleagues¹¹⁵ also found that high sputum TNF- α level was associated with *Pseudomonas*-related exacerbations, and, in those subjects without high TNF- α level, high levels of IL-8 and IL-1 β in the sputum distinguished bacterial from viral and noninfective exacerbations. An electronic nose used in the detection of cardinal volatile organic compounds has recently been used in a pilot study to distinguish bacterial from viral AECOPD,¹¹⁶ although development and proof of concept are needed before this technology can play a role in outpatient diagnostics.

A Danish study investigating biomarkers indicative of frequent exacerbators discovered that simultaneously increased fibrinogen, CRP, and white blood cell counts indicated an increased risk of frequent exacerbation.¹¹⁷ Increased plasma fibrinogen level in patients at risk of frequent exacerbation has also been replicated in further studies.^{118,119} The FDA has gone on to qualify fibrinogen as an end point of exacerbations and mortality. High levels of serum surfactant protein D have been shown to predict exacerbations when at their highest levels.¹²⁰ However, the most comprehensive study to date, which included 2000 patients and examined 90 markers, in 2 separate cohorts (Spiromics and COPDGene), found no biomarker showed a significant relationship to exacerbation frequency in either cohort (after adjustment for recognized confounders: age, gender, percentage predicted forced expiratory volume in 1 second [FEV1], smoking and health status [quality of life], and self-report of gastroesophageal reflux).¹²¹

Consequences of Exacerbations

Lung function decline

Several studies have now shown that COPD exacerbations affect disease progression. Donaldson

Table 4
Common biomarkers examined in acute exacerbations of chronic obstructive pulmonary disease

Biomarker	Study Findings
CRP	<ul style="list-style-type: none"> • Most widely used biomarker when investigating and monitoring respiratory infections • CRP level is increased consistently in AECOPD in multiple studies compared with recovery¹⁴⁵ • In 86 patients during AECOPD, the CRP levels did not distinguish viral from bacterial causes⁴⁸ • In 118 patients studied for 1 y, a slightly higher level of CRP in bacterial compared with viral AECOPD or cases in which no pathogen was identified (58.3 mg/L, IQR 21–28.2, vs 37.3 mg/L, IQR 18.6–79.1)⁴⁸ • AECOPD associated with <i>H influenzae</i> or <i>S pneumoniae</i> incurred the highest CRP levels¹⁴⁶
PCT	<ul style="list-style-type: none"> • Levels of PCT ≥ 0.25 ng/mL have been shown to indicate an AECOPD requiring hospital admission for ≥ 7 d¹⁴⁷ • A meta-analysis investigating procalcitonin-based protocols in guiding antibiotic usage during an AECOPD found that they were clinically effective and safe¹⁴⁸ • However, concerns regarding these conclusions remain because of the inclusion of suboptimal studies into the meta-analysis
BNP	<ul style="list-style-type: none"> • 60 patients with COPD (17 exacerbations) found BNP level was significantly increased with an AECOPD (79.9 ± 16.2 pg/mL at exacerbation vs 41.2 ± 8.7 pg/mL at stable state)¹⁴⁹ • Higher BNP levels indicate a more severe exacerbation and a longer hospital stay^{150,151}
Plasma fibrinogen	<ul style="list-style-type: none"> • Fibrinogen increases during COPD exacerbation (0.36 g/L SD = 0.74), and then returns to the patient's baseline over a period of 2 to 6 wk^{119,152} • This process is associated with a concurrent increase in IL-6 • A large meta-analysis of more than 154,000 participants indicated that a 1-g/L increase in plasma fibrinogen resulted in a 3.7-fold increase in COPD-specific mortality¹¹⁹
IL-6	<ul style="list-style-type: none"> • IL-6 has been shown to be a better predictor of mortality than both CRP and plasma fibrinogen¹⁵³
Urine metabolomics	<ul style="list-style-type: none"> • Few biomarkers isolated from the urine are clinically useful in AECOPD • One study that shows promise for the future has indicated that certain metabolomics can be used to differentiate COPD from asthma with a >90% accuracy¹⁵⁴
Sputum eosinophilia	<ul style="list-style-type: none"> • Sputum eosinophil levels have been found to negatively correlate with bacterial load at exacerbation¹⁵⁵ • Serum peripheral blood eosinophil count at a cutoff of 2% is likely to be the best measure of sputum eosinophilia, with Bafadhel et al³⁸ reporting a specificity of 60%, sensitivity of 90%
Exhaled nitric oxide	<ul style="list-style-type: none"> • Several studies of AECOPD show an increase, with 1 showing an increase of 1.9 ppb (–0.4 to 4.0 ppb) at exacerbation^{156,157}

Abbreviations: BNP, brain natriuretic peptide; CRP, C-reactive protein; IQR, interquartile range; PCT, procalcitonin; SD, standard deviation.

Data from Refs. ^{38,48,119,145–157}

and colleagues³ showed that patients with a history of frequent exacerbations show accelerated decline, at around 25%, whereas Kanner and colleagues¹²² also showed that episodes of respiratory infections affect FEV1 decline. However,

some of the earlier studies did not show a relationship between exacerbations and FEV1 decline.^{123–125} A review by Silverman¹²⁶ suggested that this heterogeneity could be caused by the general/unselected or chronic bronchitis/

emphysema populations studied in the early, negative studies in contrast with the COPD patient populations studied in the later, positive studies. A recent COPDGene study showed that the effect of exacerbations on decline was greatest in patients with mild (GOLD stage 1) COPD, with each event associated with an additional 23 mL/y decline.¹²⁷ On occasion, lung function following an exacerbation does not fully recover, and then a group of patients who experience frequent exacerbations (because they have more events) are likely to have a faster lung function decline than patients who have zero or few exacerbations.¹²⁸

Mortality

According to the latest Global Burden of Disease study estimates for 2015, COPD accounted worldwide for 3.2 million deaths.¹²⁹ Exacerbations are the predominant cause of mortality, and Soler-Cataluña and colleagues⁵ showed that AECOPDs requiring hospitalization are independently associated with mortality (after adjusting for confounding variables such as age, FEV₁, body mass index, and Charlson comorbidity index), and that the mortality risk increases with exacerbation frequency. A Canadian mortality study showed that rates after the first hospitalized COPD exacerbation were 50% at 3.6 years and 75% at 7.7 years.¹³⁰ The mortality risk peaks sharply in the first 7 days after hospitalization and gradually declines over the subsequent 3 months. With every new hospitalized exacerbation, the risk of death increased, and the interval between hospitalizations decreased over time. For AECOPDs requiring hospitalization, patients with older age, higher arterial PaCO₂, prolonged oral corticosteroid use, or admission to intensive care unit are more likely to die.¹³¹ In a large analysis of a UK primary care population, Rothnie and colleagues¹³² show a clear association between both the increasing frequency and the severity of AECOPDs and mortality.

Quality of life

The relationship between COPD exacerbations and health-related quality of life was first reported by Seemungal and colleagues,⁴ who found that patients with frequent exacerbations (>3 per year) had a 14.8-unit higher total St George's Respiratory Questionnaire (SGRQ) score, indicating poorer quality of life, than patients with infrequent exacerbations (≤2 per year). Patients with COPD with frequent exacerbations (>3 per year) also have a faster deterioration in SGRQ scores over time (almost 2 units per year).¹³³ Quality of life also worsens acutely at exacerbation compared with preexacerbation levels using several

difference indices. These studies include worse activity and affect SGRQ, CCQ (clinical COPD Questionnaire), EQ-5D (European Quality of Life – 5 Dimensions questionnaire), MRC (Medical Research Council) dyspnea, ADL (Activities of Daily Living), CAT (The COPD Assessment Test), and EXACT (Exacerbations of Chronic Obstructive Pulmonary Disease Tool) scores.^{17,19,134} Exacerbations also worsen patients' mental health with an increase in anxiety and depression¹³⁵ and feelings of fatigue.¹³⁶ Hospital admission and readmission for acute exacerbations have a particularly negative impact on quality-of-life scores.^{4,137}

Physical activity

Acutely at exacerbation, patients spend less time outside of their homes, and patients who experience frequent exacerbation have a faster decline in time spent outdoors compared with infrequent exacerbators.¹³⁸ Peripheral muscle weakness also deteriorates during an AECOPD.¹³⁹ Patients who maintain physical activity at a low level reduce the risk of hospital admission for COPD by 28% ($P = .033$) compared with little or no physical activity.¹³⁶

SUMMARY

AECOPDs are episodes of symptom worsening that have significant adverse consequences for patients. Exacerbations are highly heterogeneous events associated with increased airway and systemic inflammation and physiologic changes. The frequency of exacerbations is associated with accelerated lung function decline, quality of life impairment, and increased mortality. They are triggered predominantly by respiratory viruses and bacteria, which infect the lower airway and increase airway inflammation. A proportion of patients seem to be more susceptible to exacerbations, with poorer quality of life and more aggressive disease progression than those who have infrequent exacerbations. Exacerbations also contribute significantly to health care expenditure. Prevention and mitigation of exacerbations are therefore key goals of COPD management.

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