# Pneumonic versus Nonpneumonic Exacerbations of Chronic Obstructive Pulmonary Disease

Ernesto Crisafulli, MD, PhD[1,2] Alessandra Manco, MD[3] Miquel Ferrer, MD, PhD, FERS[4] Arturo Huerta, MD[4] Claudio Micheletto, MD[5] Domenico Girelli, MD, PhD[2] Enrico Clini, MD[6] Antoni Torres, MD, PhD, FERS, FCCP[4]

[1] Department of Medicine, Respiratory Medicine Unit, University of Verona and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy
[2] Department of Medicine, Section of Internal Medicine, University of Verona and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy
[3] Department of Medicine and Surgery, Respiratory Disease and Lung Function Unit, University of Parma, Parma, Italy
[4] Department of Pneumology, Respiratory Institute, Hospital Clinic of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), CIBERES (CB06/06/0028), University of Barcelona, Barcelona, Spain

**Address for correspondence** Antoni Torres, MD, PhD, FERS, FCCP, Department of Pneumology, Respiratory Institute, Hospital Clinic of Barcelona Villarroel 170, Barcelona 08036, Spain (e-mail: ATORRES@clinic.cat).

[5] Department of Cardiovascular and Thoracic, Pneumology Unit, Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy
[6] Department of Medical and Surgical Sciences, University of Modena and Reggio Emilia and University Hospital of Modena Policlinico, Modena, Italy

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## Abstract

Patients with chronic obstructive pulmonary disease (COPD) often suffer acute exacerbations (AECOPD) and community-acquired pneumonia (CAP), named nonpneumonic and pneumonic exacerbations of COPD, respectively. Abnormal host defense mechanisms may play a role in the specificity of the systemic inflammatory response. Given the association of this aspect to some biomarkers at admission (e.g., C-reactive protein), it can be used to help to discriminate AECOPD and CAP, especially in cases with doubtful infiltrates and advanced lung impairment. Fever, sputum purulence, chills, and pleuritic pain are typical clinical features of CAP in a patient with COPD, whereas isolated dyspnea at admission has been reported to predict AECOPD. Although CAP may have a worse outcome in terms of mortality (in hospital and short term), length of hospitalization, and early readmission rates, this has only been confirmed in a few prospective studies. There is a lack of methodologically sound research confirming the impact of severe AECOPD and COPD + CAP. Here, we review studies reporting head-to-head comparisons between AECOPD and CAP + COPD in hospitalized patients. We focus on the epidemiology, risk factors, systemic inflammatory response, clinical and microbiological characteristics, outcomes, and treatment approaches. Finally, we briefly discuss some proposals on how we should orient research in the future.

**Keywords**
- chronic obstructive pulmonary disease
- acute exacerbation
- community-acquired pneumonia
- pneumonic
- inflammatory response
- outcomes

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease and a leading cause of morbidity and mortality worldwide.[1] The occurrence of an acute event, defined as an acute exacerbation of COPD (AECOPD), interrupts clinical stability, and may lead to a functional[2] and clinical[3] deterioration. An AECOPD can be defined clinically as worsening dyspnea, cough, and/or sputum production beyond the normal day-to-day variability, resulting in the need for treatment change.[1] Patients with a severe AECOPD may require hospitalization[4] and specific management,[5] often with radiological evaluation by chest X-ray to exclude community-acquired pneumonia (CAP).

A finding of consolidation on chest X-ray is often taken to indicate distal airway or parenchymal infection. Although certain abnormalities seem to predict CAP (e.g., elevated hemidiaphragm, thick tracheoesophageal stripe, narrow

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cardiac silhouette, midchest pleural thickening, and prominent pulmonary artery shadow),[6] relying on such findings to define a critical transition from AECOPD to CAP may be too reductive in patients with advanced disease. In such setting, chest computed tomography (CT) can increase the chances of identifying a suspected CAP.[7] The inflammatory response may also be discriminatory, if not specific to CAP and AECOPD. C-reactive protein (CRP), for example, is a nonspecific acute phase protein produced by the liver in response to interleukin-6 (IL-6) stimulation.[8] The persistently high systemic inflammation status that is typical of severe COPD may be associated with a poor outcome,[9] influencing the immune response and the clinical expression of an acute event. AECOPD and CAP may therefore coexist in patients with severe COPD and be difficult to identify at hospital admission.[10] Indeed, it is estimated that one in five patients hospitalized with AECOPD have concomitant undiagnosed CAP.[10]

Severe AECOPD and CAP represent the two most common causes of respiratory failure in patients with COPD,[11] and many cases require intensive care unit (ICU) admission.[12] In these patients, it is still unknown whether AECOPD and CAP should be considered as separate entities with distinct clinical implications, or, alternatively, whether CAP merely represent a more invasive presentation of AECOPD. Although the recurrence of AECOPD[13] and CAP[14] are closely related to previous similar events,[15] individual susceptibility, and prognostic factors are common to both conditions. As such, severity scores are widely used in clinical decision making of adults with CAP, including the PSI (pneumonia severity index),[16] CURB65 (confusion, serum urea, respiratory rate, blood pressure, and age $\geq$ 65 years),[17] and CRB65 (serum urea removed from CURB-65).[18] Such scores have demonstrated prognostic efficacy in predicting short-term mortality and the severity of AECOPD.[19–21] Of note, a thorough evaluation of dyspnea in COPD patients during the stable phases has important prognostic implications. Indeed, a novel extended version of the Medical Research Council Dyspnea Scale (eMRCD), which adds information about the ability of patients to manage personal care (e.g., washing and dressing), has been demonstrated to predict mortality risk for patients with AECOPD complicated by CAP.[22]

In this manuscript, we review head-to-head comparisons of severe AECOPD and CAP (formerly representing nonpneumonic and pneumonic exacerbations, respectively) in patients with COPD requiring hospitalization. The choice to include not only patients admitted to ICU was related to the scarcity of published studies in the critical population and the close comparison of severe AECOPD and CAP. Methodologically, comparison has been performed in two different populations with COPD and acute events: first, CAP has been evaluated during AECOPD (AECOPD + CAP) and compared with AECOPD (AECOPD + CAP vs. AECOPD; ►**Table 1**); second, AECOPD and CAP have been compared individually (CAP vs. AECOPD; ►**Table 2**). We will start by considering the epidemiological impact and risk factors before moving on to the systemic inflammatory response, clinical and microbiological characteristics, outcomes, and treatment approaches. Finally, we will briefly propose some considerations about future research directions. We report descriptive statistics, incidence rates, odds ratios (ORs), relative risk (RR), and hazard ratios (HRs) with their 95% confidence intervals (95% CI), as appropriate.

## Search Strategy

We searched English language publications on PubMed, focusing on the past 10 years. Relevant publications were selected based on the following search terms: "chronic obstructive pulmonary disease" in combination with "exacerbation," "pneumonia," "risk factor," "inflammation," "biomarkers," "clinical," "hospitalization," "microbiology," "pathogens," "acute respiratory failure," "intensive care," "critical," "outcome," "mortality," "prognosis," and "survival." We restricted the search to human adults.

## Epidemiological Impact

Rates of hospitalization for AECOPD vary by countries, reflecting differences in the organization of health care systems.[23] A population-based survey of 4,343 patients with COPD (Continuing to Confront COPD International Patient Survey) conducted in 12 countries reported a mea n hospitalization rate of approximately 15%, with lowest rate in Japan (5%) and highest in Brazil (25%).[24] A recent analysis derived from a very large observational cohort ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; $n = 2{,}138$) that included a long follow-up (3 years) reported a higher prevalence of patients having at least one hospitalization for AECOPD (31%), with 15% having multiple events.[4]

The rate of hospitalization for CAP is approximately 10% among community-dwelling adults,[25] and the presence of COPD increases the risk of hospitalization by 49%.[25] A population analysis of >40,000 patients with COPD over 10 years reported that 8% experienced at least one CAP episode, producing an incidence rate of 22.4 per 1,000 person years (95% CI: 21.7–23.2) with no differences by sex.[26] Risk factors included age $\geq$ 80 years (46.1; 95% CI: 43.7–48.6), previous pneumonia (39.5; 95% CI: 35.4–44.1), and need of oxygen or nebulizer therapy (35.9; 95% CI: 33.8–38.1).[26] A very recent analysis of a population-based cohort in Louisville (the United States) indicated that the annual incidence of hospitalization in patients with COPD was approximately 18-fold greater than in patients without COPD (rate per 100,000 adults: 9,369 vs. 509).[27] Age $\geq$ 65 years also appears to cause an immune system dysregulation that predisposes to a greater risk of infection,[28] and the annual incidence of hospitalization for CAP was as high as 20,817 per 100,000 in adults with COPD compared with 1,188 per 100,000 in adults without COPD.[27] Due to the population aging, the trend in hospitalization for CAP increased between 2004 and 2013,[29] being higher in patients with COPD.[29] The economic burden of hospitalization is also higher in patients with COPD and CAP because of the increased severity, which in turn can lead to ICU admission.[30]

**Table 1** Comparison of characteristics by the presence of AECOPD Alone or AECOPD with CAP

| | Populations | Andreassen et al[59] | Myint et al[97] | Lu et al[62] | Yu et al[63] | Shin et al[60] | Søgaard et al[92] | Titova et al[61] |
|---|---|---|---|---|---|---|---|---|
| Year of publication | | 2014 | 2011 | 2016 | 2018 | 2019 | 2016 | 2019 |
| Country | | Norway–Sweden | The United Kingdom | China | China | Korea | Denmark | Norway |
| Design | | Retrospective | Retrospective | Retrospective | Retrospective | Prospective | Retrospective | Prospective |
| Setting | | Internal and respiratory medicine | Acute units | RICU | Respiratory ward | Respiratory centers | – | Department of thoracic medicine |
| Audit-collected data or health registry | | Yes | Yes | No | No | No | Yes | No |
| No of patients | AECOPD + CAP | 237 | 1,505 | 38 | 83 | 134 | 18,968 | 38 |
| | AECOPD | 472 | 7,833 | 42 | 81 | 174 | 33,552 | 80 |
| Radiological diagnosis of CAP | | Chest X-ray | Chest X-ray | Chest X-ray | Chest CT scan | Chest X-ray | – | Chest X-ray |
| Age, mean (y) | AECOPD + CAP | 75 | 75 | 74 | 76 | 73 | 75 (median) | 67 (median) |
| | AECOPD | 72 | 72 | 75 | 73 | 72 | 73 (median) | 71 (median) |
| Presence of CVD (%) | AECOPD + CAP | – | – | – | 42 | 28 | – | – |
| | AECOPD | – | – | – | 42 | 37 | – | – |
| ICS treatment (%) | AECOPD + CAP | 58 | – | – | 34[c] | 60 | 9 | 82[d] |
| | AECOPD | 67 | – | – | 25[c] | 57 | 10 | 71[d] |
| $FEV_1 < 50\%$ pred. (%) | AECOPD + CAP | 44 | 71 | – | 66 | 55 (mean) | – | 26 (median) |
| | AECOPD | 58 | 71 | – | 70 | 59 (mean) | – | 29 (median) |
| Prior events or admission[a] (%) | AECOPD + CAP | – | 53 | – | – | – | – | – |
| | AECOPD | – | 53 | – | – | – | – | – |
| Markers of early inflammation[b] | AECOPD + CAP | ↑ CRP | – | – | ↑ D-dimer | ↑ CRP | – | ↑ WBC, CRP, PCT |
| | AECOPD | – | – | – | – | – | – | – |
| Specific clinical sign and symptoms[b] | AECOPD + CAP | Fever | – | – | – | – | – | Fever, ↑ HR |
| | AECOPD | – | – | – | – | – | – | Expiratory wheezing, prolonged expiratory time, ↑RR |
| Specific pathogens involved[b] | AECOPD + CAP | – | – | – | – | ↑ *Streptococcus pneumoniae* | – | – |
| | AECOPD | – | – | – | – | – | – | – |
| Outcomes[b] | AECOPD + CAP | ↑ NIMV, ↑ LOS | ↑ mH, 90<br>↑ LOS | ↑ mH | ↑ LOS | ↑ m180 | ↑m30, ↑LOS, ↑NIMV, ↑ICU admission | – |
| | AECOPD | – | – | – | – | – | – | – |

Abbreviations: AECOPD acute exacerbation of chronic obstructive pulmonary disorder; CAP, community-acquired pneumonia; CRP, C-reactive protein; CT, computed tomography; CVD, cardiovascular disease; $FEV_1$, forced expiratory volume in 1 second; HR, heart rate; ICS, inhaled corticosteroids; ICU, intensive care unit; LOS, length of hospital stay; mH m30, m90, and m180, mortality at 30, 90, and 180 days; in-hospital; NIMV, noninvasive mechanical ventilation; PCT, procalcitonin; RICU, respiratory intensive care unit; RR, respiration rate; WBC, white blood cell.

[a]In the previous year.

[b]Were reported only variables significantly different between groups.

[c]Including, but not limited to, fluticasone, ambroxol, and theophylline.

[d]Regular medication, combination ICS with long-acting $\beta_2$ agonist.

Note: studies are reported in alphabetical order.

**Table 2** Comparison of characteristics by the presence of AECOPD or CAP

| | Populations | Boixeda et al[50] | Huerta et al[15] | Kim et al[51] | Sharafkhaneh et al[93] |
|---|---|---|---|---|---|
| Year of publication | | 2014 | 2013 | 2016 | 2017 |
| Country | | Spain | Spain | South Korea | The United States |
| Design | | Prospective | Prospective | Retrospective | Retrospective |
| Setting | | Internal and respiratory medicine, short stay unit. | Pneumology department | – | – |
| Audit-collected data or health registry/database | | No | No | No | Yes |
| No of patients | CAP | 20 | 116 | 236 | 3,478 |
| | AECOPD | 104 | 133 | 241 | 7,154 |
| Radiological diagnosis of CAP | | Chest X-ray | Chest X-ray | Chest X-ray | Chest X-ray or CT scan |
| Age, mean (y) | CAP | 70 | 72 | 73 | 70 |
| | AECOPD | 72 | 69 | 71 | 69 |
| Presence of CVD (%) | CAP | 50 | 29 | 9 | 41 |
| | AECOPD | 35 | 24 | 14 | 34 |
| ICS treatment (%) | CAP | – | 53 | – | 25 |
| | AECOPD | – | 56 | – | 19 |
| $FEV_1 < 50\%$ pred. (%) | CAP | 28 | 44 | 45 | – |
| | AECOPD | 69 | 61 | 57 | – |
| Prior events or admission[a] (%) | CAP | 15 | 58 | – | – |
| | AECOPD | 53 | 50 | – | – |
| Markers of early inflammation[b] | CAP | ↑ CRP | ↑ WBC, CRP, PCT, TNF-α, IL-1, IL-6, IL-8 | ↑ WBC, CRP, PCT, | – |
| | AECOPD | – | – | – | – |
| Specific clinical sign and symptoms[b] | CAP | Fever, crepitus on auscultation | Fever, chills, sputum purulence, pleuritic pain, ↑ DBP | – | – |
| | AECOPD | Rhonchi on auscultation, ↑ SBP, DBP | Dyspnea | – | – |
| Specific pathogens involved[b] | CAP | ↑ *Streptococcus pneumoniae* | ↑ *Streptococcus pneumoniae* | ↑ *Staphylococcus aureus* ↑ *Acinetobacter baumannii* | – |
| | AECOPD | ↑ *Pseudomonas aeruginosa* | ↑ *Haemophilus influenzae* | ↑ *Influenza A* | – |
| Outcomes[b] | CAP | – | – | ↑ LOS ↑ mH, m28 | ↑ mH, m30 ↑ IMV |
| | AECOPD | – | ↑ NIMV, ↑ Readmission in a period of 30 days | – | – |

Abbreviations: AECOPD acute exacerbation of chronic obstructive pulmonary disorder; CAP, community-acquired pneumonia; CRP, C-reactive protein; CT, computed tomography; CVD, cardiovascular disease; DBP, diastolic blood pressure; $FEV_1$, forced expiratory volume in 1 second; HR, heart rate; ICS, inhaled corticosteroids; ICU, intensive care unit; IL, interleukin; IMV, invasive mechanical ventilation; LOS, length of hospital stay; mH m30, m90, and m180, mortality at 30, 90, and 180 days; in-hospital; m28, mortality at 28 days; NIMV, noninvasive mechanical ventilation; PCT, procalcitonin; RICU, respiratory intensive care unit; RR, respiration rate; TNF-α, tumor necrosis factor-α; WBC, white blood cell.
Note: Studies are reported in alphabetical order.
[a]In the previous year.
[b]Were reported only variables significantly different between groups.

## Risk Factors

Several risk factors for hospitalization have been identified in patients with AECOPD,[23] including the severity of dyspnea,[31] body mass index,[32] comorbidities,[33] education and income class,[34] and marriage status.[35] Other important factors associated with an increased risk of admission for AECOPD are a previous episode requiring hospitalization within 1 year (HR = 2.71; 95% CI: 2.24–3.29), progression of airflow obstruction (HR = 1.12; 95% CI: 1.09–1.16 per 5% drop of the forced expiratory volume in 1s [$FEV_1$]), old age (HR = 1.29; 95%CI: 1.13–1.46 per 10-year increment), evidence of emphysema (HR = 1.56; 95% CI: 1.23–1.97 per 5% by radiology), poor health status (HR = 1.08; 95% CI 1.06–1.10 per four-point increase in the total St. George's Respiratory Questionnaire score), and a higher white blood cell count (WBC; HR = 1.15; 95% CI: 1.07–1.24 per $1 \times 10^9$ L of WBC).[4]

COPD is also a risk factor for CAP,[36] including greater severity[37] and the need for hospitalization.[25] Compared with individuals without COPD, those with COPD are estimated to be at a 1.3- to 13.5-fold increased risk of developing CAP.[36] The incidence has a clear seasonal pattern, with the highest rates of CAP in the winter period, especially in December.[38] Along with liver, renal, and neurological disorders, COPD is an independent host risk factor for severe CAP (OR = 1.30; 95% CI: 1.01–1.67) presenting to the emergency room with at least two organ dysfunctions.[38] These severe cases of CAP account for 11% of all cases and are associated with greater and early mortality compared with cases with one or no organ dysfunctions (12.4 vs. 3.4%).[39]

In general, hospitalization for CAP in patients with COPD is associated with the severity of airflow obstruction.[40] After adjusting for other potential confounders, COPD patients with $FEV_1$ percent predicted values of <50% (HR = 5.65; 95% CI: 3.29–9.67), and 50 to 80% (HR = 2.25; 95% CI: 1.35–3.75) were at increased risk of CAP compared with controls with normal lung function.[40] Similarly, another study underlined the increased risk of CAP in patients with severe respiratory conditions, marked by the degree of airflow limitation.[41]

Data about smoking status in patients with COPD are discordant, showing increased risk of CAP[40] or no effect.[42] Although smoking may contribute to the development of COPD by different pathways,[43] Braeken et al[42] reported that patients with COPD who currently smoked had a comparable risk of CAP to never smoking COPD patients (HR = 0.92; 95% CI: 0.82–1.02).

The presence of comorbidities as a risk factor for CAP has been often demonstrated in patients with COPD.[26,40,44] In particular, the presence of congestive heart failure (OR = 1.37; 95% CI: 1.20–1.57), dementia (OR = 2.64; 95% CI: 1.86–3.75), peptic ulcer (OR = 1.22; 95% CI: 1.06–1.41), peripheral vascular disease (OR = 1.27; 95% CI: 1.05–1.55), and connective tissue disease (OR = 1.16; 95% CI: 1.04–1.30) were shown to be significantly associated with an increased risk of CAP.[26] The retrospective study by Lin et al[44] confirmed that there was a close relationship between the presence of COPD and cardiovascular disease, with an increased risk of CAP compared with patients with COPD and no cardiovascular disease (HR = 1.31).

A common treatment for COPD, inhaled corticosteroids (ICS) use has been reported as a risk factor for CAP-related hospitalizations. After adjusting for several confounders (age, sex, serum albumin levels, smoking status, history of congestive heart failure, coronary artery disease, and COPD, current use of proton pump inhibitors, $\beta_2$ agonist and anticholinergic bronchodilators, antibiotics, iron supplement, narcotics, and nonsteroidal anti-inflammatory drugs) a case-control study in adults aged ≥ 65 years demonstrated an increasing risk of CAP in patients using ICS (adjusted OR = 2.89, 95% CI: 1.56–5.35).[45] Moreover, Lin et al also showed that ICS further increased the risk of CAP in patients with COPD and cardiovascular disease (HR = 1.64).[44] A recent Cochrane review also assessed the risk of CAP with fluticasone and budesonide use and concluded that these medications were associated with an increased risk of serious pneumonia requiring hospital admission, although mortality was not significantly affected compared with controls.[46] This finding was consistent whether ICS were delivered alone or in combination with a long-acting β2 agonist (LABA).

Recent data from the Copenhagen General Population Study has also highlighted the role of eosinophils in the promotion of CAP.[47] In patients with COPD and severe airflow obstruction ($FEV_1$ < 50% predicted), a blood eosinophil count ≥ $0.34\,10^9$ cells·$L^{-1}$ was associated with an increased risk of hospitalization due to CAP. Of note, this risk was independent of inflammatory biomarkers, ICS use, and prior pneumonia events.[47]

## Systemic Inflammatory Response

Different systemic inflammatory responses have been reported according to the presence/absence of COPD and/or the specific acute event.[48,49] Patients with CAP but without COPD have an increased systemic inflammatory response compared with those with AECOPD[48] or CAP + COPD.[49] The lower early inflammatory response in patients with COPD and CAP has been shown to be disease-specific and not completely mediated by ICS use in a prospective Spanish study.[49] Indeed, this study showed that patients with COPD and CAP have lower serum levels of tumor necrosis factor-α (TNF-α) and cytokines (IL-1 and IL-6) at hospital admission compared with those with CAP only. However, CAP produces a stronger response than AECOPD in patients with COPD in terms of white blood cells (WBC), CRP, and procalcitonin levels.[15,50,51] The higher inflammatory response in patients with COPD and CAP persists at 3 days from admission (e.g., TNF-α, IL-1, IL-6, and IL-8) and appears unaffected by the disease severity, current inhaled therapy (included ICS), and noninfectious AECOPD,[15] suggesting this is as an innate immune response of different inflammatory phenotypes.[52,53]

In healthy patients, the activity of alveolar macrophages is crucial for maintaining lung sterility. When a patient develops a bacterial infection, such as CAP, the first line of host defense involves the activation of resident phagocytes, and recruitment of further monocyte-derived macrophages, which produce multiple proinflammatory mediators, especially in the early phase.[54] Although patients with COPD have increased numbers of alveolar macrophages, such cells display a significantly

reduced capacity of bacterial phagocytosis and are prone to apoptosis (efferocytosis). This alteration may play a role in chronic bacterial colonization of the lower airways and failure to resolve inflammation.[55,56] Different mechanisms involving alveolar macrophages and/or phagocytosis in response to infection may concur in a specific early inflammatory pattern.[52,53] The microenvironment of the lungs could modify the common inflammatory response by inducing different activations and phenotypes of alveolar macrophages.[52,53] Sputum samples derived from patients with AECOPD, CAP, or CAP + COPD have been evaluated for monocytic $THP_1$ cells differentiated to macrophages, while the expressions of TNF-α, IL-6, mannose receptor, and arginase have been measured to evaluate the phenotype acquired by macrophages.[52] In patients with CAP and with AECOPD macrophages showed increased inflammatory biomarker expression with classical $M_1$- and $M_2$-like activation pathways.[52] By contrast, patients with COPD and CAP displayed nonsignificant expression of cytokines without $M_1$ or $M_2$ activation.[52] Moreover, a selective dysfunctional phagocytosis has been demonstrated for a diverse range of respiratory pathogens.[57,58] Alveolar macrophages of former and active smokers with COPD showed impaired complement-independent phagocytosis of non-typeable *Haemophilus influenzae* and *Moraxella catarrhalis*, but not *Streptococcus pneumoniae*, with this impairment being correlated to the severity of airflow limitation.[57] Subsequent studies in patients with AECOPD have demonstrated an impaired innate response of alveolar macrophages to respiratory pathogens (e.g., nontypeable *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae*) mediated by impaired response to toll-like receptors 2 and 4.[58]

Studies comparing pneumonic and nonpneumonic exacerbations of COPD confirm that CRP, procalcitonin, and WBC levels are higher in patients with AECOPD + CAP than in patients with AECOPD only.[59–61] However, a retrospective Chinese study in a small sample of critically ill COPD patients found a similar inflammatory response, with mean CRP levels of 43 and 49 mg/L for AECOPD + CAP and AECOPD, respectively.[62] Another retrospective Chinese case-control study[63] on hospitalized COPD patients also found no differences in WBC, neutrophil, and CRP levels between AECOPD + CAP and AECOPD groups, although the percentage of neutrophils increased from baseline. Generally considered a marker of bacterial infection,[64] this increase was shown to be a protective factor for pneumonia, probably due to the early use of antibiotics that delayed progression in patients with AECOPD.[63] Of note, the level of D-dimer was higher for patients with AECOPD + CAP and predicted the presence of CAP,[63] suggesting its potential utility as a diagnostic tool for identifying infection.[65]

Recently, the combination of CRP and CURB-65 has proven useful for predicting ICU admission and mortality in patients with CAP.[66] Although elevated CRP may predict the development of CT abnormalities, such as consolidation, ground glass opacities, and pleural effusion in patients with AECOPD,[67] admission levels can be used to predict CAP in patients with COPD.[15] In fact, using a lower quartile (CRP $\leq$ 3.5 mg/dL; OR = 1) as a reference, there is a progressive increase in the risk of CAP for patients with CRP levels of 3.6 to 11.9 mg/dL (OR = 4.02; 95% CI: 1.8–9.9), 12 to 20.4 mg/dL (OR = 5.75; 95% CI: 3.2–12.7), and $\geq$20 mg/dL (OR = 10.6; 95% CI: 4–25.4).[15] The best CRP cut-off for discriminating CAP versus AECOPD was 12.9 mg/dL (area under the curve 0.71; 95% CI: 0.65–0.78; $p < 0.001$).[15] Although procalcitonin cannot distinguish bacterial from viral or noninfectious causes of AECOPD,[68] its use as a single test at admission had demonstrated comparable diagnostic accuracy to CRP and WBC levels when diagnosing CAP in patients hospitalized with AECOPD.[61] Interestingly, this accuracy was not increased when combined with the presence of expiratory wheezing and increases in heart rate, respiratory rate, and body temperature.[61]

## Clinical and Microbiological Characteristics

In COPD patients, with CAP or AECOPD different clinical characteristics have been reported.[15,50,59,61,63] At hospital admission, the presence of chills (63 vs. 28%), pleuritic pain (36 vs. 13%), and purulent (or rusty) sputum (37 vs. 16%) were more specific for CAP than for AECOPD.[15] By contrast, dyspnea (98 vs. 82%) was most frequently observed in AECOPD.[15] Fever is highly prevalent in both CAP[15,50] and AECOPD + CAP,[59,61,63] and its presence at admission does not reliably predict CAP.[15] Among patients hospitalized with severe AECOPD, the presence of fever has been considered "protective" against CAP (OR = 0.42; 95% CI: 0.18–0.96; $p = 0.042$),[63] probably by inducing earlier antibiotic therapy and attention from clinicians. Although confusion has been considered a prevalent symptom of CAP (8.6 and 3.9% in AECOPD + CAP and AECOPD, respectively),[61] it is not discriminatory.[61] On the other hand, expiratory wheezing and a higher respiratory rate appear specific for AECOPD, while increased heart rate appears specific for AECOPD + CAP.[61] Crepitus and rhonchi on auscultation are characteristics of CAP (45 vs. 14%) and AECOPD (86 vs. 60%), respectively.[50]

Patients with COPD are at increased risk of infection, even by multiple pathogens,[69] with different agents often characterizing AECOPD versus CAP. Viral and/or bacterial infections account for approximately 80% of AECOPD episodes.[70] *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae* have been classically associated with an increasing risk.[71] However, retrospective data for more than 500 patients with AECOPD demonstrated that *Pseudomonas aeruginosa* was the most common pathogen, followed in decreasing order by *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Acinetobacter baumannii*, and *H. influenzae*.[72] *P. aeruginosa* was especially common in patients with severe COPD and the highest degree of airflow obstruction.[72] Recent evidence has also revealed that 40% of patients hospitalized for AECOPD with positive respiratory cultures have microorganisms resistant to conventional treatment (e.g., *P. aeruginosa*, methicillin-resistant *S. aureus*, *Stenotrophomonas maltophilia*, extended-spectrum β-lactamase-producing *Enterobacteriaceae*, and *A. baumannii*).[73]

In general, detection of the infective cause of CAP has been reported to be protective against disease progression.[74] Hospitalized patients with COPD and CAP are at increased risk of infection by pathogens with a potential antibiotic resistance (e.g., the so-called PES organisms: *P. aeruginosa*, extended-spectrum β-lactamase-producing *Enterobacteriaceae*, and

methicillin-resistant *S. aureus*; OR = 2.20; 95% CI: 1.36–3.57).[75] Patients with COPD also have a high likelihood of coinfection by bacteria and influenza A ($H_1N_1$) or another virus (OR = 9.66; 95% CI: 1.93–48.31).[76]

*S. pneumoniae* is the most frequently detected pathogen in patients with COPD and CAP[37,77,78] as compared with those with AECOPD only (43 vs. 10%; $p < 0.001$).[15] A laboratory-based study on COPD patients reported that *S. pneumoniae* serotype 3 was a common cause of CAP and AECOPD, while serotypes 1, 4, 5, and 8 were more detected in patients with CAP without COPD.[79] Increased respiratory epithelial expression of the platelet-activating factor receptor (PAFr), a bacterial adhesion factor, could explain the increased risk of infection by *S. pneumoniae* in patients with COPD.[80] Interestingly, this mechanism was not present for non-typeable *H. influenza*, and it was hypothesized that the impact of smoking was strongly related to epithelial PAFr protein levels.[80] Consistently, although *H. influenzae* has been reported to be frequently associated with CAP in patients with COPD,[81,82] a Spanish prospective study reported that this pathogen was more prevalent in AECOPD.[15]

*P. aeruginosa* and *M. catarrhalis*, which are rarely detected in adults with CAP without COPD, may play important roles as pathogens in COPD, particularly in patients with advanced disease.[49,83] In fact, a multicenter study on >3,000 hospitalized patients with CAP confirmed the higher prevalence of *P. aeruginosa* infection (42.9%) compared with non-*P. aeruginosa* infection (25.4%).[84] Airflow limitation has shown as an independent risk factor for *P. aeruginosa* infection,[85] patients with severe COPD having a more than doubled risk of this infection (OR = 2.76; 95% CI: 1.25–6.06).[84] The prevalence rates of atypical pathogens (e.g., *Legionella species*, *Coxiella burnetii*, *Mycoplasma pneumoniae*, and *Chlamydia species*) are low (3.8%) compared with other pathogens (57.2%) in patients with COPD.[86] Compared with AECOPD, a higher percentage of *S. aureus* infection was found in patients with COPD (10%) and CAP (3%), with most being methicillin sensitive (75%).[51] Multivariate regression analyses accounting for age and comorbidities have been used to predict specific causal pathogens in CAP. For example, one study reported that COPD was associated with *S. aureus* (OR = 2.80; 95% CI: 1.24–6.30) and *P. aeruginosa* (OR = 2.69; 95% CI: 1.46–4.97) in patients aged > 65 years, and with *H. influenzae* (OR = 3.39; 95% CI: 1.06–10.83) in patients aged 45 to 65 years.[87] Infections by respiratory viruses were frequently identified as causes of AECOPD, and as concomitant pathogens of CAP.[51] A retrospective cohort study reported viral causes of exacerbation in 42% and 33% of patients with AECOPD and CAP, respectively.[51] The most common viruses in patients with AECOPD and COPD + CAP were influenza (34%; typically influenza A) and human coronavirus (24%; typically 229-E/NL63), respectively.[51]

## Outcomes

The occurrence of an AECOPD negatively affects COPD progression,[88,89] whereas CAP may[90] or may not[83] result in worse clinical outcomes. In patients with pneumococcal CAP, the presence of COPD has been reported to be protective against pulmonary complications (e.g., pleural effusion, empyema, or multilobar infiltrates).[91] Comparing pneumonic and nonpneumonic exacerbations, several potential methodological criticisms of published studies may explain the conflicting outcomes. First, COPD cohorts may include coexisting respiratory comorbidities, such as sleep apnea-hypopnea syndrome,[50] asthma,[92] lung cancer,[93] pulmonary thromboembolism,[93] or bronchiectasis.[50,94,95] Second, COPD cohorts may include other nonrespiratory comorbidities, such as immunosuppression (e.g., hematopoietic stem cell transplant or chemotherapy treatments),[51] chronic liver disease,[51,93,96] and advanced neurological disease,[93] which may increase the risk of food aspiration resulting in less diagnostic accuracy. Third, studies were highly heterogeneous with respect to comparator groups (e.g., non-COPD patients[93]), design (e.g., retrospective[51,59,62,63]), or data source (e.g., from audit data[59,97] or from health care resource databases[92,93]).

Patients with severe AECOPD have higher mortality risk.[4,88] In a study with a follow-up period of 3 years, the mortality rate in patients hospitalized with AECOPD was 9.4%.[4] This was independent of the severity of airflow limitation, and was higher in patients reporting ≥ 1 hospitalization for AECOPD during the first year of follow-up (15 vs. 5% in those with no previous admission 5%).[4] Having had at least one previous hospitalization for AECOPD also predicted early readmission within 30 days of discharge.[98] Readmission, a marker of more severe disease accounting for 18% of patients hospitalized with AECOPD, was also shown to be an independent risk factor for mortality in both short- and long-term follow-up.[99,100] Several predictors of early readmission with AECOPD have been described.[101–103] A Canadian study considering a long follow-up (17 years) in a large cohort of hospitalized patients with COPD (>70,000) reported a mortality rate of 69%, with deaths peaking in the first week of hospitalization.[88] Several factors have been associated with the increased mortality in severe AECOPD,[23] including older age, male sex, prior hospitalization, weight loss/low body mass index, pulmonary hypertension, lung cancer, and need for long-term oxygen therapy at discharge.[23] Mortality has been also associated with preexisting comorbidities (e.g., coronary heart disease and stroke),[104] while other negative outcomes may be merely related to treatment failure[105] or to a prolonged length of hospital stay (LOS).[106]

Recent epidemiological data estimates mortality rate for COPD patients hospitalized with CAP at 30 days, 6 months, and 1 year, of 6, 12, 24, and 33%, respectively.[27] The impact of COPD on mortality in CAP patients[36,83,90,107] may be partially related to the functional stage of the disease assessed by spirometry[83,90,108] and data on prediction of 30-days mortality were conflicting.[83,90] Patients with COPD and pneumococcal bacteremia have not shown an increased risk of death.[109] A recent meta-analysis[107] demonstrated that preexisting COPD in hospitalized patients with CAP did not affect mortality in prospective studies (RR = 1.20; 95% CI: 0.92–1.56), while it was reduced in case-control studies (RR = 0.82; 95% CI: 0.74–0.90). Although the in-hospital mortality, 30-day mortality, and 6-month mortality rates were not influenced by COPD, the mortality risk at 1 year

was significantly increased by a diagnosis of COPD (25% greater).[27]

The presence of host risk factors may play a confounding role in patients with COPD. For instance, the age of patients hospitalized with CAP, appears to be an important risk factor for long-term mortality in both the general population (HR = 1.83 per decade; 95% CI: 1.47–2.28)[110] and in patients with COPD.[111] In either case, an age $\geq$ 80 years should be considered a risk factor for poor outcomes from CAP.[112] The presence of a prior cardiovascular disease has also been shown to increase mortality at 90 days, 6 months, and 1 year[113] in elderly COPD patients hospitalized for CAP.

Factors related to CAP severity also affect mortality in COPD patients, including the presence of hypoxemia[90] and hypercapnia[90] at admission, or the need for noninvasive mechanical ventilation (NIMV).[114] However, although the presence of COPD at admission has been demonstrated to be a risk factor for acute respiratory failure (OR = 2.08; 95% CI: 1.60–2.70),[115] severe sepsis (OR = 1.75; 95% CI: 1.50–2.04),[116] and acute respiratory failure plus severe sepsis (OR = 1.85; 95% CI: 1.34–2.56),[115] prior COPD did not influence in-hospital mortality (OR = 1.00; 95% CI: 0.68–1.47).[115] Also, although prior ICS treatment has not been shown to alter the clinical presentation in patients with AECOPD,[117] it may reduce the incidence of some complication (e.g., parapneumonic effusion) in patients with CAP.[118] Similarly, systemic corticosteroid treatment reduces treatment failure rates in patients with severe CAP[119] and has a protective role against mortality for patients COPD admitted to ICU with CAP.[120] Typically, LOS and time to clinical stability are also similar between patients with CAP and CAP + COPD.[27,107]

Meaningful comparisons between nonpneumonic and pneumonic exacerbations of COPD are difficult for the many reasons outlined above. In general, studies comparing AECOPD with CAP have failed to demonstrate differences in LOS,[15,50] treatment failure,[50] use of invasive mechanical ventilation,[50] ICU admission,[15,50] and short- or long-term follow-up outcomes.[15,50] Of note, more AECOPD patients with require long-term oxygen therapy and NIMV at admission (6%) as compared with CAP patients (1%),[15] likely due to their greater lung function impairments. Moreover, although the rate of early readmission was higher in AECOPD, readmission at 90 days or 1 year were similar to CAP.[15] A retrospective study by Kim et al[51] yielded discordant results concerning LOS, mechanical ventilation, in-hospital mortality, and 28-day mortality,[51] all reported worse in CAP as compared with AECOPD. In CAP patients, in-hospital mortality differed according to the presence of viral infection (2.6%), bacterial infection (25.8%), and viral-bacterial coinfection (17.5%; $p = 0.01$), while different infections did not influence mortality in AECOPD.[51] AECOPD + CAP and AECOPD also did not differ with respect to the need of NIMV ICU admission,[63] or mortality during hospitalization,[59] at 1[63] and 5 years.[121] However, a prospective study[60] reported a worse cumulative survival at 6 months for AECOPD + CAP compared with AECOPD alone (HR = 1.98; 95% CI: 1.16–3.37; $p = 0.012$); interestingly, this effect was influenced by early readmission.[60]

With regard to critical COPD patients admitted to ICU the risk rate of death due to CAP was significantly high (HR 1.27; 95% CI 1.01 to 1.59)[12]: 59% of reasons for ICU mortality were related to CAP.[122] Similarly, in ICU patients with AECOPD + CAP in-hospital mortality was higher than in AECOPD patients without CAP (42 vs. 33.3%).[62] However, this study did not report the ICU admission criteria for severe CAP,[123] which may have influenced patient mortality independent of the presence of CAP.[124]

## Treatment Considerations

Steroids and antibiotics are frequently used in cases of severe AECOPD and CAP. In patients with AECOPD, systemic steroids have proven efficacy in improving functional variables (e.g., oxygenation and airflow obstruction), as well as in reducing LOS, and treatment failure rates.[125–127] Short-term treatment with prednisone/prednisolone is the preferred regimen.[128] Studies on critically ill patients[127,129] have partially confirmed the efficacy of steroids in AECOPD. In acidotic patients admitted to ICU, the use of methylprednisolone reduced the median duration of mechanical ventilation compared with placebo,[127] whereas the use of prednisone had no effect on ICU mortality, duration of mechanical ventilation, or ICU stay.[129] Differences in the steroid doses[127,129] and in severity of respiratory acidosis[129] may explain these conflicting results. In patients with severe CAP, a recent Cochrane review concluded that short-term treatment with systemic steroids has proven safe and useful in reducing mortality, likely through a specific effect on the dysregulated inflammatory response.[130] Other important advantages included reduction of the length of ICU stay, overall LOS, respiratory failure, and shock.[130] In-hospital corticosteroid treatment was associated with a lower incidence of myocardial infarction in adults hospitalized with CAP.[131] All these benefits are evident in patients with CAP, irrespective of preexisting COPD and CAP. Of note, the Cochrane review[130] did not perform a subgroup analysis in CAP patients with or without COPD because of the paucity of trials providing relevant data. Anyway a key to the success of steroids appears to be the inflammatory response at admission. A study on patients with severe CAP and a high inflammatory response at admission (CRP > 150 mg/L), reported that methylprednisolone for 5 days reduced treatment failure (a composite outcome of clinical disease progression until death).[119] However, that trial included few patients with preexisting chronic pulmonary disease (16%).

Antibiotics are typically administered to AECOPD patients with suspected bacterial infection, which in turn is the more prevalent cause of exacerbation.[70] Sputum color is considered to predict a positive culture.[132] In AECOPD requiring mechanical ventilation, potentially pathogenic microorganisms and a positive serology were present in 72%.[133] Thus, antibiotic use is recommended in AECOPD, especially for patients with severe presentations. A Cochrane review[134] further showed that patients admitted to ICU gain the greatest benefits from antibiotics among patients with severe AECOPD requiring hospitalization. In patients requiring

mechanical ventilation, the use of ofloxacin compared with placebo reduced hospital and ICU mortality rates, the need for additional antibiotic courses, and combined events.[135] Patients treated with ofloxacin also had fewer days of mechanical ventilation, shorter LOS, and shorter ICU stays.[135] In another trial of patients with severe AECOPD,[136] the efficacy of trimethoprim-sulfamethoxazole was similar to ciprofloxacin. It is commonly accepted that early antibiotic treatment is required for patients with CAP,[137] but to date, no randomized trials have specifically assessed this approach in patients with severe disease. Overall, the optimal strategy is still far from being established, highlighting the need of developing new approaches.[138]

*S. pneumoniae* remains the main cause of CAP, but COPD increases the risk for infection with specific pathogens, such as *P. aeruginosa*[84] or PES organisms.[75] Such risk must be considered when choosing antibiotics, with particular reference to fluoroquinolones.[139] In CAP, there is a general consensus[140] on the use of β-lactams (cefotaxime, ceftriaxone, or ampicillin sulbactam) plus either azithromycin or a respiratory fluoroquinolone,[140] as first choice in patients admitted to ICU. Although the same efficacy has been demonstrated for patients treated with a β-lactam monotherapy and a β-lactam plus macrolide or quinolone,[141] in CAP patients with preexisting COPD the risk of other etiologies may justify the use of empirical broader spectrum therapy, which should also include a carbapenem to cover both *S. pneumoniae* and *H. influenzae*.[138]

In severe AECOPD with acute respiratory acidosis at admission ($pH < 7.35$), NIMV has proven efficacy and is strongly recommended.[142] NIMV has also been proposed for patients without acidosis, although this remains a low-evidence conditional recommendation.[142] Few studies have evaluated the management of severe CAP in patients with acute respiratory failure. In one study, the success of NIMV ranged from 20 to 76% and appeared to correlate with the underlying mechanism, with the greatest benefits in patients with hypercapnic COPD or cardiogenic pulmonary edema.[143] Helmet-delivered continuous positive airway pressure was also proven to ameliorate oxygenation in CAP patients with moderate hypoxemic acute respiratory failure.[144]

Oxygen therapy by high-flow nasal cannula (HFNC) is a recently developed simple therapeutic option to deliver high fractions of inspired oxygen ($FiO_2$). It generates a low level of positive pressure and a washout of the nasopharyngeal dead space to improve oxygenation and breathing patterns, thereby reducing the work of breathing.[145] Although HFNC has been considered as an alternative approach in ICU patients with severe hypoxemic acute respiratory failure,[146] a Cochrane review with limited data was unable to confirm its superiority as compared with other oxygenation devices.[147] Similarly, HFNC showed no clear benefits over NIMV in severe AECOPD and moderate hypercapnic acute respiratory failure.[148] In severe CAP with acute respiratory failure, the ratio of pulse oximetry/fraction of inspired oxygen to respiratory rate (defined as ROX-index, i.e., respiratory rate-oxygenation) predicted HFNC failure and the need for mechanical ventilation.[149]

No studies have evaluated the role of HFNC in patients with COPD and acute respiratory failure due to severe CAP.

## Future Directions

From the discussion above, it is clear the need of more methodologically sound research comparing nonpneumonic and pneumonic exacerbations in COPD cohorts without confounding factors. Indeed, only few studies were prospective,[15,50,60,61] and enrolled limited number of CAP patients (e.g., $n < 40$[50,61]; ►**Tables 1** and **2**). Retrospective analyses including[59,92,93,97] wide cohorts allowed some insights, but preclude any definitive conclusion. An interesting aspect that is yet to be clarified is the predictive value of baseline specific immune-pathological status in the lung periphery (cell lines) and how this integrates with blood-based mediators. This aspect could suggest the presence of susceptibility to a given pneumonic or nonpneumonic event.[13–15] The possibility of identifying selective predictors of an early inflammatory response in a preevent phase could pave the way for meaningful preventive therapy.

## Conclusion

COPD is highly prevalent worldwide, with CAP and AECOPD being the two most prevalent frequent acute events. They appear to be related to abnormal host defense mechanisms toward infection. The specificity of the systemic inflammatory response (which is incompletely related to COPD severity, ICS use, and infective etiology), and the typology of recurrent events suggest that acute events are influenced by different immune-pathological profiles. Although CAP may be expected having a worse outcome than AECOPD, this has not confirmed by most prospective studies. The likelihood of detecting CAP early in the course of an AECOPD by increased clinical vigilance is likely crucial. Also, timely and appropriate evaluation of biomarkers like CRP may be useful in patients with unclear infiltrates, especially when advanced lung impairment makes particularly difficult their identification. In patients with a high-inflammatory pattern, chest CT may increase the diagnostic accuracy and help to optimize therapy.

### Authors' Contributions

Drafting the work or revising it critically for important intellectual content was done by E.C., A.M., M.F., A.H., D.G., C.M., E.C. Final approval of the version submitted for publication by E.C. and A.T.

### Conflict of Interest

None declared.

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