

# The recent advances of phenotypes in acute exacerbations of COPD

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**Abstract:** Exacerbations of COPD are clinically relevant events with therapeutic and prognostic implications. Yet, significant heterogeneity of clinical presentation and disease progression exists within acute exacerbations of COPD (AECOPD). Currently, different phenotypes have been widely used to describe the characteristics among patients with AECOPD. This has proved to be significant in the treatment and prediction of the outcomes of the disease. In this review of published literature, the phenotypes of AECOPD were classified according to etiology, inflammatory biomarkers, clinical manifestation, comorbidity, the frequency of exacerbations, and so on. This review concentrates on advancements in the use of phenotypes of AECOPD.

**Keywords:** COPD, acute exacerbation, phenotype, treatment, prognosis

## Abbreviations

ACOS, asthma–COPD overlap syndrome; AECOPD, acute exacerbations of COPD; BODE, body mass index, airflow obstruction, dyspnea, and exercise capacity; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; CRP, C-reactive protein; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; FeNO, fractional exhaled nitric oxide; FEV<sub>1</sub>, forced expiratory volume in 1 second; GesEPOC, Spanish COPD guidelines; GOLD, Global Initiative for Chronic Obstructive Lung Disease; 4-HNE, 4-human neutrophil elastase; ICS, inhaled corticosteroids; ICU, intensive care unit; IL-6, interleukin-6; MBL, mannose-binding lectin; MMP-9, matrix metalloproteinase-9; mMRC, modified medical research council; MPO, myeloperoxidase; NETT, National Emphysema Treatment Trial; PF4, platelet factor 4; PCT, procalcitonin; SAA, serum amyloid protein A; SP-D, serum surfactant protein-D; TNT, troponin-T; VEGF, vascular endothelial growth factor.

## Introduction

AECOPD is an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variation and leads to change in medication.<sup>1</sup> At first glance, this definition seems straightforward. However, it has several caveats and unknowns that differ according to each patient's pathobiological heterogeneity and different clinical presentation and management needs.

COPD phenotype is defined as “a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes”. Therefore, the phenotype should be able to be used to classify patients into subgroups with a prognostic value that allows determining the best treatment in order to achieve better clinical results.<sup>2</sup> In this way, we can take on a more personalized treatment according to the severity of the airflow obstruction and

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conditioned by the clinical phenotype. Recent findings suggest that exacerbations of COPD are heterogeneous events and that this heterogeneity might have clinically relevant therapeutic and prognostic effects.<sup>3</sup> In a viewpoint published in the journal *The Lancet Respiratory Medicine*,<sup>4</sup> the authors proposed a two-axis classification of exacerbations of COPD by considering the pathobiological and clinical heterogeneity of exacerbations of COPD. They stratified patients into four groups (E1–E4), each of which might need a different treatment strategy and have a different short-term risk, and hence the need for a different care setting. Unfortunately, phenotype in AECOPD is still in a stage of exploration. It has always been classified based on different etiologies, clinical manifestations, biomarkers, comorbidities, frequencies of exacerbation, and so on. In this review, we mainly focus on the phenotypes that have been proven to have a therapeutic or prognostic effect on patients with AECOPD.

## Methods

### Search strategy

A review was performed to identify research articles or meta-analysis from 1986 to 2016 that assessed the characteristics, including etiology, manifestation, inflammatory cells, comorbidity, and frequency of exacerbation, which are related to different therapies or prognosis of patients with AECOPD. This review was performed on September 5, 2016, in PubMed. The search strategy is shown in Table 1.

### Eligibility criteria for study selection

Studies including articles or meta-analysis that focused on any one of the characteristics associated with different therapies or prognosis of the patients with AECOPD were included. Patients must be subjects older than 40 years diagnosed with AECOPD. Articles were excluded if they did not show the different traits based on the phenotypes, subgroups, or heterogeneity. Studies that tested empirically defined phenotypes without an analytical justification of these phenotypes and those that concentrated on the phenotypes in stable

COPD were excluded. Moreover, the abstracts of the articles not published in English were excluded. Two independent authors (AZ and ZZ) reviewed the title and abstract against the inclusion criteria. Disagreements between reviewers were resolved through the third reviewer by discussion.

### Etiology phenotypes

It is well known that AECOPD may be triggered by infection with bacteria or viruses or by noninfectious environmental (eg, temperature, pollution, allergens, and diet) or internal (immune dysregulation) factors. The cause of approximately one-third of exacerbations cannot be identified.<sup>5–7</sup> Patients with detectable respiratory pathogens have been shown to exhibit a more marked impact on lung function and longer duration of hospitalization than patients with exacerbations of noninfectious etiology.<sup>8</sup> With in-depth studies of microorganisms, some research concludes that there are differences in the clinical manifestation, treatment, and prognosis between bacterial infections and viral infections. Sore throat, cough, dyspnea, and chills are more common in viral infections than in bacterial infections.<sup>9</sup> Viral exacerbations are associated with higher IL-6 levels,<sup>10</sup> lower levels of CRP,<sup>11</sup> and longer duration of hospital stay (average 9 days).<sup>12</sup> However, as for antiviral treatment, the current therapies for the virus-induced exacerbations are not very effective.<sup>12</sup> The guideline about the lower respiratory tract infection treatment published in 2011 by the European Respiratory Society pointed out that AECOPD patients usually were not recommended to have empiric antiviral treatment. However, if in flu season, or at high risk of flu, patients with typical influenza symptoms (such as fever, muscle pain, muscle weakness, and respiratory infection symptoms), if onset is within 2 days, should have antiviral treatment as early as possible.<sup>13</sup> In bacterial exacerbations, purulent sputum is the typical symptom, as is neutrophil inflammation in both blood and airway. Levels of CRP and PCT would be higher than those in non-bacterial exacerbations.<sup>14</sup> Cited guidelines suggest that exacerbations of COPD with purulence of sputum are the most important symptom, which calls for the use of antibiotics.<sup>15,16</sup> Altogether, knowing the characteristics of various etiologies may have important therapeutic implications and provide evidence for local surveillance of AECOPD pathogens and appropriate choice of antimicrobials. This may give clinicians some indications to avoid abusing antibiotics to some extent.

### Inflammatory phenotypes

Patients with AECOPD also display heterogeneous inflammation. At present, the diagnosis of AECOPD mainly

**Table 1** Search strategy

PubMed strategy	
Step	Search terms
#1	"Acute exacerbation of Chronic Obstructive Pulmonary Disease" [Mesh]
#2	"Exacerbation of COPD" [Mesh]
#3	#1 OR #2
#4	Phenotype[Text Word] OR subgroups[Text Word]OR heterogeneity[Text Word] OR different characteristic [Text Word]
#5	#3 AND #4

depends on clinical symptoms. There is lack of quantitative indicators. Inflammatory markers as a kind of quantitative indicator are widely used in judging acute exacerbation and assessing prognosis. Systemic inflammatory markers mainly include CRP,<sup>17–19</sup> PCT,<sup>20,21</sup> serum amyloid A,<sup>22</sup> SP-D,<sup>23</sup> fibrinogen,<sup>24</sup> inflammation cell chemotactic factor,<sup>25</sup> and so on. All the markers mentioned earlier will increase in AECOPD patients and decrease in recovery. As a result of these investigations using biomarkers, the patients were divided into different phenotypes.

CRP is one of the most important biomarkers. A small study reported that a cutoff value of 19.65 mg/L has a sensitivity of 78% and a specificity of 84% to identify the bacterial origin of exacerbations of COPD. In patients with AECOPD with mucoid sputum, an elevated CRP level of >15.21 mg/L indicates bacterial infection.<sup>18</sup> However, a study published recently found that PCT and CRP cannot differentiate between bacterial and viral infections in the exacerbations of COPD requiring emergency department visits.<sup>26</sup> Another study showed that CRP >100 mg/mL was associated with a near fourfold increased probability of adverse outcome.<sup>27</sup> PCT is also a very important marker in AECOPD. PCT level >0.5 ng/mL is independently associated with bacterial isolation in severe AECOPD.<sup>21,28</sup> In addition, in patients who required intubation and mechanical ventilation, PCT levels are independently associated with increased risk for ICU mortality.<sup>21</sup> Yet, a post hoc analysis of a randomized, placebo-controlled trial that failed to show a positive effect of antibiotics in COPD exacerbations suggested that patients with low PCT concentrations during a COPD exacerbation might also benefit from antibiotic treatment.<sup>29</sup> Above all, the results from a meta-analysis suggest that PCT-guided treatment can safely reduce antibiotic overuse in patients with AECOPD,<sup>30</sup> but the cutoff of PCT to use antibiotics has no consensus; further studies are needed to evaluate the utility of PCT measurement.<sup>31</sup>

Some biomarkers, such as fibrinogen,<sup>32,33</sup> TNT,<sup>34</sup> VEGF,<sup>35</sup> 4-HNE,<sup>36</sup> PF4,<sup>37</sup>  $\beta$ -thromboglobulin,<sup>38</sup> and copeptin,<sup>19</sup> may also reflect the severity of AECOPD and can be used as prognostic markers. However, there is no cut point enabling these markers to differentiate between patients with different phenotypes. In the period of AECOPD, the airway inflammation is more severe than that in stable COPD. The most widely used biomarkers of airway inflammation are FeNO and induced sputum analysis. Currently, FeNO is regarded as the most promising indicator.<sup>39</sup> Some studies have reported that patients with high FeNO levels will have a good response to corticosteroids and greater improvement in FEV<sub>1</sub>.<sup>39,40</sup> The reason for this result may be due to the fact that the

FeNO level correlated well with the eosinophils, which is a good predictor for the response to corticosteroids.<sup>41,42</sup> Antus et al<sup>43</sup> pointed out that the optimum cutoff point for FENO as a predictor for significant increase in FEV<sub>1</sub> was 26.8 ppb (sensitivity: 74% and specificity: 75%). In addition, induced sputum analysis has beneficial effects on the treatment and prognosis of patients with AECOPD. Patients can be divided into different phenotypes according to the type of inflammatory cells. These inflammatory phenotypes are clinically relevant due to potential differences in the response to therapeutic interventions. Gao et al<sup>44</sup> recently identified the following four subgroups: eosinophilic predominant, neutrophilic predominant, paucigranulocytic predominant, and mixed granulocytic predominant. The eosinophilic phenotype (EO) is so named when sputum eosinophils are >2.5% of total cells, the neutrophilic phenotype (NE) is the subgroup having neutrophils >61%, the paucigranulocytic phenotype (PA) has eosinophils  $\leq$ 2.5% and neutrophils  $\leq$ 61%, and the mixed granulocytic phenotype (MC) has eosinophils >2.5% and neutrophils >61%. Different phenotypes have different pathological and physiological characteristics. The results of this study showed that the patients with mixed granulocytic or neutrophilic AECOPD had a higher BODE score, more sputum inflammatory cells, lower lung function, and longer hospital stay, accompanied by higher concentrations of sputum MMP-9, IL-6, and CRP and serum SAA, IL-6, and CRP. Notably, 83% of patients with neutrophilic AECOPD displayed evidence of bacterial infection and many of them responded poorly to standard therapies. Patients with EO, especially when combined with asthma, have a better response to corticosteroids than the rest of the other types.<sup>45</sup> Similar results were later reported by Bafadhel et al.<sup>46</sup> Therefore, the classification of inflammatory cells in sputum and the level of FeNO are of great importance in assessing the prognosis of patients and guiding whether or not to use corticosteroids. However, although the identification of inflammatory phenotype is meaningful for AECOPD, the sensitivity, specificity, and multiindex application of this method on the efficiency of the diagnosis remain to be further studied.<sup>47</sup>

## Clinical manifestation of phenotypes

As mentioned earlier, AECOPD is a heterogeneous disease and this heterogeneity can also be reflected in the symptoms. In exacerbations, the most important symptoms are increased dyspnea, sputum volume, and sputum purulence. Nowadays, the recognized criterion used to classify AECOPD according to symptoms is the Anthonisen standard.<sup>48</sup> Anthonisen et al<sup>48</sup> divided exacerbations into three types. Type 1 exacerbations

involve increased dyspnea, sputum volume, and sputum purulence, Type 2 involve any two of the latter symptoms, and Type 3 just involves one of those symptoms combined with cough, wheeze, or symptoms of an upper respiratory tract infection. In Type 1 exacerbations, patients had an improved response to the antibiotic therapy and the CRP level in Type 1 was more elevated than in the other two types. It is recommended that antibiotics are used as early as possible in Type 1 exacerbations.<sup>49</sup> Moreover, Stockley et al<sup>50</sup> found that the presence of green (purulent) sputum indicates a clear subset of patients identified at presentation who are likely to benefit most from antibiotic therapy. In addition, before an episode of exacerbation, the prodromes are different among patients. Aaron et al<sup>51</sup> divided the exacerbations of COPD into two distinct patterns, such as sudden and gradual onsets, according to worsening respiratory symptoms from diary cards. Patients who experienced sudden onset exacerbations had greater mean daily symptom scores, greater peak symptom scores, earlier peak symptoms, and shorter median recovery times back to baseline health status. Above all, these prodromes are important in differentiating the triggers of exacerbations. For instance, dyspnea, common colds, sore throat, and cough increase significantly during the prodromal phase, indicating that the triggers are more likely to be viral. Colds are even associated with longer and more severe exacerbations, and there is no doubt that a COPD patient who develops a cold should be considered for early therapy.<sup>52</sup>

It is well known that the severity of COPD is assessed not only by lung function, but CAT, mMRC questionnaires, and CCQ also have great importance in assessing the disease severity and estimating the risk of exacerbations. In GOLD 2013, CAT and mMRC were used for grading and different grades corresponded to different treatments.<sup>53</sup> According to the clinical manifestation of the phenotype, the clinician can therefore provide more purposeful and individualized treatment.

## Comorbidity phenotypes

AECOPD is often accompanied by comorbidities, which include not only the pulmonary disease but also the extrapulmonary disease. Comorbidities during hospital admission are associated with increased length of stay, mortality, and poor outcomes in patients with AECOPD.<sup>54</sup> In terms of the pulmonary comorbidity, it is very common to see a great number of patients who suffer COPD accompanied by asthma,<sup>55</sup> pneumonia,<sup>56</sup> and lung cancer.<sup>57</sup> Patients having the characteristics that are attributed to both COPD and asthma are called mixed phenotypes. A study has shown that between

20% and 40% of COPD patients can be carriers of a mixed phenotype.<sup>55</sup> This newly described phenotype is called as the ACOS.<sup>58,59</sup> Patients with a history of asthma are more likely to have a good response to corticosteroids,<sup>55</sup> and the FEV<sub>1</sub> decreased faster than that in patients who have no asthma.<sup>60</sup> Furthermore, in GOLD 2014, bronchiectasis has been added to the comorbidities of COPD. Patients with the diagnosis of COPD who share the comorbidity of bronchiectasis will experience longer exacerbations. The pathogens in patients with AECOPD and bronchiectasis are complex and will usually need broad-spectrum antibiotics.<sup>61,62</sup>

COPD can no longer be considered as a disease, which only affects the lungs. Increasing evidence supports the presence of a systemic inflammatory component, which is thought to provide the link between COPD and other extrapulmonary comorbidities.<sup>63,64</sup> These include cardiovascular disorders, skeletal muscle dysfunction, diabetes, osteoporosis, anxiety, and depression.<sup>65–68</sup> Similarly, a multicenter Spanish study identified four COPD exacerbation types (subtypes A–D, classified on the basis of their clinical severity and presence or absence of comorbidities). Patients with these different subtypes of the disease required different hospital setting needs (regular ward vs intensive care unit): subtype A (n=934), neither high comorbidity nor severe exacerbation; subtype B (n=682), moderate comorbidities; subtype C (n=562), severe comorbidities related to mortality; and subtype D (n=309), very severe exacerbation significantly related to mortality and admission to an intensive care unit. Subtype D experienced the highest rate of mortality, admission to an intensive care unit, and need for noninvasive mechanical ventilation. This was closely followed by subtype C, while subtypes A and B were primarily related to other serious complications. Hospitalization rate was >50% for all the subtypes, although significantly higher for subtypes C and D than for subtypes A and B.<sup>69</sup> These results could help to identify characteristics in order to categorize AECOPD patients for more appropriate care. They could also help in assessing interventions and treatments in subgroups with poor evolution and outcomes.

## Frequent exacerbations phenotypes

The frequency of AECOPD is variable among patients. Recently, a “frequent exacerbator” phenotype has been postulated and examined in clinical studies. The pathophysiology underlying the frequent exacerbations phenotype includes increased airway and systemic inflammation, dynamic lung hyperinflation, changes in lower airway bacterial colonization, increased susceptibility to viral infection, and increased

risk from comorbid extra pulmonary diseases. However, as for the definition of frequent exacerbators, there is no uniform standard at present. Most clinical research defined frequent exacerbators as those having a greater number of exacerbations than the median of the study population every year, those needing a course of oral antibiotics or oral glucocorticoid therapy, or those who needed to be hospitalized twice a year because of acute exacerbations.<sup>70,71</sup> In the ECLIPSE study of COPD exacerbation susceptibility, ~20% of patients with GOLD stage II disease and as many as 47% of those with stage IV disease were classified as frequent exacerbators (defined as two or more exacerbations annually). A previous study has shown that patients with frequent exacerbations and those with infrequent exacerbations tended to remain in the same category of exacerbation frequency for the full 3 years of the study, although a few patients may have shifted from one category to another.<sup>70</sup> This stability could suggest that the frequency of exacerbations is related to the susceptibilities of the patients. A recent review has concluded the possible reasons for the frequency of AECOPD. It concludes that high levels of inflammation, high susceptibility to viral infection and bacterial colonization, fast FEV<sub>1</sub>, functional decline, poor health care status, and worsened comorbidity will increase the risk of exacerbation.<sup>72</sup> Moreover, other studies also pointed out some meaningful factors that are related to the frequency, as listed in Table 2. Patients with a history of frequent exacerbations have an increased rise in both systemic inflammation and airway inflammation,<sup>73,74</sup> more rapid decline of lung function, worse quality of life,<sup>75</sup> and higher mortality rates<sup>76,77</sup> compared to patients with infrequent exacerbations. However, the classification of these frequent exacerbations phenotype is based on clinical records and/or patient recall, and the history of exacerbations is provided by the patients themselves. It is therefore important to ask about the history of exacerbations in the clinical interview in order to identify patients who may require anti-inflammatory medication. The treatment recommended in GOLD is also different for frequent exacerbators, such as long-term inhalation of corticosteroids. Adopting anti-inflammatory and anti-infection treatments in frequent exacerbators may be nontherapeutic. In the summary of the GesEPOC,<sup>78</sup> the frequent exacerbators are further divided into the following two types: those with emphysema predominant and those with chronic bronchitis predominant. The treatment for the two types is also different. For the emphysema phenotype, the basis of pharmacological treatment is long-acting bronchodilators, and in some cases with ICS. The bronchitis-predominant exacerbator patients may be treated with bronchodilators and ICS, and in contrast

to exacerbators with emphysema, they respond to treatment with Roflumilast. Selected cases with frequent exacerbations may respond to long-term treatment with macrolides,<sup>79</sup> and when ICS cannot be used, mucolytics may be effective in reducing exacerbations.<sup>80</sup> However, another study shows that whatever the declining degree of lung function, it is recommended that patients with frequent exacerbations use ICS combined with bronchial relaxation, which can significantly reduce the number of exacerbations and improve the quality of life.<sup>81</sup> The use of ICS is still a hot topic that needs large-scale, randomized, double-blind, controlled studies in order to assess its effectiveness. In summary, the frequent exacerbation phenotype as a distinct phenotype is of great significance and clinicians could develop a professional treatment for these patients, which can be used for health economic purposes.<sup>82</sup>

## Discussion

The literature relating to AECOPD phenotypes in this review mainly focuses on the significant heterogeneity among the patients. The Anthonisen standard<sup>48</sup> based on clinical manifestations (published in 1987) was the most widely recognized classification in many studies and is thought to have clinical implications. Clinicians may speculate on the kind of etiology, draw up an individual therapy protocol, and also evaluate the prognosis of patients with AECOPD according to their clinical manifestations. In an in-depth study of microorganisms, a respiratory infectious phenotype was classified by Dai et al<sup>8</sup> who found that respiratory infectious phenotypes are associated with a greater length of stay in hospital and greater severity of symptoms in AECOPD. However, this study did not check all the relevant factors or diseases associated with a prolonged stay in hospital, which therefore may have affected their results. Further investigation is needed to assess the clinical implication of this phenotype. In terms of inflammatory phenotype, two studies<sup>44,46</sup> classified AECOPD patients with inflammatory cells or biomarkers. Nevertheless, there are some differences between the classifications; in the study conducted by Gao et al,<sup>44</sup> the patients were sorted into four groups, including EO, NE, PA, and MC. They conclude that there are some differences among these groups. While another study<sup>46</sup> used cluster analysis to classify the patients into bacteria, virus, and eosinophil groups based on biomarkers. In this study, they used two methods to investigate biomarkers in AECOPD. The first method used unbiased statistical tools, identified biological COPD exacerbation phenotypes, and characterized exacerbations into four biological clusters, while the second method

**Table 2** The factors related to the frequency of exacerbations

Author	Populations	Year	Location	The severity of COPD	Duration	Outcome	Definition of exacerbations
Lin et al <sup>64</sup>	215 patients with COPD	2011	Taipei, Taiwan	Stages II to IV	3 years	MBL deficiency increases the risk of recurrent infective exacerbation	A change in the patient's baseline dyspnea, cough, and/or sputum
Foreman et al <sup>65</sup>	389 non-Hispanic white participants with COPD	2008	USA	Stages III to IV	9 years (postmortem analysis of NETT)	Variants in surfactant protein B are associated with COPD exacerbation frequency	COPD-related emergency room visits or hospitalizations
Hurst et al <sup>70</sup>	2,138 patients with COPD	2010	Multicentral	Stages II to IV	3 years (postmortem analysis of ECLIPSE)	The severity of COPD, a history of gastroesophageal reflux or heartburn, poorer quality of life, and elevated white-cell count were independently associated with the frequency of exacerbations	Events led a care provider to prescribe antibiotics or corticosteroids (or both) or hospitalization
Wells et al <sup>66</sup>	3,690 COPD patients	2012	21 clinical centers in USA	Stages II to IV	3 years	Ratio of the diameter of the pulmonary artery to the diameter of the aorta > 1 would be associated with severe COPD exacerbations	Severe exacerbation: increased dyspnea, cough, or sputum production or required admission. Mild-to-moderate: treated with antibiotics or systemic glucocorticoids in the outpatient setting or during an emergency room visit
Sarinc Ulasli et al <sup>67</sup>	128 patients of COPD	2013	Turkey	Stages I to II	1 year	Thyroid function has an effect in exacerbation frequency of COPD	Worsening symptoms and leading to an increase in the use of maintenance medications
Huerta et al <sup>68</sup>	209 patients with COPD	2015	UK	Stages II to IV	8 years	Upper airway symptoms increasing over time in patients with COPD are related to the frequent exacerbation phenotype	Any change in one major symptom (dyspnea, sputum purulence, sputum volume) with at least one other major or minor (nasal discharge and/or congestion, wheezing, sore throat, and cough) for 2 consecutive days
Morrow et al <sup>69</sup>	248 Caucasian COPD subjects	2015	USA	Stages III to IV	1 year	Myeloperoxidase was associated with the number of recent exacerbations	Requiring outpatient treatment with antibiotics or oral steroids or one requiring hospitalization
Oh et al <sup>90</sup>	380 COPD patients	2014	Korea	Stages I to IV	7 years	Severity of emphysema, and serum lower protein levels are the independent predictors of frequent exacerbations in COPD patients	Dyspnea, cough, or sputum requiring treatment with systemic steroids or antibiotics, a visit to the emergency room, and/or admission to a hospital
Singh et al <sup>91</sup>	215 COPD patients	2014	UK	Stages II to IV	3 years (postmortem analysis of ECLIPSE)	B3GNT, LAF4, and ARHGGEF10 are associated with frequent exacerbations	Requiring oral corticosteroids and/or antibiotics or hospitalized

**Abbreviations:** ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; MBL, mannose-binding lectin; NETT, National Emphysema Treatment Trial.

employed the currently used clinical exacerbation phenotypes of COPD related to potential etiology and inflammation (namely exacerbations that are associated with bacteria, virus, or a sputum eosinophilia). The biological exacerbation clusters were bacterial, viral, eosinophilic-predominant, and pauci-inflammatory. It was found that these clusters were remarkably similar to the clinical exacerbation phenotypes. Thus, in addition to identifying potential biomarkers to direct therapy and evaluate prognosis, these clinical exacerbation phenotypes are likely to represent distinct pathophysiological entities with specific biomarker signatures. In studies concerned with the comorbidity phenotype, Arostegui et al<sup>69</sup> characterized the AECOPD patients into four types according to the severity of the current exacerbation and the comorbidities. Subtype D (defined as having very severe exacerbations with low or mild comorbidity) was significantly related to mortality and admission to an intensive care unit. Although this study did not offer detailed suggestions for the treatment of AECOPD, it evoked awareness in clinicians of the need to treat patients comprehensively. It was reported that the frequent exacerbations were related to many factors, as is well known. The current GOLD classification of COPD acknowledges the complexity of the disease, and the frequency of the exacerbation is also considered when classifying patients. It was suggested that patients with frequent exacerbations should have treatment with ICS. However, the definition of the frequent exacerbator and the subjects themselves varied among the studies. In a retrospective study, the frequency of the exacerbation could be influenced by the memory of the patients. In addition, there are some unreported exacerbations. Due to the difference in the frequency, the range of the patients who should be treated with ICS would be different too. Thus, in terms of the use of ICS, it requires large-scale, randomized, double-blind, controlled studies to gather more evidence supporting its use.

Limitations of our review include the following: the language restriction that articles not published in English were excluded in this review may induce a language bias. Moreover, the studies were extracted only from PubMed, which may result in missing some articles; nevertheless, we also make a simple glance over the articles related to the phenotypes of AECOPD in Web of Science and Embase, and there are no crucial studies that were not selected in the review. Another limitation is that we excluded studies that focused on the phenotypes in stable COPD. This may remove a potential phenotype from our review, which may also have prognostic value in the exacerbations of COPD. However, the exclusion was as per protocol, with the aim of producing

a review, which is focused on answering a specific question related solely to AECOPD.

## Conclusion

AECOPD is a heterogeneous disease. Investigations of the different phenotypes of AECOPD have resulted in the definition of different types of patients with prognostic and therapeutic significance. Because the diversity of the phenotypes of each condition is better understood, clinicians will be presented with opportunities to evolve from a “one size fits all” approach to personalized approaches, with the ultimate goal of improving care and reducing potential adverse effects from unnecessary therapies.<sup>83</sup> However, research into AECOPD phenotypes is still in its infancy, and with a detailed study of the phenotypes of AECOPD, it is possible that a new phenotype allowing individualized treatment and estimation of prognosis will be found. This means that there is an urgent need for well-designed clinical studies focused on AECOPD phenotypes.

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## Disclosure

The authors report no conflicts of interest in this work.

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