exacerbation broad. Once a clinical diagnosis of a COPD exacerbation is made, maximal effort should be undertaken to better characterize endotypes and identify treatable traits, instead of contemplating the correct clinical label.

The current method for severity classification is determined by healthcare systems. The Rome proposal instead uses the visual analog scale for dyspnea, heart rate, respiratory rate, and C-reactive protein. The thresholds were derived from observational cohorts of hospitalized patients. However, this lacks specificity because most patients treated in the outpatient setting are also tachypneic and tachycardic and have a visual analog scale score for dyspnea greater than 5 (4), and C-reactive protein is frequently raised in patients with COPD exacerbations treated in the community (5). Furthermore, in hospitalized exacerbations from the BACE (Azithromycin for Acute Exacerbations Requiring Hospitalization) study (6), many patients would not even meet the criteria for a moderate event (Figure 1).

Overall, the Rome proposal is a bold step forward to break the mold of our healthcare use–based definition of COPD exacerbations. More work is needed to continue to improve on this to define treatable traits of exacerbations. The CICERO (Collaboration in COPD Exacerbations) program (7) will capture all exacerbations seen in the hospital, inclusive of worsening of comorbidities, with detailed assessments to determine the above. ■

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Sanjay Ramakrishnan, M.D.*‡
University of Oxford
Oxford, United Kingdom
and
Edith Cowan University
Perth, Australia

Iwein Gyselinck, M.D.*
Universitair Ziekenhuis Leuven
Leuven, Belgium
and
Katholieke Universiteit Leuven
Leuven, Belgium

Mona Bafadhel, M.D., Ph.D.
University of Oxford
Oxford, United Kingdom
and
King's College London
London, United Kingdom

Wim Janssens, M.D., Ph.D.
Universitair Ziekenhuis Leuven
Leuven, Belgium
and
Katholieke Universiteit Leuven
Leuven, Belgium

ORCID IDs: 0000-0002-3003-7918 (S.R.); 0000-0002-4068-7228 (I.G.); 0000-0002-9993-2478 (M.B.); 0000-0003-1830-2982 (W.J.).

*These authors contributed equally to this work.
‡Corresponding author (e-mail: sanjay.ramakrishnan@ndm.ox.ac.uk).

References

1. Celli BR, Fabbri LM, Aaron SD, Agusti A, Brook R, Criner GJ, *et al.* An updated definition and severity classification of chronic obstructive pulmonary disease exacerbations: the Rome proposal. *Am J Respir Crit Care Med* 2021;204:1251–1258.
2. Bafadhel M, Criner G, Dransfield MT, Janssens W, McDonald VM, Vogelmeier CF, *et al.* Exacerbations of chronic obstructive pulmonary disease: time to rename. *Lancet Respir Med* 2020;8:133–135.
3. 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.
4. Bafadhel M, McKenna S, Terry S, Mistry V, Pancholi M, Venge P, *et al.* Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2012;186:48–55.
5. 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.
6. Vermeersch K, Gabrovska M, Aumann J, Demedts IK, Corhay J-L, Marchand E, *et al.* Azithromycin during acute chronic obstructive pulmonary disease exacerbations requiring hospitalization (BACE). A multicenter, randomized, double-blind, placebo-controlled trial. *Am J Respir Crit Care Med* 2019;200:857–868.
7. Janssens W, Bafadhel M; Chairs of the CICERO Clinical Research Collaboration; This article was written on behalf of the CICERO Clinical Research Collaboration members. Founding members. The CICERO (Collaboration In COPD ExaceRbatiOns) Clinical Research Collaboration. *Eur Respir J* 2020;55:2000079.

Reply to Bhatt and to Ramakrishnan *et al.*

From the Authors:

We appreciate the positive comments of Dr. Bhatt and Dr. Ramakrishnan and colleagues on the Rome proposal for an updated definition and severity classification of chronic obstructive pulmonary disease exacerbations (ECOPD) (1).

Dr. Bhatt expresses concerns that no minimum timing threshold was proposed for an ECOPD onset. About 50% of patients have a symptom worsening in the hours before ECOPD onset (2, 3), whereas the remaining 50% experience a prodrome of progressive increase of symptoms, including cough (2, 4). Importantly, not having an onset in the timing of ECOPD is supported by the fact that early intervention might impact favorably on outcomes of ECOPD (3, 4). A threshold in the change in the severity of individual or combined symptoms has been used to differentiate day-to-day symptom variation from the onset of an ECOPD (2); empirical research will validate the suggested threshold values that we have proposed (1).

The Rome proposal does not regard cough as a minor symptom. Indeed, Table 2 of the manuscript includes cough in the definition

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itself and the diagnostic approach to the patient. What was not done is to include cough as an objective measure of ECOPD severity, as we could not find any studies to support this. Further comments by Dr. Bhatt related to the difficulty in the use of the dyspnea visual analog scale are not well-founded since the visual analog scale has been used in several ECOPD studies and has been validated against respiratory loads in patients with COPD (5, 6). The same can be said for the use of respiratory rate, heart rate, and, most of all, oxygenation levels, now widely used in this time of the most severe ECOPDs experienced by some of our patients in their lifetime due to coronavirus disease (COVID-19) (7). Finally, Dr. Bhatt suggests that the criterion arterial oxygen saturation (Sa_{O_2}) <92% may be problematic, particularly in patients treated with oxygen. However, Sa_{O_2} is just one of the five easy-to-evaluate parameters that we recommend to assess severity at the point of care (1).

Dr. Ramakrishnan and colleagues support the Rome proposal in adding objective markers of diagnosis and severity of ECOPD and the importance of comorbidities for ECOPD. However, they decry the specificity of the markers agreed on by the experts to include in the proposal. By including serum C-reactive protein, we decided to highlight the importance of inflammation in the assessment of ECOPD severity (1). We believe it is wise to learn from other fields, particularly the successful story of the diagnosis of myocardial injury, which started as a clinical syndrome of angina, to which was first added electrocardiogram changes, and subsequently the abnormal elevation of noncardiac-specific enzyme markers (creatine phosphokinase, serum glutamic oxalacetic transaminase, and lactate dehydrogenase). The specific troponin marker (8) has only been in use in the last three decades but resulted from a progressive evolution, narrowing the definition to a specific event defined as myocardial injury. Remaining anchored to a subjective definition that includes different episodes that may resemble an ECOPD, where the event ends up being only "a diagnosis of exclusion" will not facilitate novel approaches to better manage the episode. None of the major acute events such as acute respiratory distress syndrome, myocardial infarction, stroke, and sepsis, which cause as many deaths as ECOPD, are diagnosed by "exclusion." Progress in their management has been driven by definitions based on subjective and objective markers that have evolved over time. Finally, the argument that, currently, many outpatients develop values that are above the thresholds suggested in the Rome proposal (and that many inpatients do not) is precisely the reason to grade severity based on objective parameters determined at the point of contact. Perhaps some of those patients were managed in the wrong setting.

Dr. Bhatt wisely states that "Rome was not built in one day." We agree, as our work is a "proposal" that intends to improve on a definition that has not evolved, notably Laennec's work in 1821 (9). Using another Italian saying, "perfection is the enemy of the good," the Rome proposal may not be perfect, but through empirical research, it can serve as the foundation to move this field forward. ■

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Bartolome R. Celli, M.D.*
Brigham and Women's Hospital and Harvard Medical School
Boston, Massachusetts

Leonardo M. Fabbri, M.D.
University of Ferrara
Ferrara, Italy

On behalf of all the authors

ORCID IDs: 0000-0002-7266-8371 (B.R.C.); 0000-0001-8894-1689 (L.M.F.).

*Corresponding author (e-mail: bcelli@copdnet.org).

References

1. Celli BR, Fabbri LM, Aaron SD, Agusti A, Brook R, Criner GJ, *et al.* An updated definition and severity classification of COPD exacerbations: The Rome proposal. *Am J Respir Crit Care Med* 2021;204:1251–1258.
2. 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.
3. Chandra D, Tsai CL, Camargo CA Jr. Acute exacerbations of COPD: delay in presentation and the risk of hospitalization. *COPD* 2009;6:95–103.
4. Calverley P, Pauwels Dagger R, Löfdahl CG, Svensson K, Higenbottam T, Carlsson LG, *et al.* Relationship between respiratory symptoms and medical treatment in exacerbations of COPD. *Eur Respir J* 2005;26: 406–413.
5. 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.
6. 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.
7. Gandhi RT, Lynch JB, Del Rio C. Mild or moderate Covid-19. *N Engl J Med* 2020;383:1757–1766.
8. Hamm CW, Ravkilde J, Gerhardt W, Jørgensen P, Peheim E, Ljungdahl L, *et al.* The prognostic value of serum troponin T in unstable angina. *N Engl J Med* 1992;327:146–150.
9. Laennec R. A treatise on the diseases of the chest. In: Forbes J, editor. London: T and G Underwood; 1821.