An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations

The Rome Proposal

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Over 200 years ago, René Laennec published the first description of emphysema, an important pathobiological element of what is today known as chronic obstructive pulmonary disease (COPD) (1). He stated that the disease was characterized by persistent dyspnea punctuated by acute episodes of worsening, frequently associated with newly developed and/or worsening cough and sputum (labeled as "acute catarrh") that could lead to "suffocation." These episodes have subsequently been termed "exacerbations of COPD" (ECOPDs) (2, 3). Over 150 years later, Anthonisen and colleagues (4) provided a definition, similar to Laennec's, that has remained relatively unchanged over the last 35 years and forms the basis of the European Respiratory Society/American Thoracic Society definition: "In a patient with underlying COPD, exacerbations are episodes of increasing respiratory symptoms, particularly dyspnea, cough and sputum production, and increased sputum purulence" (5). A slightly modified definition has been used primarily in the research field: "A sustained worsening of the patient's condition from the stable state and beyond normal day-to-day variations, necessitating a change in regular medication in a patient with underlying COPD" (6). This definition is similar to that in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document, which reads, "An acute worsening of respiratory symptoms that results in additional therapy" (7). GOLD

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then classifies ECOPD severity as mild when only symptoms are reported and the patient is treated with inhaled short-acting bronchodilators; moderate when the patient receives antibiotics, systemic corticosteroids, or both; and severe when the patient visits an emergency room or is hospitalized because of the event (6, 7). Without denying the therapeutic progress made in the prevention of ECOPDs (5–8), treatment of the episodes *per se* has remained relatively unchanged (5, 7, 9).

Shortcomings of the Current ECOPD Definition

The current definition of ECOPD has several shortcomings that adversely affect clinical and healthcare decisions (*see* Table E1 in the online supplement). First, it relies exclusively on a patient's subjective perception of increased respiratory symptoms, which varies from patient to patient (10) and can be mimicked and/or aggravated by other conditions such as pneumonia, cardiac events, or pulmonary embolism (6, 7, 11, 12). Second, it does not relate the symptoms to measurable pathophysiological variables that could characterize the event itself. Third, it lacks a framework for timing of the event's evolution, an element that can help differentiate ECOPDs from other processes with similar symptoms. Finally, severity is established *post hoc* by the healthcare resource used to treat the event (13, 14), with this subjectivity introducing variability due to differences between practitioners and healthcare systems. A novel approach is therefore needed because precise, practical, and objective point-of-care definitions and severity assessments for acute medical events are needed by clinicians and researchers if they are to effectively diagnose them at the point of contact, assess the prognosis, and implement precision treatment (15). All of these shortcomings could be overcome by integrating knowledge gathered from observational and interventional studies, as well as with the help of currently available technology capable of measuring in real time the clinical and laboratory variables that can serve as surrogate markers of event severity.

Scope of this Perspective

This perspective proposes an updated definition and severity classification of ECOPDs based on the principles outlined by Scadding (16) for the taxonomy of diseases, integrating symptoms, function, and surrogate markers of the process underlying ECOPDs. It intends to be objective, practical, and useful to clinicians and researchers alike. In its development, the authors acknowledge that episodes of the worsening of respiratory symptoms similar to ECOPDs may occur in patients with chronic diseases other than COPD, and these potential causes should be considered in the differential diagnosis of the event (7, 17). The process itself was initiated and coordinated by B.R.C. and L.M.F., aided by a medical writer (D.Y.), who identified experts with international recognition who have conducted research and published on the definition, diagnosis, pathobiology, and/or treatment of ECOPDs as well as similar events in closely related fields. A modified Delphi method (18, 19) was considered the most appropriate scientific tool to achieve the desired goals because *1*) it is a valid method to obtain consensus based on informed opinions; *2*) it provides a structured mechanism to maintain a fluid communication process, allowing individuals to deal with a complex problem; *3*) the issue in question does not lend itself to precise analytical techniques but can benefit from subjective judgments on a collective basis; and *4*) the method is based on anonymous responses to the selected items, thus decreasing the chance that the dominant personality of one or more of the participants may drive the final conclusions.

Because of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, an initial face-to-face meeting to be held in January of 2020 in Rome, Italy—hence the name of this proposal—was replaced with a virtual meeting to define the project. Given the need to maintain continuous interaction and as suggested by Delphi methodologists (18, 19), a target panel size of 15–20 experts was agreed on, and of the 19 members contacted, 17 accepted (Table E2). The method consisted of sequential rounds of questions, each followed by virtual meetings with open discussions of results (modified Delphi method), which were aimed at facilitating consensus building. Details of the 1-year process, the 80 items evaluated, and Delphi references are included in the online supplement (Figure E1, Tables E3–E7, and text of the online supplement). The results and the different drafts of the manuscript were circulated to the panelists, all of whom contributed to this perspective.

The ECOPD Conceptual Model and Proposed Definition

Current evidence indicates that an ECOPD is characterized by an acute burst of airway inflammation due to bacteria, viruses, environmental pollutants, or other stimuli (Figure 1) (2–4, 20–28). This has been documented by carefully conducted studies in the outpatient and inpatient settings (21, 29), with many studies showing that the inflammatory process may expand systemically (29). This inflammatory burst, coupled with worsening of the existing airflow limitation, increases the work of breathing in patients with limited respiratory reserve. A vicious cycle of increased airways resistance and tachypnea leads to gas trapping in the lungs, respiratory muscle dysfunction, worsening dyspnea, and $\dot{V}/\dot{Q}$ mismatch manifesting as arterial hypoxemia with or without hypercapnia (30–35). In some patients, ventilatory demand exceeds reserve, leading to ventilatory insufficiency, hypercapnia, and respiratory acidosis that, if untreated, may cause death (34).

On the basis of this conceptual model, the panel agreed to propose the following definition: "In a patient with COPD, an exacerbation is an event characterized by dyspnea and/or cough and sputum that worsen over $\leq$14 days, which may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insult to the airways." These events can be life-threatening and require adequate evaluation and treatment.

Timing of ECOPD

A review of the literature provides reasonable support of a time frame for exacerbations to develop. Indeed, a study of 4,439 exacerbations showed that the time from first onset of worsening respiratory symptoms to a

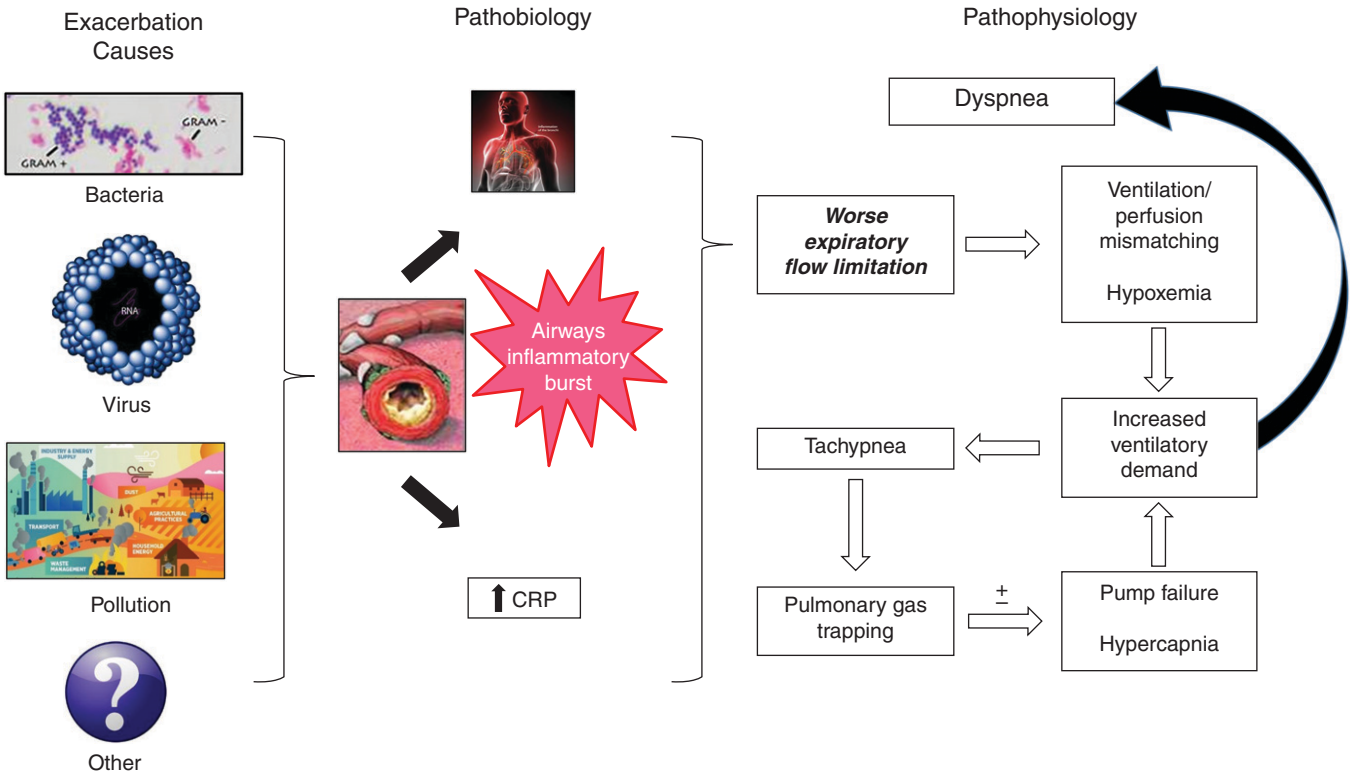

Figure 1. Causes, pathobiological mechanisms, and pathophysiological consequences in an exacerbation of chronic obstructive pulmonary disease (7, 35). CRP = C-reactive protein.

full ECOPD ranged from 0–5 days in 90% of patients, with an overall range of 0–14 days being shown (36). This is similar to an observational study that, by using diary cards, described prodromal symptoms over 4–7 days, with lung function then decreasing abruptly on the day of documentation of the ECOPD (37). Importantly, subjects with COPD experimentally infected with rhinovirus develop upper respiratory symptoms 2–3 days after the inoculation, with lower respiratory symptoms and breathlessness peaking 4–10 days after infection (38). These observations helped with reaching a consensus that the upper time limit for an ECOPD to develop is 14 days from first onset of symptom worsening and that an ECOPD may develop over just hours in some cases. The timing of the resolution of ECOPDs is less well established. In a study of 101 patients observed over 2.5 years, median recovery times from the onset of ECOPDs were 6 days (interquartile range, 1–14 d) for the peak expiratory flow (PEF) and 7 days (interquartile range, 4–14 d) for the daily total symptom score (37). Recovery of the PEF to baseline values occurred in only 75.2% of ECOPDs by 35 days and in 92.9% of ECOPDs by 91 days. In a small proportion of patients, PEF values or symptoms never returned to normal, an observation similar to that of another study of 145 patients (39). The use of objective variables that are readily measurable to determine severity, as proposed in this perspective, could improve knowledge about the time of resolution, a much-needed metric to compare the effectiveness of therapies.

Grading the Severity of an ECOPD

The current grading of the severity of an ECOPD, based on *post facto* use of healthcare resources, is a major limitation of the current definition. Because of global variability in the available resources to treat patients and local customs affecting the criteria for hospital visits and admissions, there is substantial variability in reported ECOPD outcomes (13, 40). This is of particular importance in the interpretation of results of interventional studies and in the planning of future clinical trials (13). To address this limitation, the panelists propose three mutually exclusive severity categories (mild, moderate, and severe), which integrate six objectively measured variables that serve as markers of event severity: dyspnea, oxygen saturation, respiratory rate, heart rate, serum CRP (C-reactive protein), and, in selected cases, arterial blood gases (Table 1). These variables were agreed on through consensus from a potential list of 21 that were the subject of a thorough literature review and discussion. Of these potential variables, the worsening of cough and sputum deserved special attention. A cough and sputum increase and/or a sputum color change can occur during an ECOPD and, in a proportion of cases, may be the most relevant symptoms or signs (20); however, their intensity has not been properly measured, making it difficult to include them in an ECOPD severity classification. However, although the cough and sputum variables remain an integral part of the ECOPD definition, the panelists agreed that worsening dyspnea is the most relevant symptom for most patients, and because it is measurable, it is useful when grading the episode's severity.

Table 1. The Rome Proposal for an Updated Definition and Severity Classification of COPD Exacerbations

Definition	In a patient with COPD, an exacerbation is an event characterized by dyspnea and/or cough and sputum that worsen over ⩽14 d, which may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insult to the airways.
Diagnostic approach	1. These events can be life-threatening and require adequate evaluation and treatment. 2. Complete a thorough clinical assessment for evidence of COPD and potential respiratory and nonrespiratory concomitant diseases, including consideration of alternative causes for the patient's symptoms and signs: primarily pneumonia, heart failure, and pulmonary embolism. 3. Assess: a. Symptoms, severity of dyspnea as determined by using a VAS, and documentation of the presence of cough. b. Signs (tachypnea, tachycardia), sputum volume and color, and respiratory distress (accessory muscle use). 4. Evaluate severity by using appropriate additional investigations such as pulse oximetry, laboratory assessment, and CRP and/or arterial blood gases. 5. Establish the cause of the event (viral, bacterial, environmental, other).

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; VAS = visual analog scale.

Measurable Variables Useful for Grading the Severity of an ECOPD

Dyspnea

In COPD clinical studies, dyspnea changes over time have been measured by using several scales, including diary cards (36, 37), the Transitional Dyspnea Index (41), and the EXAcerbations of Chronic pulmonary disease tool (EXACT-PRO) (42). However, most patients with COPD do not routinely quantify their daily dyspnea intensity. Consensus was reached to recommend the visual analog scale (VAS), which has been validated against ventilatory loads (43), can be represented by a numerical scale from 0 (no shortness of breath) to 10 (maximal shortness of breath ever experienced) (43), and has a minimally clinical important difference of 1 (44). The resting VAS dyspnea values range from 0 to 3 in patients with COPD (10, 43, 45), whereas when measured in the emergency ward or in the hospital, values are higher than 4 (30, 35, 46). Experts agreed that a VAS score ⩾5 (on a scale of 0–10) in the context of a suspected ECOPD indicates severe dyspnea. This pragmatic approach removes the need to consider a change in dyspnea from a previous baseline VAS value.

Respiratory and Heart Rates

Studies have shown that both the heart rate and the respiratory rate increase in the days preceding, during, and after an ECOPD (30, 31, 47, 48) and are measurable by widely available noninvasive methods, offering a window to the severity of the episodes (48–51). The resting heart rate increases with COPD severity and is associated with mortality risk (52), regardless of etiology or medication use. Heart rates >85 beats per minute (bpm) or increases in heart rates by 10–15 bpm compared with baseline were reported during an acute exacerbation (49). Respiratory rates >24 breaths per minute, with shortened expiratory time leading to gas trapping, have been consistently reported in most studies conducted in hospitalized patients (51, 53), whereas respiratory rates of 18–20 breaths per minute were documented in patients receiving outpatient care (53). The panel reached a consensus that a heart rate <95 bpm and a respiratory rate <24 breaths per minute could help separate mild ECOPDs from moderate ECOPDs.

Hypoxemia and Hypercapnia

$\dot{V}/\dot{Q}$ imbalance is the most important mechanism responsible for the gas exchange abnormalities in COPD (32, 33). Given that stable COPD can be associated with arterial hypoxemia with or without hypercapnia, both absolute measurements and a change in values would be useful as determinants of severity. Assessment of blood gases is ideal, but it is not available in all clinical settings, whereas pulse oximetry is practical and widely available, although we acknowledge that it may be less accurate in Black patients (7). It is known that decompensated hypercapnic respiratory failure is associated with increased mortality (34), which is reduced by noninvasive ventilation (34, 54). Although expert societies recommend titrating supplemental oxygen during an ECOPD to an Sa_{O2} of 88–92% (7, 55), studies of ECOPDs suggest the average reduction in Sa_{O2} was not more than 2% (56, 57). On the basis of this evidence, the panel agreed that when the change from baseline is known, a mild ECOPD would be characterized by an Sa_{O2} ⩾92% and/or a change ⩽3%, a moderate event would be characterized by an Sa_{O2} <92% and/or a change >3%, and a severe event would be characterized by acidotic hypercapnic respiratory failure (i.e., a Pa_{CO2} >45 mm Hg and a pH <7.35).

Serum CRP

Healthy subjects, smokers without COPD, and patients with stable COPD usually have CRP values <10 mg/L (58, 59), with higher values within this range being associated with an increased risk of hospitalization and death (60, 61). Serum CRP levels increase in both viral and bacterial ECOPDs (25, 26), although they are usually higher in the latter (22, 26), which is why values may be used at the point of care to guide antibiotic therapy (26, 62). In outpatients with COPD who are suffering an ECOPD, CRP levels increase modestly from basal values (23, 63). In patients in the emergency ward or admitted to the hospital, higher CRP values have been reported, ranging from 8 to 156 mg/L (63–65). Although the panel acknowledged the lack of specificity of using serum CRP as a marker of airway or lung inflammation, consensus was reached that a CRP value ⩾10 mg/L can help separate mild ECOPDs from moderate ECOPDs. We do not assign CRP a weight any different from those of the heart rate, respiratory rate, or oxygen saturation. A patient could have a more severe episode defined exclusively by a combination of the clinical signs without a CRP >10 mg/L. Our proposal aims to help push the inclusion of at least one measurable point-of-care marker, the threshold of which can be amended over time if this proposal is implemented and the results so suggest.

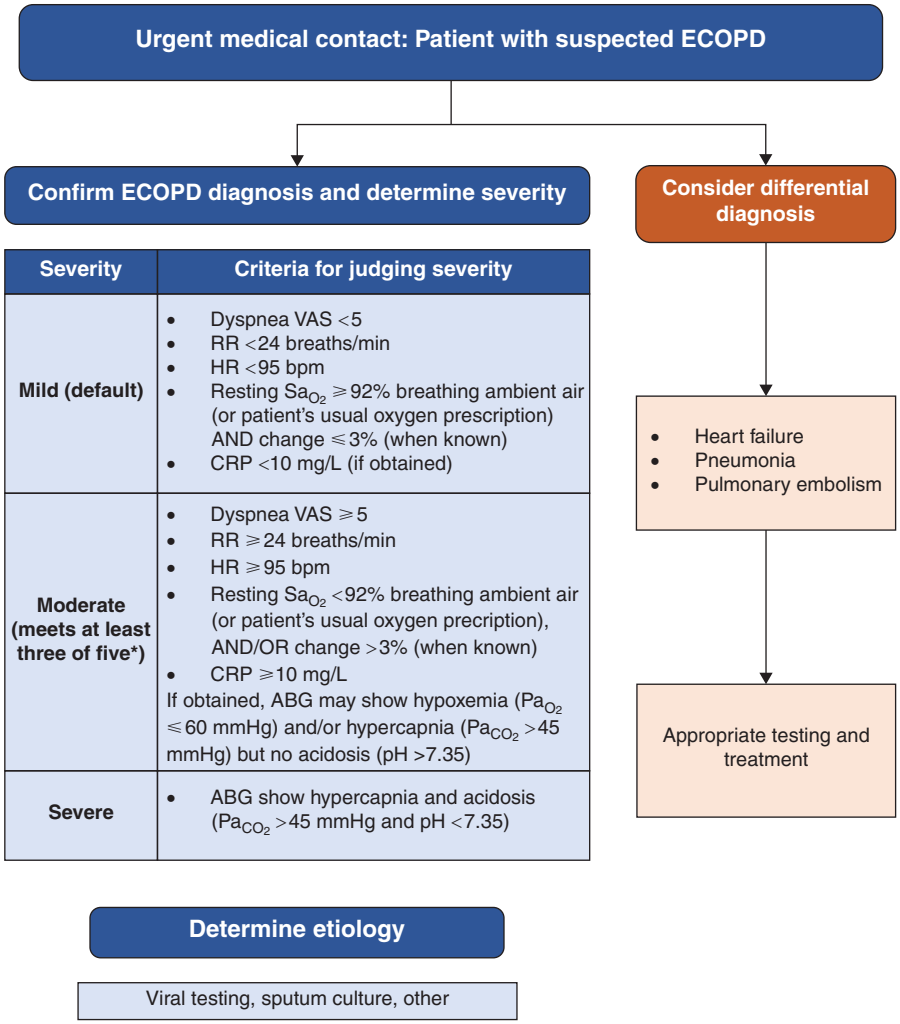

Figure 2. Diagnostic approach to a patient suspected of an ECOPD. *Dyspnea (as determined by using a VAS), RR, HR, oxygen saturation (absolute and/or change), and CRP. ABG = arterial blood gas; CRP = C-reactive protein; ECOPD = exacerbation of chronic obstructive pulmonary disease; HR = heart rate; RR = respiratory rate; VAS = visual analog scale.

Integration of the Variables into a Practical Severity Classification Scale

The panelists agreed that integration of the five easy-to-evaluate parameters (dyspnea, respiratory rate, heart rate, oxygen saturation, and serum CRP) should be used to assess the severity of an ECOPD, both in the clinical evaluation of patients and in research and clinical trials (Table 1 and Figure 2). The default severity classification is that of a mild event. For an episode to be considered moderate, at least three of these five parameters, all of which carry a similar weight, should be worse than those threshold values characteristic of a mild ECOPD. The panelists also agreed that for an ECOPD to be considered severe, a sixth variable, arterial blood gas values, must indicate the presence of hypercapnia ($Pa_{CO2} > 45$ mm Hg) and respiratory acidosis (pH < 7.35).

Other Important Tests

The panelists reviewed 16 other clinical and laboratory tests used in the diagnosis and severity classification of ECOPDs (Tables E3 and E4). Of these, several require some comments. Routine spirometry or any lung function assessment cannot be reliably obtained during an ECOPD, as patients are usually too sick to perform an adequate spirometry maneuver, changes from baseline are often small, and pre-ECOPD results may not be available. Panelists also believed that efforts made to develop accurate devices that can help monitor lung function over time would provide a major advance in our capacity to integrate this variable into future improvements on this proposal. Peripheral blood eosinophils would have potential use for therapeutic guidance, particularly regarding the use of systemic steroids (66), but eosinophil levels have not been used for ECOPD diagnosis or severity classification. Chest roentgenograms are useful for differentiating pneumonia (and other conditions that may mimic an ECOPD, such as pneumothorax or pleurisy) from an ECOPD (67), and they are frequently obtained in patients seen in healthcare facilities, but this tool has not been used to define or classify the severity of an ECOPD.

Confounding Morbidities

A review of the literature revealed at least 28 conditions that may clinically mimic an ECOPD (Table E5), and the panelists reached a strong consensus that three deserved special consideration (heart failure, pneumonia, and pulmonary embolism) (7, 17, 31, 67–71), not only because of their frequency but also because they require specific and prompt management to improve outcomes. The panel acknowledged that these conditions may coexist with ECOPDs and influence the evolution of each other. As summarized in Table 1 and Figure 2, a thorough clinical evaluation is often adequate to exclude these conditions; however, further diagnostic testing such as additional imaging studies and biomarker measurements may be required. Although the panel acknowledged the difficulty with categorizing events, or their synchronic occurrence, as the single or main cause of clinical decompensation in some patients, it should be possible in most healthcare settings to establish a correct diagnosis. Other comorbid conditions did not receive unanimous agreement or disagreement but deserve some comments; five (pneumothorax, acute anxiety, asthma attack, myocardial infarction, and arrythmias) were believed to have specific clinical, radiological, and laboratory characteristics that facilitate their diagnosis. For the remaining potential confounders, the panelists believed their inclusion was of lesser importance (i.e., strong disagreement over their inclusion) and should only be considered in rare circumstances. A practical approach to patients with symptoms consistent with an ECOPD is summarized in Figure 2. The Rome proposal for an updated definition and severity classification of ECOPDs will not preclude a more precise approach based on treatable traits in future studies (72).

Limitations of this Proposal

The panelists acknowledge that there are some limitations to this proposal. First, the present document was drafted by experts from North America and Western Europe. This choice was influenced by the SARS-CoV-2 pandemic and the need to host discussions by videoconference, which would have made discussions difficult across discordant time zones. The inclusion of experts from eight countries and six main specialties does provide some confidence about the wide scope of the panelists' expertise. In addition, the validation of the elements contained in this proposal is open for everyone to test. Second, the number of participants selected may seem arbitrary; however, it is within the optimal number recommended by experts in the methodology of the Delphi process, allowing for ample discussion during the virtual meetings (*see* the text of the online supplement). Third, the selection of the thresholds for the different variables included in the severity classification and for the timing of the ECOPD may seem arbitrary and not based on prospectively validated studies. However, they were agreed on by anonymous consensus after review of the available literature and intense discussion between rounds (Table E6), significant features of the Delphi methodology. Of note, in this era of technological devices, continuous accurate monitoring of measurable variables may better help with detecting the onset of an event and its resolution over time, facilitating not only the evaluation of novel therapies but also the implementation of early interventions before the event progresses.

Conclusions

The Rome proposal for an updated definition and severity classification of ECOPDs was drafted by an international panel of experts by using a framework that focused on feasibility and potential validity. The consensus was reached by using a modified Delphi methodology, informed by data from studies reporting objective measurements of symptoms, signs, physiological variables, and biomarkers. The predictive value of the variables classifying the severity was assessed by using the potential intensity of care needed for treatment and stabilization of the patient. This revised definition addresses many of the shortcomings of the current definition and should better inform clinical care, research, and health service planning but needs to be validated prospectively in adequately designed and powered studies. ■

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References

1. Laennec RTH; Forbes J, editor. A treatise on the diseases of the chest. London, UK: T & G Underwood; 1821.
2. Wedzicha JA, Donaldson GC. Exacerbations of chronic obstructive pulmonary disease. *Respir Care* 2003;48:1204–1213, discussion 1213–1215.
3. Celli BR, Barnes PJ. Exacerbations of chronic obstructive pulmonary disease. *Eur Respir J* 2007;29:1224–1238.
4. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987;106:196–204.
5. Wedzicha JA, Calverley PMA, Albert RK, Anzueto A, Criner GJ, Hurst JR, *et al.* Prevention of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J* 2017;50:1600791.
6. Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. *Chest* 2000;117:398S–401S.
7. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Fontana, WI: Global Initiative for Chronic Obstructive Lung Disease; 2021; [accessed 2021 May 24]. Available from: https://goldcopd.org/2021-gold-reports/.
8. Celli BR, Wedzicha JA. Update on clinical aspects of chronic obstructive pulmonary disease. *N Engl J Med* 2019;381:1257–1266.
9. Niewoehner DE, Erbland ML, Deupree RH, Collins D, Gross NJ, Light RW, *et al.*; Department of Veterans Affairs Cooperative Study Group. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1999;340:1941–1947.
10. Scioscia G, Blanco I, Arismendi E, Burgos F, Gistau C, Foschino Barbaro MP, *et al.* Different dyspnoea perception in COPD patients with frequent and infrequent exacerbations. *Thorax* 2017;72:117–121.
11. Donaldson GC, Hurst JR, Smith CJ, Hubbard RB, Wedzicha JA. Increased risk of myocardial infarction and stroke following exacerbation of COPD. *Chest* 2010;137:1091–1097.
12. Kunisaki KM, Dransfield MT, Anderson JA, Brook RD, Calverley PMA, Celli BR, *et al.*; SUMMIT Investigators. Exacerbations of chronic obstructive pulmonary disease and cardiac events: a *post hoc* cohort analysis from the SUMMIT randomized clinical trial. *Am J Respir Crit Care Med* 2018;198:51–57.

13. Calverley PMA. Minimal clinically important difference: exacerbations of COPD. *COPD* 2005;2:143–148.
14. Effing TW, Kerstjens HAM, Monninkhof EM, van der Valk PDLPM, Wouters EFM, Postma DS, *et al.* Definitions of exacerbations: does it really matter in clinical trials on COPD? *Chest* 2009;136:918–923.
15. Botsis T, Ball R. Automating case definitions using literature-based reasoning. *Appl Clin Inform* 2013;4:515–527.
16. Scadding JG. Health and disease: what can medicine do for philosophy? *J Med Ethics* 1988;14:118–124.
17. Divo M, Celli BR. Multimorbidity in patients with chronic obstructive pulmonary disease. *Clin Chest Med* 2020;41:405–419.
18. Grime MM, Wright G. Delphi method. In: Brandimarte P, Everitt B, Molenberghs G, Piegorsch W, Ruggeri F, editors. Wiley StatsRef: Statistics Reference Online. New York, NY: John Wiley and Sons; 2016. pp. 1–6.
19. Diamond IR, Grant RC, Feldman BM, Pencharz PB, Ling SC, Moore AM, *et al.* Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. *J Clin Epidemiol* 2014;67:401–409.
20. Stockley RA, O'Brien C, Pye A, Hill SL. Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. *Chest* 2000;117:1638–1645.
21. Bozinovski S, Hutchinson A, Thompson M, Macgregor L, Black J, Giannakis E, *et al.* Serum amyloid a is a biomarker of acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008;177:269–278.
22. Gallego M, Pomares X, Capilla S, Marcos MA, Suárez D, Monsó E, *et al.* C-reactive protein in outpatients with acute exacerbation of COPD: its relationship with microbial etiology and severity. *Int J Chron Obstruct Pulmon Dis* 2016;11:2633–2640.
23. Hurst JR, Donaldson GC, Perera WR, Wilkinson TMA, Bilello JA, Hagan GW, *et al.* Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006;174: 867–874.
24. Li J, Sun S, Tang R, Qiu H, Huang Q, Mason TG, *et al.* Major air pollutants and risk of COPD exacerbations: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2016;11:3079–3091.
25. Papi A, Bellettato CM, Braccioni F, Romagnoli M, Casolari P, Caramori G, *et al.* Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med* 2006;173:1114–1121.
26. Miravitlles M, Moragas A, Hernández S, Bayona C, Llor C. Is it possible to identify exacerbations of mild to moderate COPD that do not require antibiotic treatment? *Chest* 2013;144:1571–1577.
27. Perera WR, Hurst JR, Wilkinson TMA, Sapsford RJ, Müllerova H, Donaldson GC, *et al.* Inflammatory changes, recovery and recurrence at COPD exacerbation. *Eur Respir J* 2007;29:527–534.
28. Sethi S, Evans N, Grant BJB, Murphy TF. New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 2002;347:465–471.
29. Chen Y-WR, Leung JM, Sin DD. A systematic review of diagnostic biomarkers of COPD exacerbation. *PLoS One* 2016;11:e0158843.
30. Pinto-Plata VM, Livnat G, Girish M, Cabral H, Masdin P, Linacre P, *et al.* Systemic cytokines, clinical and physiological changes in patients hospitalized for exacerbation of COPD. *Chest* 2007;131:37–43.
31. Diaz O, Iglesia R, Ferrer M, Zavala E, Santos C, Wagner PD, *et al.* Effects of noninvasive ventilation on pulmonary gas exchange and hemodynamics during acute hypercapnic exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997;156: 1840–1845.
32. Rodriguez-Roisin R. Nonpulmonary influences on gas exchange. *Compr Physiol* 2014;4:1455–1494.
33. Barberà JA, Roca J, Ferrer A, Félez MA, Díaz O, Roger N, *et al.* Mechanisms of worsening gas exchange during acute exacerbations of chronic obstructive pulmonary disease. *Eur Respir J* 1997;10:1285–1291.
34. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, *et al.* Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J* 2017;50:1602426.
35. O'Donnell DE, Parker CM. COPD exacerbations: 3. Pathophysiology. *Thorax* 2006;61:354–361.
36. Aaron SD, Donaldson GC, Whitmore GA, Hurst JR, Ramsay T, Wedzicha JA. Time course and pattern of COPD exacerbation onset. *Thorax* 2012;67:238–243.
37. 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: 1608–1613.
38. Mallia P, Message SD, Gielen V, Contoli M, Gray K, Kebadze T, *et al.* Experimental rhinovirus infection as a human model of chronic obstructive pulmonary disease exacerbation. *Am J Respir Crit Care Med* 2011;183:734–742.
39. Cote CG, Dordelly LJ, Celli BR. Impact of COPD exacerbations on patient-centered outcomes. *Chest* 2007;131:696–704.
40. Barbosa-Lorenzo R, Ruano-Ravina A, Fernández-Villar A, López-Pardo E, Carballeira-Roca C, Barros-Dios JM. COPD prevalence and hospital admissions in Galicia (Spain): an analysis using the potential of new health information systems. *Pulmonology* 2018;24:323–329.
41. Mahler DA, Waterman LA, Ward J, McCusker C, ZuWallack R, Baird JC. Validity and responsiveness of the self-administered computerized versions of the baseline and transition dyspnea indexes. *Chest* 2007; 132:1283–1290.
42. Celli BR, Vestbo J. The EXACT-Pro: measuring exacerbations of COPD. *Am J Respir Crit Care Med* 2011;183:287–288.
43. Gift AG, Narsavage G. Validity of the numeric rating scale as a measure of dyspnea. *Am J Crit Care* 1998;7:200–204.
44. Ekström M, Johnson MJ, Huang C, Currow DC. Minimal clinically important differences in average, best, worst and current intensity and unpleasantness of chronic breathlessness. *Eur Respir J* 2020;56: 1902202.
45. Marin JM, Montes de Oca M, Rassulo J, Celli BR. Ventilatory drive at rest and perception of exertional dyspnea in severe COPD. *Chest* 1999; 115:1293–1300.
46. Noell G, Cosío BG, Faner R, Monsó E, Peces-Barba G, de Diego A, *et al.* Multi-level differential network analysis of COPD exacerbations. *Eur Respir J* 2017;50:1700075.
47. Parker CM, Voduc N, Aaron SD, Webb KA, O'Donnell DE. Physiological changes during symptom recovery from moderate exacerbations of COPD. *Eur Respir J* 2005;26:420–428.
48. Hurst JR, Donaldson GC, Quint JK, Goldring JJP, Patel ARC, Wedzicha JA. Domiciliary pulse-oximetry at exacerbation of chronic obstructive pulmonary disease: prospective pilot study. *BMC Pulm Med* 2010;10:52.
49. Tseng CY, Chang JCY, Chen YC, Huang HH, Lin CS, How CK, *et al.* Changes of heart rate variability predicting patients with acute exacerbation of chronic obstructive pulmonary disease requiring hospitalization after emergency department treatment. *J Chin Med Assoc* 2018;81:47–52.
50. Rubio N, Parker RA, Drost EM, Pinnock H, Weir CJ, Hanley J, *et al.* Home monitoring of breathing rate in people with chronic obstructive pulmonary disease: observational study of feasibility, acceptability, and change after exacerbation. *Int J Chron Obstruct Pulmon Dis* 2017;12: 1221–1231.
51. Elvekjaer M, Aasvang EK, Olsen RM, Sørensen HBD, Porsbjerg CM, Jensen JU, *et al.*; WARD-Project Group. Physiological abnormalities in patients admitted with acute exacerbation of COPD: an observational study with continuous monitoring. *J Clin Monit Comput* 2020;34:1051–1060.
52. Jensen MT, Marott JL, Lange P, Vestbo J, Schnohr P, Nielsen OW, *et al.* Resting heart rate is a predictor of mortality in COPD. *Eur Respir J* 2013;42:341–349.
53. Borel JC, Pelletier J, Taleux N, Briault A, Arnol N, Pison C, *et al.* Parameters recorded by software of non-invasive ventilators predict COPD exacerbation: a proof-of-concept study. *Thorax* 2015;70:284–285.
54. Osadnik CR, Tee VS, Carson-Chahhoud KV, Picot J, Wedzicha JA, Smith BJ. Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2017: CD004104.
55. O'Driscoll BR, Howard LS, Earis J, Mak V, British Thoracic Society Emergency Oxygen Guideline Group; BTS Emergency Oxygen Guideline Development Group. BTS guideline for oxygen use in adults in healthcare and emergency settings. *Thorax* 2017;72:ii1–ii90.

56. Al Rajeh AM, Hurst JR. Monitoring of physiological parameters to predict exacerbations of chronic obstructive pulmonary disease (COPD): a systematic review. *J Clin Med* 2016;5:108.
57. Al Rajeh AM, Aldabayan YS, Aldhahir A, Pickett E, Quaderi S, Alqahtani JS, *et al.* Once daily versus overnight and symptom versus physiological monitoring to detect exacerbations of chronic obstructive pulmonary disease: pilot randomized controlled trial. *JMIR Mhealth Uhealth* 2020;8:e17597.
58. Nuñez A, Marras V, Harlander M, Mekov E, Esquinas C, Turel M, *et al.* Association between routine blood biomarkers and clinical phenotypes and exacerbations in chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2020;15:681–690.
59. Andelid K, Andersson A, Yoshihara S, Åhrén C, Jirholt P, Ekberg-Jansson A, *et al.* Systemic signs of neutrophil mobilization during clinically stable periods and during exacerbations in smokers with obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2015; 10:1253–1263.
60. Leuzzi G, Galeone C, Taverna F, Suatoni P, Morelli D, Pastorino U. C-reactive protein level predicts mortality in COPD: a systematic review and meta-analysis. *Eur Respir Rev* 2017;26:160070.
61. Dahl M, Vestbo J, Lange P, Bojesen SE, Tybjaerg-Hansen A, Nordestgaard BG. C-reactive protein as a predictor of prognosis in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;175:250–255.
62. Butler CC, Gillespie D, White P, Bates J, Lowe R, Thomas-Jones E, *et al.* C-reactive protein testing to guide antibiotic prescribing for COPD exacerbations. *N Engl J Med* 2019;381:111–120.
63. Bafadhel M, McKenna S, Terry S, Mistry V, Reid C, Haldar P, *et al.* Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med* 2011;184:662–671.
64. Stolz D, Christ-Crain M, Morgenthaler NG, Leuppi J, Miedinger D, Bingisser R, *et al.* Copeptin, C-reactive protein, and procalcitonin as prognostic biomarkers in acute exacerbation of COPD. *Chest* 2007; 131:1058–1067.
65. Dev D, Wallace E, Sankaran R, Cunniffe J, Govan JRW, Wathen CG, *et al.* Value of C-reactive protein measurements in exacerbations of chronic obstructive pulmonary disease. *Respir Med* 1998;92: 664–667.
66. Bafadhel M, Greening NJ, Harvey-Dunstan TC, Williams JEA, Morgan MD, Brightling CE, *et al.* Blood eosinophils and outcomes in severe hospitalized exacerbations of COPD. *Chest* 2016;150:320–328.
67. Crisafulli E, Manco A, Ferrer M, Huerta A, Micheletto C, Girelli D, *et al.* Pneumonic versus nonpneumonic exacerbations of chronic obstructive pulmonary disease. *Semin Respir Crit Care Med* 2020;41:817–829.
68. Berliner D, Schneider N, Welte T, Bauersachs J. The differential diagnosis of dyspnea. *Dtsch Arztebl Int* 2016;113:834–845.
69. Hawkins NM, Petrie MC, Jhund PS, Chalmers GW, Dunn FG, McMurray JJV. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. *Eur J Heart Fail* 2009;11: 130–139.
70. Couturaud F, Bertoletti L, Pastre J, Roy PM, Le Mao R, Gagnadoux F, *et al.*; PEP Investigators. Prevalence of pulmonary embolism among patients with COPD hospitalized with acutely worsening respiratory symptoms. *JAMA* 2021;325:59–68.
71. Aleva FE, Voets LWLM, Simons SO, de Mast Q, van der Ven AJAM, Heijdra YF. Prevalence and localization of pulmonary embolism in unexplained acute exacerbations of COPD: a systematic review and meta-analysis. *Chest* 2017;151:544–554.
72. Hiles SA, Gibson PG, Agusti A, McDonald VM. Treatable traits that predict health status and treatment response in airway disease. *J Allergy Clin Immunol Pract* 2021;9:1255–1264, e2.