



## Use of adjunct cardiovascular therapy in patients hospitalised for acute exacerbations of COPD

To the Editor:

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is one of the most frequent diagnoses in patients presenting with acute dyspnoea or respiratory failure. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) document, it is defined clinically as acute worsening of respiratory symptoms that result in additional therapies, bronchodilators, corticosteroids and antibiotics being the cornerstone of acute management [1].

However, comorbidities in COPD, including cardiac disease, contribute significantly to the heterogeneity of single acute episodes in real-life practice [2]. This might determine changes in pharmacological treatment with adjunct therapy such as diuretics [3]. Therefore, it is sometimes difficult to discriminate between true exacerbations of COPD and acute worsening of a patient's condition due to associated comorbidities [4]. Furthermore, the lung-heart interplay is complex and AECOPD has been also correlated with alteration of haemodynamics [5]. Nevertheless, data are still scarce on the actual use of therapies such as diuretics during hospitalisation for AECOPD. Therefore, we were interested in evaluating how patients admitted to the hospital with a clinical diagnosis of AECOPD were managed at admission and we analysed the therapeutic approach at onset of AECOPD in hospitalised patients, aiming to assess the adjunct use of diuretic therapy.

This study was a retrospective, observational, single-centre study based on hospital records. The study population included all patients admitted to the unit of respiratory disease at our university hospital with a clinical diagnosis of AECOPD and respiratory failure from September 1, 2014, to September 30, 2015. Cases were identified retrospectively by evaluating International Classification of Diseases (Ninth Revision) diagnosis-related group codes then hospital records were reviewed for each patient to confirm inclusion. Patients with a previous clinical and/or functional diagnosis of COPD presenting to the hospital for respiratory failure (*i.e.* ratio between arterial blood partial oxygen pressure and inspired oxygen fraction  $<300$  and an arterial blood partial carbon dioxide pressure  $>45$  mmHg) were considered for inclusion. Exclusion criteria were incomplete data on medications used, absence of a previous clinical diagnosis of COPD and respiratory failure due to a different cause (*e.g.* pneumothorax, acute cardiac disease, pulmonary embolism or acute heart failure, excluded both through the clinical assessment achieved with bedside cardiac transthoracic echocardiography and the results of serological evaluation of cardiac enzymes).

The following data were collected for each patient at admission: demographics and past medical history, Anthonisen criteria for lung infection [6], clinical signs of fluid overload (*i.e.* dyspnoea plus at least one of pulmonary rales, pulmonary oedema, peripheral oedema, orthopnoea or ascites [7]), signs of fluid overload (upper zone flow redistribution, lung interstitial oedema, alveolar pulmonary oedema or bilateral pleural effusion [8]) on the chest radiograph and/or computed tomography scan, blood gases, and laboratory tests. Short-term outcomes and vital status were recorded for completeness but were outside the scope of the current analysis. The study protocol was presented to the institutional ethics committee, which authorised data extraction. Informed consent was not required.



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**In real-life practice, acute exacerbation of COPD is often treated as a cardiopulmonary syndrome** <http://ow.ly/uAnk30luMYz>

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Summary descriptive statistics were used to describe the study population and a multivariable logistic regression model was used to evaluate clinical features related to the use of diuretics. Independent variables were age, sex, number of comorbidities, Anthonisen criteria (present/absent), and radiological and clinical signs of overload (present/absent). All analyses were performed by means of R 3.3.2 statistical software (The R Foundation for Statistical Computing, Vienna, Austria) at the 95% confidence level.

The study population included 122 elderly patients (average age 75.2 years, *SD* 9 years) with AECOPD, of whom 14 had two hospitalisations within the study period and four had three or more hospitalisations. The total number of recorded episodes was 146.

57% of the patients were male and 91% were current or former smokers. All had a confirmed or reported diagnosis of COPD, of whom 8% were mild–moderate and 49% severe. Comorbidities were very frequent. Cardiac diseases such as heart failure, ischaemic heart disease and arrhythmias were common, and were reported in 71 (58.2%) patients, often with the same patients presenting more than one diagnosis (*i.e.* 24 patients reported ischaemic heart disease, 44 reported heart failure, and 42 reported atrial fibrillation and/or other arrhythmias). Similarly, hypertension, diabetes, gastroenteric diseases and neoplasms were frequent in the study sample (55.2%, 26.7%, 32% and 30.2%, respectively). Associated lung disorders were not as common, with 8% reporting pulmonary hypertension and 6.5% reporting previous pulmonary embolism.

At admission, all patients presented significant worsening dyspnoea but clinical signs of fluid overload were present only in a minority of cases (28%). Conversely, radiological signs were reported in 49%, the majority being interstitial oedema and bilateral pleural effusion. Symptoms suggesting lung infections were present in 40%. Cardiac biomarkers such as brain natriuretic peptide (BNP) and cardiac troponin T (cTnT) were available only in six and 42 patients, respectively, and proved, on average, to be raised (BNP 570 pg·mL<sup>-1</sup> and cTnT 0.14 ng·mL<sup>-1</sup>). The diagnosis of associated heart failure was, however, confirmed and reported in hospital in only 9% of subjects.

Patients were mostly hypoxic and hypercapnic (mean arterial oxygen tension 64 mmHg and carbon dioxide tension 54 mmHg) without severe or life-threatening acidosis. 25% of admitted patients required noninvasive ventilation, followed by endotracheal intubation in three of them.

Not surprisingly, the majority of patients received bronchodilators, corticosteroids and antibiotics but, quite interestingly, the vast majority of them (81%) received adjunct loop diuretics, mostly furosemide (mean dosage 48 mg, *SD* 59 mg). Cardiac medications, proton-pump inhibitors and antidepressants were prescribed frequently.

Table 1 describes the frequency of drugs used as the first approach to manage AECOPD and reports factors associated with the use of diuretics assessed by means of multivariable logistic regression performed on the sample of 114 patients who had complete data for the variables of interest.

Our study is a description of current medical practice in patients hospitalised with respiratory failure and AECOPD episodes, defined clinically as in the GOLD document, and provides data on drug management during AECOPD episodes in real-life practice.

Overall, the population in study was old and multimorbid, which is in wide agreement with recent literature [9]. Similarly, the clinical presentation was not surprising: the AECOPD patients presented with alterations in gas exchange, half of them had pulmonary crackles, the majority presented wheezing and there were signs of congestion in ~20% of cases [10, 11].

However, acute management with drug strategies at bedside offer some interesting insights. As expected, bronchodilators, corticosteroids and antibiotics were widely used in our population. However, in 17% of the episodes, patients were not started on bronchodilators; nonetheless, half of them received systemic corticosteroids. Antibiotics were used in 58% of the cases, which is lower than reported in other observational data on COPD [12, 13]. On the contrary, cardiac drugs and diuretics were used more frequently than expected (*e.g.*  $\beta$ -blockers in 35%). The factors that were significantly related to the use of diuretics were age, clinical signs of fluid overload and Charlson comorbidity index, with clinical signs of fluid overload having five-fold higher odds. Conversely, neither Anthonisen criteria nor radiological signs of overload were correlated.

Data from the literature generally report lower use of diuretics during AECOPD: loop diuretics were used in 35% of >84000 episodes across the USA, with only 13% of patients taking  $\beta$ -blockers [14]. In contrast, a smaller study specifically investigating heart failure in patients with AECOPD reported that diuretics were used in 31% of cases overall but the rate increased to 76% when patients with known concomitant COPD and heart failure were considered [15].

Taken together, the present data indicate that the clinical diagnosis of AECOPD, as performed in everyday practice, is rather unspecific, and a variety of clinical scenarios may be included under the umbrella of the

TABLE 1 Drugs used during acute exacerbation of chronic obstructive pulmonary disease episodes and predictive factors related to the use of diuretics

Drug	Patients	
Antibiotics (intravenous)	86 (77), 58.9%	
Nebulised bronchodilators	99, 67.8%	
LABA	20, 13.7%	
LAMA	16, 10.9%	
ICS	19, 13.0%	
Corticosteroids (intravenous)	104 (96), 71.2%	
Diuretics (intravenous)	118 (59), 80.8%	
$\beta$ -blockers	52, 35.6%	
Antihypertensive drugs	77, 52.7%	
Antiplatelet drugs	57, 39.0%	
Anticoagulants	42, 28.7%	
Statins	50, 34.2%	
Mineral receptor antagonists	43, 29.4%	
Digitalis	9, 6.0%	
Antidiabetic agents (insulin/oral hypoglycaemic drugs)	29 (17/15), 19.8%	
Proton pump inhibitors	105, 71.9%	
Antidepressants	71, 48.6%	
Variable	OR (95% CI)	p-value
Age	1.10 (1.03–1.17)	0.0032
Female sex <i>versus</i> male	0.94 (0.30–2.92)	0.9108
Charlson comorbidity index	1.86 (1.29–2.69)	0.0009
Anthonisen criteria present <i>versus</i> absent	0.79 (0.45–1.39)	0.4067
Radiologic signs of overload present <i>versus</i> absent	0.57 (0.16–2.07)	0.3944
Clinical signs of overload present <i>versus</i> absent	5.19 (1.05–25.62)	0.0434

LABA: long-acting  $\beta$ -agonist; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroid.

same diagnosis. For example, the low rate of clinical signs of infection (and therefore, the relatively low use of antibiotics) is rather unexpected, since infection is generally indicated as the most common cause of AECOPD [2]. Similarly, we expected that diuretics would have been used commonly but we did not expect to find more patients being treated with diuretics than with nebulised bronchodilators. As our population comprised elderly, multimorbid patients, we hypothesised that the acute exacerbations of COPD were probably associated with alteration of the heart loading conditions and, thus, with impairment of heart function. Possibly, the majority of patients presented clinical features evocative of heart failure, and thus were deemed to benefit from adjunctive treatment. Furthermore, it is known that heart failure is frequent among patients with COPD and that AECOPD is a well-known cause of worsening heart failure [9–15]. Thus, some of our patients hospitalised for AECOPD could have a clinical presentation evocative of associated heart failure, albeit without a formal diagnosis of overt cardiac disease. Whether heart failure may be a cause of AECOPD as common as lung infection is unknown but our data suggest that it is a field worth exploring.

Notwithstanding, our findings should be interpreted with caution due to the retrospective nature of the study. In particular, the diagnosis of COPD was not confirmed by spirometry in all patients, data were missing for ECG and echocardiography, and the small number of patients limits analysis and impairs causal correlation. More specifically, the study data do not allow a throughout analysis of the aetiology underlying the acute exacerbation of respiratory symptoms in patients with COPD and therefore, our findings should be regarded mainly as hypothesis generating. However, it is reasonable to deduce that the attending physician felt the need for adjunctive diuretics beyond standard respiratory treatment in the majority of patients hospitalised with a diagnosis of exacerbation of COPD, which is a rather novel finding in AECOPD literature.

In conclusion, we could argue that in real-life practice, acute exacerbation of COPD is often treated as a cardiopulmonary syndrome. Although speculative, our findings warrant further evaluation, with appropriate prospective studies to explore this topic.

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