

Acute exacerbations of COPD: risk factors for failure and relapse

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Abstract: Acute exacerbations are a leading cause of worsening COPD in terms of lung function decline, quality of life, and survival. They also have a relevant economic burden on the health care system. Determining the risk factors for acute exacerbation and early relapse could be a crucial element for a better management of COPD patients. This review analyzes the current knowledge and underlines the main risk factors for recurrent acute exacerbations. Comprehensive evaluation of COPD patients during stable phase and exacerbation could contribute to prevent treatment failure and relapses.

Keywords: infections, prevention, treatment, COPD, exacerbations

Introduction

Acute exacerbation of COPD (AECOPD) represents a key moment in the progression of COPD. The association between AECOPD and decline in health status and lung function is well recognized.^{1,2} These events absorb around 50% of direct cost for COPD.³

The true incidence of AECOPD is quite difficult to assess because about 50% of exacerbations are not reported by patients.⁴ However, it is known that AECOPD causes 2.4% of acute hospitalizations in England. The median length of hospital stay is around 7 days with an overall mortality rate of 11.6%, which increases up to 37% in patients who required readmission.⁵

Mortality rate during the 3 months following hospitalization is approximately 15%. These data are confirmed by the retrospective subanalysis of the UPLIFT study published in 2012.^{6,7}

AECOPD-related costs are estimated around \$4069/year per patient, but costs increase with exacerbation frequency and severity and with the presence of comorbidities.⁸ Hospitalization represents more than 70% of all COPD-related health care costs.^{9,10} In addition, relapses have even higher costs, estimated to be 18% greater than for patients who do not require new hospitalization.¹¹

Some patients experience frequent episodes and have an increased risk of recurrence or relapse following the initial episode.¹² Patients with a high exacerbation rate have an increased annual decline of lung function,¹³ poorer health outcomes and increased hospital admissions.¹⁴⁻¹⁶

In the USA, in a cohort of Medicare fee-for-service patients, the rate of AECOPD patients with early readmittance was estimated to be approximately 20%.^{17,18} Similar to other complex clinical conditions that need strict monitoring post discharge (such as congestive heart failure),^{17,18} there is a strong interest in identifying which clinical

factors increase the risk of relapse in COPD patients, given the high impact of readmissions.^{19,20}

Reducing the treatment failure and relapse of AECOPD could contribute to reduce the burden of disease and improve the management of COPD patients.

This narrative review of the literature analyzes the definition and factors associated with treatment failure and relapses of AECOPD to understand how to perform an early diagnosis and prompt intervention to reduce the risk of failure and relapse of AECOPD.

Definition of failure and early relapse of AECOPD

Main goals of the treatment are cure, defined as the complete resolution of signs and symptoms associated with the exacerbation and improvement and defined as a resolution or reduction in the symptoms and signs without new symptoms and signs associated with the exacerbation.²¹

Clinical success is considered when either cure or improvement is observed at the end of the treatment.²²

Failure of AECOPD treatment is differently defined on the basis of the severity and clinical setting where the patients need to be managed.

In outpatients, with mild-to-moderate exacerbation, failure is generally defined as an incomplete resolution, persistence or worsening of symptoms that require a new course of antibiotics and/or oral corticosteroids or hospitalization.^{22,23}

In severe COPD patients who need hospitalization or access to emergency room, failure is defined as death due to AECOPD or its complication, initiation of mechanical ventilation after the second hospital day, intubation with mechanical ventilation, intensification of pharmacologic therapy or hospital readmission for COPD within 30 days of discharge.^{24–26}

Even after a clinical success in the treatment of acute exacerbation, patients could experience a recurrence of AECOPD. Although there is no uniform characterization regarding length of time, a new hospitalization between day 7 and day 30 following discharge is defined as an “early readmission.”²⁷ Generally, the need for readmission may be related to a further COPD exacerbation or to other causes (ie, pneumonia and heart failure).²²

From a clinical point of view, the early readmission to hospital should be considered as a marker of a more severe disease with a worse prognosis.²⁸ A readmission for a new event of AECOPD in a period of 30 days of discharge is proved to have an impact on mortality in a short- and long-term follow-up;²⁹ in the readmitted patients, in fact, the

estimated absolute risk of death was 4%, 17%, 19% and 24% at 30 days, 6 months, 1 year and 3 years, respectively.²⁹

Risk factors for relapse and failure of AECOPD

A significant number of patients (12%–32% of patients depending on the severity of underlying disease, comorbidities and time from previous exacerbation) treated for AECOPD tend to relapse in the days and weeks after treatment.³⁰

Same factors are associated with the risk of failure and relapse,³¹ and clinicians should identify them in every AECOPD patient to implement effective interventions.

Severity of underlying COPD

Several studies have identified clinical and conventional laboratory parameters associated with higher rates of readmission following an AECOPD. These variables include age,³² sex,^{33–35} physical capacity,³² levels of partial arterial oxygen pressure (PaO₂)^{35,36} and partial arterial carbon dioxide pressure (PaCO₂),^{37,38} global and respiratory muscle weakness,^{39,40} socioeconomic status, health-related quality of life and anxiety or depression,^{35,40–44} cured meat consumption⁴⁵ and adherence to inhaled therapy and follow-up.⁴⁶ The severity of underlying COPD mostly influences outcomes.⁴⁷ In particular, a higher risk of relapse was seen in patients with markers of disease severity such as low body mass index (BMI), use of systemic corticosteroids and the need of LAMA and LABA treatments for severe obstruction and hyperinflation.⁴⁶

In addition, the frequency of exacerbations is related to a higher readmission rate within 90 days.⁴⁸

Clinical factors related to early readmission include lung function and dyspnea perception.^{22,43,49} Two studies, one prospective³⁶ and one retrospective,⁴³ both performed with a period of 1-year observation and performed on 340³⁶ and 186⁴³ AECOPD patients, respectively, found airflow obstruction severity, measured by forced expiratory volume in 1 second (FEV₁) to be an important predictor factor for AECOPD readmission during stable phase. In general, FEV₁ values below 50% of predicted are associated with a higher risk of COPD readmission. An English prospective trial,⁴⁹ recruiting more than 900 severe COPD patients and aimed at evaluating the role of dyspnea in AECOPD, confirmed a readmission rate of 19% at 28 days and 33% at 90 days following discharge.

Severity of AECOPD

The European COPD Audit in 2016 found respiratory acidosis and the subsequent need for ventilator support as

predictors of failure and poor outcome, both during hospital stay and 3 months after discharge.⁴⁹ Thus, arterial blood gas analysis must be performed in every AECOPD patient, as a prompt noninvasive ventilation trial could be effective on patient outcomes.

At presentation, respiratory rate and self-reported activity limitations are significantly associated with later relapse.³³

Comorbidities

Clinical factors related to lung involvement are not the only elements involved in the risk of an early relapse after an AECOPD. Almagro et al⁵⁰ in a longitudinal, multicenter Spanish study evaluated the influence of chronic comorbidities as risk factors for readmission and short-term prognosis of AECOPD patients. The authors enrolled more than 600 patients with an acute exacerbation and found a 20% rate of readmission in the 3-month period after discharge. New findings of this study are related to the ability of high values of the Charlson index, coupled with the number of comorbidities, to act as predictive factors for a new AECOPD readmission. In particular, the stratification of the Charlson index in two or more points (2 or >2 comorbidities other than COPD) increased the risk of readmission. Moreover, the Charlson index was significantly higher in patients who required a rehospitalization also for causes other than AECOPD (particularly heart failure and infections). However, data of Almagro et al⁵⁰ were not confirmed when the role of two common comorbidities associated with COPD such as diabetes and hypertension was evaluated.³⁷ McGhan et al⁵¹ in a large cohort of Veterans Affairs (VA) patients (>50,000), quantified a 25% readmission rate at 1 year, and a 44% rate at 5 years. The authors identified an increasing risk for some comorbidities (asthma and pulmonary hypertension), but a reduced risk of readmission for other comorbidities such as diabetes and arterial hypertension (protective effect). Although diabetes and hypertension were found to exert a weak protective influence on COPD severity (as measured by health care utilization),⁵² the study by McGhan et al⁵¹ used a retrospective administrative database with non-confirmed definitions of chronic conditions associated with COPD, and this aspect may play an important role in this discrepancy.⁵² In addition, a recent Spanish prospective study, defining predictors of early readmission for AECOPD (30 days after discharge), found that patients with a greater prevalence of diabetes have a high risk of readmission. Moreover, diabetes was one of three only significant variables predicting an early readmission to hospital.⁵³ In terms of single and specific comorbidities related to relapse, the association of COPD

with the presence of cancer,^{27,43,54} heart failure,^{36,37} coronary disease,³⁶ chronic cor pulmonale, moderate or severe liver disease,⁵² osteoporosis,³⁷ anxiety³⁷ or depression,³⁷ unilateral pulmonary infiltrates,²⁶ malnutrition³⁶ and hyperproteinemia⁴¹ exerts a negative role in promoting readmission to hospital. Surprisingly, the presence of obesity³⁶ in association with COPD conversely shows a protective role.

The presence of bronchiectasis as comorbidity of COPD is considered a considerable risk factor for COPD exacerbations and for worse long-term outcomes (ie, mortality and quality of life).^{55,56} Different risk factors have been identified to predict the risk of bronchiectasis in COPD: male sex, high serum Ig, previous tuberculosis, severe airflow obstruction, isolation of a pathogen microorganism from sputum and at least one hospital admission for exacerbations in the previous year.^{57,58}

Biomarkers

As the underlying biology in COPD is complex and as yet not completely understood, biomarkers could be useful in the study of different COPD phenotypes and in differentiating patients with frequent exacerbations or at risk for early relapse. The ECLIPSE study revealed some biomarkers, including C-reactive protein (CRP), fibrinogen, serum interleukin 8 (IL-8) surfactant protein D (SP-D), club cell protein-16 (CC16) and club cell protein-18 (CC18), which could predict lung functional decline and acute exacerbations and assess mortality risk.⁵⁹

Fibrinogen seems to be the more stable and reproducible biomarker in COPD clinical studies, and in combination with leukocytosis and high CRP during the stable phase, allows the identification of patients who are predisposed to frequent exacerbations.^{60,61}

CRP alone was studied in two prospective studies performed on outpatients⁶² and inpatients⁵⁹ to predict early relapse after an AECOPD. Following an exacerbation, higher serum levels of CRP at day 14⁶² and at discharge of hospitalization⁶⁰ following the event were respectively predictive of a recurrent exacerbation event within 50 days of the index exacerbation,⁶³ and in an early period following discharge (30 days).⁶⁰ Interestingly, in the latter study,⁶⁰ high levels of CRP at discharge were not related to any of the clinical, therapeutic or severity variables included, suggesting that a residual bacterial infection or a superinfection during treatment could underlie enhanced CRP levels after treatment, similarly to what happens in non-resolving exacerbations.⁶³

About treatment failure, a Spanish prospective study on 378 AECOPD patients treated with both antibiotics and

steroids and aimed to determine in-hospital predictors of treatment failure in a period ≤ 7 days found that +1 mg/dL of CRP at admission (odds ratio [OR] 1.07; 95% CI 1.01–1.13, $P=0.014$) increases the risk of failure.⁶⁴

In addition, the level of serum magnesium⁵⁶ and levels of serum D-dimer⁶⁵ were studied and found to be associated with treatment failure and relapse.

Notwithstanding the scientific interest and promising results in clinical trial in distinguishing patients with early relapse or with frequent exacerbations, no biomarker is currently ready for use in the clinical management of AECOPD because of suboptimal performance.⁶⁶

Microbiology

Recently, the expression “lung microbiome” has been used to describe the entire community of microorganisms that inhabit the lower respiratory tract and is investigated through modern molecular techniques which identify bacteria on the basis of ribosomal RNA sequences. These techniques have demonstrated that the bronchial tree is not a sterile environment, even in healthy people and that the respiratory microbiome changes in chronic lung diseases.⁶⁷ The presence of these bacteria in the airways may increase chronic inflammation that drives COPD pathogenesis and/or progression.⁶⁸ Even in patients with stable COPD, bacterial pathogens are detected in the lower respiratory tract of 25%–50% of cases when examined by the analysis of sputum, bronchoalveolar lavage, bronchial brushings or bronchial biopsies; this bacterial chronic “colonization/infection” is associated with host inflammatory and immune responses. The increased risk of “colonization/infection” and airway inflammation has been associated with lower FEV₁% and active smoking.^{69,70}

In COPD, the lung microbiome changes during exacerbations, irrespective of prescribed treatment regimens (antibiotics only, oral corticosteroids only or both).⁶⁸ Interestingly, a recent study in severe COPD patients with *Pseudomonas aeruginosa* (PA) colonization revealed that lung microbiome composition changes during exacerbations and becomes similar to non-PA-colonized patients, where no predominant PA is usually found.⁷¹ These findings suggest that antibiotic therapy of exacerbations in COPD patients colonized by PA should not necessarily be directed exclusively at covering this microorganism.

In AECOPD patients, a key point related to an improvement in clinical outcomes is the success of therapy.⁷² Data on sputum culture suggest that bacterial infections may often be the cause of AECOPD. A clear relationship has been proven between sputum purulence and the presence of bacteria.⁷³

However, some patients treated with antibiotics show incomplete resolution, persistence or worsening of AECOPD symptoms/signs, defining an in-hospital treatment failure.⁷⁴ Failure may be related to inadequate antibiotic efficacy, which through incomplete resolution of the initial exacerbation and persistent bacterial infection is likely to influence the risk of future relapse.⁷⁵ In AECOPD inpatients, reported treatment failure rates vary between 10% and 39% of patients treated with both antibiotics and systemic steroids.^{76,77}

Different trials have been conducted to demonstrate that antibiotic choice impacts on long-term outcomes in AECOPD, specifically in reducing clinical relapses, the need for additional antibiotics and prolonging the time to following exacerbation.^{78–81} However, not all studies demonstrated differences in long-term outcomes between different antibiotic regimens (beta-lactams, quinolones, etc.). The mechanisms by which antibiotics improve long-term outcomes of COPD are not completely clear, but it is likely that the complete eradication of the bacteria involved in the exacerbation plays a major role.⁸²

Patient-reported outcomes

Steer et al⁴⁹ found that dyspnea intensity, measured by the Medical Research Council Dyspnea scale (MRC) correlated with a progressive risk of readmission. Moreover, a new version of MRC, defined as extended MRC (eMRC), evaluating patient ability in washing and dressing, has a better predictive ability in identifying patients requiring readmittance.

In addition, the ESFERA study showed that a simple tool such as the COPD Severity Scale (COPDSS),⁸³ which evaluate the level of dyspnea at the moment of the evaluation, and in the previous 14 days, the need of rescue medications and the number and severity of hospitalization in the past 5 years, could be used as the measurement of disease severity and therefore as a predictor of outcomes.^{84,85}

Conclusion and recommendations

AECOPD patients, especially those requiring hospitalization, have a worse prognosis in terms of loss of lung function, quality of life and mortality. Increased exacerbation risk is related to the severity of COPD, comorbidities and, potentially, the presence of a chronic airways infection (ie, PA) other than by different underlying biologic characteristics as listed in Table 1.

Strategies to identify different factors related to clinical characteristics of COPD patients and the identification of risk factors of failure and relapse may allow a more precise

Table I Risk factor for failure and early relapse of AECOPD

Severity of the disease	FEV ₁ < 50% of predicted Dyspnea Previous exacerbations Respiratory acidosis Respiratory rate
Comorbidities	Comorbidities with Charlson index > 2 Bronchiectasis Diabetes
Biomarkers	Leukocytosis in stable phase Elevated CRP in stable phase Elevated CRP at admission Elevated CRP at discharge of hospitalization High fibrinogen in stable phase D-dimer in acute phase
Microbiology	Inadequate antibiotic treatment Chronic bacterial infection
Patient-reported outcome	MRCD COPDSS

Abbreviations: AECOPD, acute exacerbation of COPD; COPDSS, COPD Severity Scale; CRP, C-reactive protein; FEV₁, forced expiratory volume in 1 second; MRCD, Medical Research Council Dyspnea scale.

approach with specific strategies or interventions targeting the individual needs of patients, with the aim of reducing the readmission rate in COPD patients.

Disclosure

MM reports travel grant and congress participation from Boehringer Ingelheim, Menarini, Vivisol and Astra Zeneca and personal fees from Guidotti-Malesci and Grifols. PR has participated as a lecturer, speaker and advisor in scientific meetings and courses under the sponsorship of Almirall, AstraZeneca, Biofutura, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Menarini Group, Mundipharma and Novartis. The Department of Systems Medicine of the University of Rome “Tor Vergata” was funded by Almirall, Boehringer Ingelheim, Novartis and Zambon to conduct research in the respiratory field. EP reports fees and consultancies from Bayer, consultancies for Insmad, Grigols and Polyphor and fees from Menarini, Zambon and Pfizer. AG reports research grant from Boehringer, travel grant and congress participation from Menarini and advisory board participation from Vertex. MC has participated as a lecturer, speaker and advisor in scientific meetings and courses under the sponsorship of Almirall, AstraZeneca, Biofutura, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmith Kline, Menarini Group, Lallemand, Mundipharma, Novartis, Pfizer, Verona Pharma and Zambon and is or has been a consultant to Chiesi Farmaceutici, Lallemand, Novartis, Verona Pharma and Zambon. FB reports personal fees from AstraZeneca, Bayer, Chiesi, Dompé, GSK, Guidotti, Grifols,

Menarini, Novartis, Pfizer and Zambon and grants from Bayer, Chiesi, Guidotti, Menarini, Pfizer, Teva and Zambon. MDP, EC and MG report no conflicts of interest in this work.

References

- Doll H, Miravittles M. Health-related QOL in acute exacerbations of chronic bronchitis and chronic obstructive pulmonary disease: a review of the literature. *Pharmacoeconomics*. 2005;23(4):345–363.
- Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax*. 2002;57(10):847–852.
- Anzueto A, Leimer I, Kesten S. Impact of frequency of COPD exacerbations on pulmonary function, health status and clinical outcomes. *Int J Chron Obstruct Pulmon Dis*. 2009;4:245–251.
- Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2000;161(5):1608–1613.
- Pozo-Rodriguez F, Lopez-Campos JL, Alvarez-Martinez CJ, et al. Clinical audit of COPD patients requiring hospital admission in Spain: AUDIPOC study. *PLoS One*. 2012;7(7):e42156.
- Patil SP, Krishnan JA, Lechtzin N, Diette GB. In-hospital mortality following acute exacerbations of chronic obstructive pulmonary disease. *Arch Intern Med*. 2003;163(10):1180–1186.
- Halpin DMG, Decramer M, Celli B, Diette GB. Exacerbation frequency and course of COPD. *Int J COPD*. 2012;7:653–661.
- Pasquale MK, Sun SX, Song F, Hartnett HJ, Stenkowski SA. Impact of exacerbation on health care cost and resource utilization in chronic obstructive pulmonary disease patients with chronic bronchitis from a predominantly Medicare population. *Int J COPD*. 2012;7:757–764.
- Strassels SA, Smith DH, Sullivan SD, Mahajan PS. The cost of treating COPD in the United States. *Chest*. 2001;119:344–352.
- FitzGerald JM, Haddon JM, Bradly-Kennedy C, Kuramoto L, Ford GT; RUSIC Study Group. Resource use study in COPD (RUSIC): a prospective study to quantify the effects of COPD exacerbations on health care resource use among COPD patients. *Can Respir J*. 2007;14(3):145–152.
- Elixhauser A, Au DH, Podulka J. Readmissions for chronic obstructive pulmonary disease, 2008: statistical brief #121. *Healthcare Cost and Utilization Project (HCUP) Statistical Briefs*. Rockville, MD: Agency for Healthcare Research and Quality (US); 2011.
- Hurst JR, Donaldson GC, Quint JK, Goldring JJ, Baghai-Ravary R, Wedzicha JA. Temporal clustering of exacerbations in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2009;179(5):369–374.
- Makris D, Moschandreas J, Damianaki A, et al. Exacerbations and lung function decline in COPD: new insights in current and ex-smokers. *Respir Med*. 2007;101(6):1305–1312.
- Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax*. 2005;60:925–931.
- Krumholz HM, Parent EM, Tu N, et al. Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. *Arch Intern Med*. 1997;157(1):99–104.
- Friedman B, Jiang HJ, Elixhauser A. Costly hospital readmissions and complex chronic illness. *Inquiry*. 2008;45(4):408–421.
- Baker CL, Zou KH, Su J. Risk assessment of readmissions following an initial COPD-related hospitalization. *Int J Chron Obstruct Pulmon Dis*. 2013;8:551–559.
- Nantsupawat T, Limsuwat C, Nugent K. Factors affecting chronic obstructive pulmonary disease early rehospitalization. *Chron Respir Dis*. 2012;9(2):93–98.
- Centers for Disease Control and Prevention (CDC). Deaths from chronic obstructive pulmonary disease. United States, 2000–2005. *MMWR Morb Mortal Wkly Rep*. 2008;57(45):1229–1232.

20. Overbeek JA, Penning-van Beest FJ, Balp MM, Dekhuijzen PN, Herings RM. Burden of Exacerbations in Patients with Moderate to Very Severe COPD in the Netherlands: a real-life study. *COPD*. 2015; 12(2):132–143.
21. Chow AW, Hall CB, Klein JO, et al. Evaluation of new anti-infective drugs for the treatment of respiratory tract infections. *Clin Infect Dis*. 1992;15:S62–S88.
22. Wilson R, Anzueto A, Miravittles M, et al. A novel study design for antibiotic trials in acute exacerbations of COPD: MAESTRAL methodology. *Int J Chron Obstruct Pulmon Dis*. 2011;6: 373–383.
23. Daniels JM, Snijders D, de Graaff CS, Vlasplolder F, Jansen HM, Boersma WG. Antibiotics in addition to systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2010;181(2):150–157.
24. Erbland ML, Deupree RH, Niewoehner DE. Systemic corticosteroids in chronic obstructive pulmonary disease exacerbations (SCCOPE): rationale and design of an equivalence trial. Veterans Administration Cooperative Trials SCCOPE Study Group. *Control Clin Trials*. 1998; 19(4):404–417.
25. Niewoehner DE, Erbland ML, Deupree RH, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. *N Engl J Med*. 1999;340(25):1941–1947.
26. Vermeersch K, Gabrovská M, Deslypere G, et al. The Belgian trial with azithromycin for acute COPD exacerbations requiring hospitalization: an investigator-initiated study protocol for a multicenter, randomized, double-blind, placebo-controlled trial. *Int J Chron Obstruct Pulmon Dis*. 2016;11:687–696.
27. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med*. 2009; 360(14):1418–1428.
28. Crisafulli E, Guerrero M, Chetta A, Torres A. Readmission in COPD patients: should we consider it a marker of quality of care or a marker of a more severe disease with a worse prognosis? *Eur Respir J*. 2016; 48(1):279–281.
29. Guerrero M, Crisafulli E, Liapikou A, et al. Readmission for acute exacerbation within 30 days of discharge is associated with a subsequent progressive increase in mortality risk in COPD patients: a long-term observational study. *PLoS One*. 2016;11(3):e0150737.
30. Kim S, Emerman CL, Cydulka RK, et al; MARC Investigators. Prospective multicenter study of relapse following emergency department treatment of COPD exacerbation. *Chest*. 2004;125(2):473–481.
31. Crisafulli E, Ortega S, Torres A. Predictors of readmission in a period of 30 days or less in acute exacerbation of chronic obstructive pulmonary disease. *Clin Pulm Med*. 2015;22(4):172–176.
32. Zapatero A, Barba R, Ruiz J, et al. Malnutrition and obesity: influence in mortality and readmissions in chronic obstructive pulmonary disease patients. *J Hum Nutr Diet*. 2013;26(suppl 1):16–22.
33. Sharif R, Parekh TM, Pierson KS, Kuo YF, Sharma G. Predictors of early readmission among patients 40 to 64 years of age hospitalized for chronic obstructive pulmonary disease. *Ann Am Thorac Soc*. 2014; 11(5):685–694.
34. Chan FW, Wong FY, Yam CH, et al. Risk factors of hospitalization and readmission of patients with COPD in Hong Kong population: analysis of hospital admission records. *BMC Health Serv Res*. 2011; 11:186.
35. Garcia-Aymerich J, Farrero E, Félez MA, et al; Estudi del Factors de Risc d'Agudització de la MPOC investigators. Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. *Thorax*. 2003;58(2):100–105.
36. González C, Servera E, Marín J. Importance of noninvasively measured respiratory muscle overload among the causes of hospital readmission of COPD patients. *Chest*. 2008;133(4):941–947.
37. Lin J, Xu Y, Wu X, et al. Risk factors associated with chronic obstructive pulmonary disease early readmission. *Curr Med Res Opin*. 2014;30(2):315–320.
38. Almagro P, Barreiro B, Ochoa de Echaguen A, et al. Risk factors for hospital readmission in patients with chronic obstructive pulmonary disease. *Respiration*. 2006;73(3):311–317.
39. Vilaró J, Ramirez-Sarmiento A, Martínez-Llorens JM, et al. Global muscle dysfunction as a risk factor of readmission to hospital due to COPD exacerbations. *Respir Med*. 2010;104(12):1896–1902.
40. Cao Z, Ong KC, Eng P, Tan WC, Ng TP. Frequent hospital readmissions for acute exacerbation of COPD and their associated factors. *Respirology*. 2006;11(2):188–195.
41. Gudmundsson G, Gislason T, Janson C, et al. Risk factors for rehospitalisation in COPD: role of health status, anxiety and depression. *Eur Respir J*. 2005;26(3):414–419.
42. Coventry PA, Gemmell I, Todd CJ. Psychosocial risk factors for hospital readmission in COPD patients on early discharge services: a cohort study. *BMC Pulm Med*. 2011;11:49.
43. Wong AW, Gan WQ, Burns J, Sin DD, van Eeden SF. Acute exacerbation of chronic obstructive pulmonary disease: influence of social factors in determining length of hospital stay and readmission rates. *Can Respir J*. 2008;15(7):361–364.
44. Dahlén I, Janson C. Anxiety and depression are related to the outcome of emergency treatment in patients with obstructive pulmonary disease. *Chest*. 2002;122(5):1633–1637.
45. de Batlle J, Mendez M, Romieu I, et al; PAC-COPD Study Group. Cured meat consumption increases risk of readmission in COPD patients. *Eur Respir J*. 2012;40(3):555–560.
46. Ozyilmaz E, Kokturk N, Teksüt G, Tatlicioglu T. Unsuspected risk factors of frequent exacerbations requiring hospital admission in chronic obstructive pulmonary disease. *Int J Clin Pract*. 2013;67(7): 691–697.
47. Wilson R, Anzueto A, Miravittles M, et al. Prognostic factors for clinical failure of exacerbations in elderly outpatients with moderate-to-severe COPD. *Int J Chron Obstruct Pulmon Dis*. 2015;10: 985–993.
48. Hartl S, Lopez-Campos JL, Pozo-Rodríguez F, et al. Risk of death and readmission of hospital-admitted COPD exacerbations: European COPD Audit. *Eur Respir J*. 2016;47(1):113–121.
49. Steer J, Norman EM, Afolabi OA, Gibson GJ, Bourke SC. Dyspnoea severity and pneumonia as predictors of in-hospital mortality and early readmission in acute exacerbations of COPD. *Thorax*. 2012;67(2): 117–121.
50. Almagro P, Cabrera FJ, Diez J, et al; Working Group on, COPD, Spanish Society of Internal Medicine. Comorbidities and short-term prognosis in patients hospitalized for acute exacerbation of COPD: the EPOC en Servicios de medicina interna (ESMI) study. *Chest*. 2012;142(5):1126–1133.
51. McGhan R, Radcliff T, Fish R, Sutherland ER, Welsh C, Make B. Predictors of rehospitalization and death after a severe exacerbation of COPD. *Chest*. 2007;132(6):1748–1755.
52. Wang YC, Lin JM, Li CY, Lee LT, Guo YL, Sung FC. Prevalence and risks of chronic airway obstruction: a population cohort study in Taiwan. *Chest*. 2007;131(3):705–710.
53. Crisafulli E, Torres A, Huerta A, et al. C-reactive protein at discharge, diabetes mellitus and ≥ 1 hospitalization during previous year predict early readmission in patients with acute exacerbation of chronic obstructive pulmonary disease. *COPD*. 2015;12(3):306–314.
54. Bhatt SP, Khandelwal P, Nanda S, Stoltzfus JC, Fioravanti GT. Serum magnesium is an independent predictor of frequent readmissions due to acute exacerbation of chronic obstructive pulmonary disease. *Respir Med*. 2008;102(7):999–1003.
55. Du Q, Jin J, Liu X, Sun Y. Bronchiectasis as a comorbidity of chronic obstructive pulmonary disease: a systematic review and meta-analysis. *PLoS One*. 2016;11(3):e0150532.
56. Mao B, Lu HW, Li MH, et al. The existence of bronchiectasis predicts worse prognosis in patients with COPD. *Sci Rep*. 2015;5:10961.
57. Jin J, Yu W, Li S, Lu L, Liu X, Sun Y. Factors associated with bronchiectasis in patients with moderate-severe chronic obstructive pulmonary disease. *Medicine (Baltimore)*. 2016;95(29):e4219.

58. Martínez-García MÁ, Soler-Cataluña JJ, Donat Sanz Y, et al. Factors associated with bronchiectasis in patients with COPD. *Chest*. 2011; 140(5):1130–1137.
59. Faner R, Tal Singer R, Riley J, et al. Lesson from ECLIPSE: a review of COPD biomarkers. *Thorax*. 2014;69:666–672.
60. Thomsen M, Ingebrigtsen TS, Marott JL, et al. Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease. *JAMA*. 2013;309(22):2353–2361.
61. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med*. 2010;363: 1128–1138.
62. Perera WR, Hurst JR, Wilkinson TM, et al. Inflammatory changes, recovery and recurrence at COPD exacerbation. *Eur Respir J*. 2007; 29(3):527–534.
63. Sethi S, Wrona C, Eschberger K, Lobbins P, Cai X, Murphy TF. Inflammatory profile of new bacterial strain exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2008; 177(5):491–497.
64. Crisafulli E, Torres A, Huerta A, et al. Predicting in-hospital treatment failure (≤ 7 days) in patients with COPD exacerbation using antibiotics and systemic steroids. *COPD*. 2016;13(1):82–92.
65. Hu G, Wu Y, Zhou Y, et al. Prognostic role of D-dimer for in-hospital and 1-year mortality in exacerbations of COPD. *Int J Chron Obstruct Pulmon Dis*. 2016;11:2729–2736.
66. Sin DD, Hollander Z, DeMarco ML, MxManus BM, Ng RT. Biomarker development for COPD: From discovery to clinical implementation. *Am J Respir Crit Care Med*. 2015;192(10):1162–1170.
67. Cabrera-Rubio R, Garcia-Núñez M, Setó L, et al. Microbiome diversity in the bronchial tracts of patients with chronic obstructive pulmonary disease. *J Clin Microbiol*. 2012;50(11):3562–3568.
68. Huang YJ, Sethi S, Murphy T, Nariya S, Boushey HA, Lynch SV. Airway microbiome dynamics in exacerbations of chronic obstructive pulmonary disease. *J Clin Microbiol*. 2014;52(8):2813–2823.
69. Patel I, Seemungal T, Wilks M, Lloyd-Owen SJ, Donaldson GC, Wedzicha JA. Relationship between bacterial colonisation and the frequency, character, and severity of COPD exacerbations. *Thorax*. 2002;57(9):759–764.
70. Monso E, Rosell A, Bonet G, et al. Risk factors for lower airway bacterial colonization in chronic bronchitis. *Eur Respir J*. 1999;13(2): 338–342.
71. Millares L, Ferrari R, Gallego M, et al. Bronchial microbiome of severe COPD patients colonised by *Pseudomonas aeruginosa*. *Eur J Clin Microbiol Infect Dis*. 2014;33(7):1101–1111.
72. Wilkinson TM, Donaldson GC, Hurst JR, Seemungal TA, Wedzicha JA. Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2004;169(12): 1298–1303.
73. Miravittles M, Kruesmann F, Haverstock D, Perroncel R, Choudhri SH, Arvis P. Sputum colour and bacteria in chronic bronchitis exacerbations: a pooled analysis. *Eur Respir J*. 2012;39(6):1354–1360.
74. Chow AW, Hall CB, Klein JO, Kammer RB, Meyer RD, Remington JS. Evaluation of new anti-infective drugs for the treatment of respiratory tract infections. Infectious Diseases Society of America and the Food and Drug Administration. *Clin Infect Dis*. 1992;15(suppl 1): S62–S68.
75. White AJ, Gompertz S, Bayley DL, et al. Resolution of bronchial inflammation is related to bacterial eradication following treatment of exacerbations of chronic bronchitis. *Thorax*. 2003;58(8):680–685.
76. Soler N, Esperatti M, Ewig S, Huerta A, Agustí C, Torres A. Sputum purulence-guided antibiotic use in hospitalised patients with exacerbations of COPD. *Eur Respir J*. 2012;40(6):1344–1353.
77. Stolz D, Christ-Crain M, Bingisser R, et al. Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. *Chest*. 2007;131(1):9–19.
78. Wilson R, Allegra L, Huchon G, et al. Short and long-term outcomes of moxifloxacin compared to standard antibiotic treatment in acute exacerbations of chronic bronchitis. *Chest*. 2004;125:953–964.
79. Ruiz-Gonzalez A, Gimenez A, Gomez-Arbones X, et al. Open-label, randomized comparison trial of long-term outcomes of levofloxacin versus standard antibiotic therapy in acute exacerbations of chronic obstructive pulmonary disease. *Respirology*. 2007;12(1):117–121.
80. Lode H, Eller J, Linnhoff A, Ioanas M. Evaluation of therapy free interval in COPD patients study group. Levofloxacin versus clarithromycin in COPD exacerbation: focus on exacerbation-free interval. *Eur Respir J*. 2004;24:947–953.
81. Chodosh S, Schreurs A, Siami G, et al. Efficacy of oral ciprofloxacin vs. clarithromycin for treatment of acute bacterial exacerbations of chronic bronchitis. *Clin Infect Dis*. 1998;27:730–738.
82. Wilson R, Anzueto A, Miravittles M, et al. Moxifloxacin vs amoxicillin/clavulanic acid in outpatient acute exacerbations of COPD: MAESTRAL results. *Eur Respir J*. 2012;40:17–27.
83. Eisner MD, Trupin L, Katz PP, et al. Development and validation of a survey-based COPD severity score. *Chest*. 2005;127(6):1890–1897.
84. Burrows B, Earle RH. Course and prognosis of chronic obstructive lung disease: a prospective study of 200 patients. *N Engl J Med*. 1969; 280:397–404.
85. Miravittles M, Izquierdo I, Herrejón A, et al; ESFERA Investigators. COPD severity score as a predictor of failure in exacerbations of COPD. The ESFERA study. *Respir Med*. 2011;105(5):740–747.

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