an emergency response. *JAMA* [online ahead of print] 13 Mar 2020; DOI: 10.1001/jama.2020.4031.
10. Parodi SM, Liu VX. From containment to mitigation of COVID-19 in the US. *JAMA* [online ahead of print] 13 Mar 2020; DOI: 10.1001/jama.2020.3882.
11. Murthy S, Gomersall CD, Fowler RA. Care for critically ill patients with COVID-19. *JAMA* [online ahead of print] 11 Mar 2020; DOI: 10.1001/jama.2020.3633.
12. Fan E, Del Sorbo L, Goligher EC, Hodgson CL, Munshi L, Walkey AJ, *et al*.; American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2017;195: 1253–1263.
13. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, *et al*. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis* [online ahead of print] 24 Feb 2020; DOI: 10.1016/S1473-3099(20)30086-4.
14. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, *et al*. A trial of lopinavir-ritonavir in adults hospitalized with severe covid-19. *N Engl J Med* [online ahead of print] 18 Mar 2020; DOI: 10.1056/NEJMoa2001282.
15. Gautret P, Lagiera J-C, Parola P, Hoang VT, Meddeb L, Mailhea M, *et al*. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* [online ahead of print] 20 Mar 2020; DOI: 10.1016/j.ijantimicag.2020.105949.
16. Hollander JE, Carr BG. Virtually perfect? Telemedicine for covid-19. *N Engl J Med* [online ahead of print] 11 Mar 2020; DOI: 10.1056/NEJMp2003539.

Guidance for the Better Care of Patients with Chronic Obstructive Pulmonary Disease

Writing guidelines is hard work. At first sight, it seems simple to summarize what you believe to be optimal care, but beliefs should be based on evidence, and that can be hard to identify in an unbiased way. To reduce the risk of bias when preparing guidelines, a range of complex methodologies have been developed. Documents such as the standards of care for chronic obstructive pulmonary disease (COPD) developed jointly by the American Thoracic Society (ATS) and European Respiratory Society in 2004 (1) would not be methodologically acceptable today. The newer approach has narrowed the scope of the guidance offered, improving the certainty of the conclusions drawn at the cost of restricting the number of questions addressed. Although there have been moves in the guidelines community to open up the types of evidence considered, most published guidelines try to identify randomized controlled trials (RCTs) that offer evidence directly or indirectly with which the guideline writers can address the clinical question they are trying to understand. Limiting acceptable answers to questions for which RCT evidence is present can lead to some strange anomalies, as we found when writing the European Respiratory Society/ATS guidance about the management of acute exacerbations of COPD (2). Although observational studies suggested that stopping smoking had a beneficial on exacerbation numbers, we could not make a recommendation about this, because no RCT to test this idea was ethically possible! However, there are still questions to consider for which RCT data can provide answers, even in a well-worked area such as COPD care, and this was the challenge taken up by a group of North American and British physicians (pp. e56–e69) who developed the clinical practice guideline on the pharmacologic management of COPD published in this issue of the *Journal* (3).

The expert group considered six questions in relation to the effectiveness of drug treatment in COPD and assigned a priority to a range of outcomes that differed between the interventions. Thus, the risk of pneumonia was prioritized above efficacy outcomes for questions that related to corticosteroids, but it is not discussed in connection with long-acting bronchodilator therapy or opiate use to manage breathlessness. This suggests that prior knowledge of the field does influence the weighting given to particular outcomes. Clinical practice guidance needs to address people other than practicing clinicians with both patients and payers. The authors explain clearly the interests of these different stakeholders and use carefully nuanced language to support their conclusions and what these conclusions might mean to these interest groups. Whether people reading the summary of the document will take in these subtleties is unclear, and this would be a fertile area for further research. Understanding why guideline writers reached their conclusions is always interesting, and this is set out in the section on committee discussion, which, together with a series of research needs, accompanies each question.

So, what conclusions do the authors draw? First, there is strong evidence that initial therapy for symptomatic patients with COPD should be administered with both a long-acting β-agonist (LABA) bronchodilator and a long-acting muscarinic antagonist (LAMA) bronchodilator rather than either drug singly. This analysis is in line with recommendations from the UK National Institute for Health and Care Excellence, which used the same methodology to ask a similar question of much the same data (4). Reproducibility is always a welcome finding in any area of medicine, although the cost-effectiveness of this treatment policy is likely to vary from region to region, reflecting local cost issues and healthcare access. The next two questions looked at the need for additional inhaled

Originally Published in Press as DOI: 10.1164/rccm.202002-0459ED on April 13, 2020

corticosteroid (ICS) treatment in patients already using inhaled LABA/LAMA therapy. The authors make a conditional recommendation to use ICS to prevent exacerbations in patients receiving LABA + LAMA therapy who experience one or more exacerbations but to stop ICS in patients in stable condition while receiving triple therapy. No recommendation is offered about how to use the blood eosinophil count to stratify the likely treatment benefits of ICS, except to support the use of ICS in patients with one or more exacerbations. This is a complex topic, with relatively few prospective studies collecting these data (although there are abundant and consistent *post hoc* analyses of the relationship between eosinophil count and exacerbation frequency). Given the evidence that the relationship between blood eosinophils and exacerbation frequency is a continuous variable (5) and that the critical threshold for benefit varies with the number of prior exacerbations and the background therapy (6), analysis of this question using the existing guideline methodology was always going to be tricky. The authors wisely decide against recommending maintenance oral corticosteroids in patients with stable COPD, although the evidence on this topic was very heterogeneous and not collected primarily to determine whether oral corticosteroids should be continued in the longer term. Even weaker are the data about the use of opiates to manage breathlessness, for which a very cautious suggestion that these might be considered after careful discussion with the patient is made.

This guideline has considerable strengths, reflecting the expertise of the clinicians who interpreted the data and posed the questions as well as the skill of the methodologists following the well-tested ATS process. Although it is easy for a "COPD geek" such as myself to be picky about the individual study selection, the conclusions reached seem very appropriate and relevant. However, this guideline does tell us something about the guideline-writing process and its limitations. One of the most important of these is the issue of study duration. The data included in the analysis of opiates ranged from 3 hours to 6 weeks of exposure, with the longest study identified having a negative result (7). This is a real concern when opioids show pharmacologically predictable tachyphylaxis and is highly relevant in a clinical recommendation. Although there is much emphasis on RCT data, there is less concern about the purpose for which the study was conducted and hence about the strength of the secondary outcomes. Thus, the study by Weir and Burge was set up to determine whether high-dose ICS had a physiological effect similar to that of oral corticosteroids rather to establish whether oral corticosteroids would be of benefit to all patients with COPD as a maintenance treatment (8). Perhaps most important, as the authors acknowledge, this guideline was developed without patient input, which is a pity, given the ATS's long history of working with patient groups. The patient's perspective on what the important clinical outcomes are and why this is the case would be invaluable in any future revision of this document.

There is clearly a role for the consumer in this process as well. Guidelines are likely to be most effective when they meet the needs of the practicing doctor, which may explain the continuing popularity of broader management strategy documents such as the one regularly updated by the Global Initiative for Chronic Obstructive Lung Disease (9). Understanding where uncertainty exists in the daily office practice of nonacademic doctors might aid the uptake of guidelines in general and especially those relating to COPD. Whatever the source of the information, offering patients the most appropriate and up-to-date advice remains an essential part of good clinical management, and this new clinical practice guideline will certainly help in that process. ■

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

Peter M. A. Calverley, M.B. Ch.B., D.Sc.*
Institute of Ageing and Chronic Disease
University of Liverpool
Liverpool, United Kingdom

ORCID ID: 0000-0003-4676-9993 (P.M.A.C.).

*P.M.A.C. is Associate Editor of *AJRCCM*. His participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

References

1. Celli BR, MacNee W; ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;23:932–946. [Published erratum appears in *Eur Respir J* 27:242.]
2. 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: 1602265.
3. Nici L, Mammen MJ, Charbek E, Alexander PE, Au DH, Boyd CM, *et al*.; American Thoracic Society Assembly on Clinical Problems. Pharmacologic management of chronic obstructive pulmonary disease: an official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med* 2020;201:e56–e69.
4. Hopkinson NS, Molyneux A, Pink J, Harrisingh MC; Guideline Committee (GC). Chronic obstructive pulmonary disease: diagnosis and management: summary of updated NICE guidance. *BMJ* 2019;366:l4486.
5. Bafadhel M, Peterson S, De Blas MA, Calverley PM, Rennard SI, Richter K, *et al*. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. *Lancet Respir Med* 2018;6:117–126.
6. Calverley PMA, Tetzlaff K, Vogelmeier C, Fabbri LM, Magnussen H, Wouters EFM, *et al*. Eosinophilia, frequent exacerbations, and steroid response in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2017;196:1219–1221.
7. Weir DC, Burge PS. Effects of high dose inhaled beclomethasone dipropionate, 750 micrograms and 1500 micrograms twice daily, and 40 mg per day oral prednisolone on lung function, symptoms, and bronchial hyperresponsiveness in patients with non-asthmatic chronic airflow obstruction. *Thorax* 1993;48:309–316.
8. Poole PJ, Veale AG, Black PN. The effect of sustained-release morphine on breathlessness and quality of life in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157:1877–1880.
9. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, *et al*. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 report: GOLD executive summary. *Am J Respir Crit Care Med* 2017;195:557–582.