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Chronic obstructive pulmonary disease exacerbations: Do all roads lead to Rome?

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5. Criner GJ, Cole T, Hahn KA, Kastango K, Eudicone JM, Gilbert I. Use of a digital chronic obstructive pulmonary disease respiratory tracker in a primary care setting: a feasibility study. *Pulm Ther* 2021;7:533–547.

Chronic Obstructive Pulmonary Disease Exacerbations: Do All Roads Lead to Rome?

To the Editor:

The Rome chronic obstructive pulmonary disease (COPD) exacerbation proposal is a welcome step forward (1). Celli and colleagues have attempted to revise the definition and propose a new severity classification, based on measurable clinical and laboratory variables instead. The central role of healthcare use when defining exacerbations has held us back from a better understanding of these critical events.

We agree that it is appealing to direct the definition of an exacerbation toward causation and measurable pathophysiological variables instead of symptoms alone (2). We also sympathize with the concept of a genuine exacerbation being an "inflammatory burst" caused by an "insult to the airways" on a background of chronic inflammation. However, practical implications of narrowing acute COPD exacerbations to these primary inflammatory events need to be considered. The clinical reality is that we have no universal marker that is specific for this implied inflammatory burst and that, despite a thorough work-up, we still do not identify a cause in many exacerbations (3). Currently, exacerbations remain a diagnosis of exclusion. Acute exacerbations of symptoms that are induced by comorbidities such as heart failure or even a panic attack require a different treatment approach. For patients, however, these events are equally frightening and just as much part of the reality of living with COPD. We believe that the emphasis of the Rome proposal on the inflammatory paradigm may shift the focus away from such events. Moreover, in practice, exacerbations of comorbidities and exacerbations of airway inflammation are not mutually exclusive but often coincide. Rather, we would keep the concept of an acute COPD

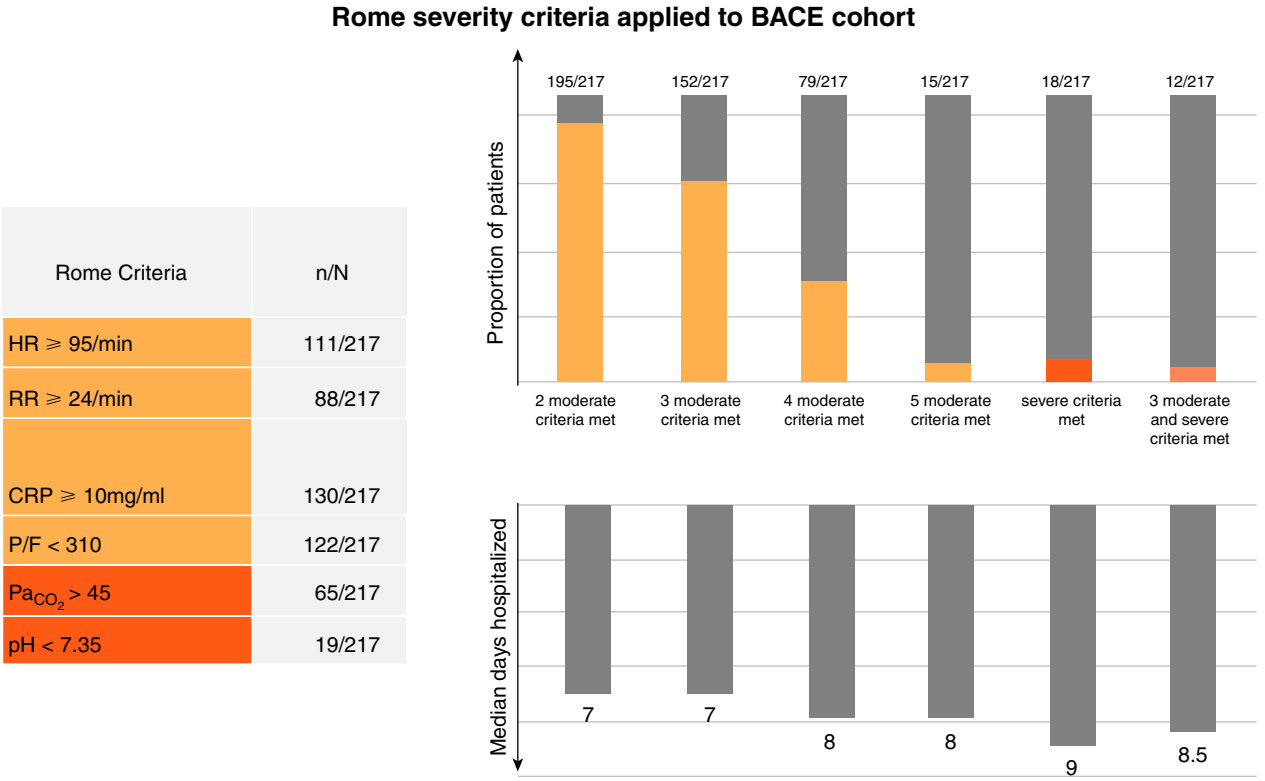

Figure 1. The BACE cohort consisted of 301 patients with chronic obstructive pulmonary disease (COPD) hospitalized for an acute COPD exacerbation. The Rome severity criteria could not be assessed in 84 of 301 patients because of missing variables. Visual analog scale score for dyspnea was not available in the BACE cohort, but it was assumed to be ⩾5 in all patients. Saturation without oxygen was not available for all patients and was replaced by Po_2-to-Fi_{O_2} ratio (P/F) <310, which corresponds to 92% saturation at ambient air. BACE = Azithromycin for Acute Exacerbations Requiring Hospitalization; CRP = C-reactive protein; HR = heart rate; RR = respiratory rate.

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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. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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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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