

## Clinical Practice Guideline: Summary for Clinicians

### Management of COPD Exacerbations: An European Respiratory Society/ American Thoracic Society/ (ERS/ATS) Clinical Practice Guideline

Laura C. Feemster<sup>1,2</sup>, Susan D. Pasnick<sup>3</sup>, Tanya Weinstock<sup>4</sup>, Rohini S. Chatterjee<sup>5</sup>, Jerry A. Krishnan<sup>6</sup>, Marc Miravittles<sup>7</sup>, Jadwiga A. Wedzicha<sup>8</sup>, Kevin C. Wilson<sup>9</sup>, Carey C. Thomson<sup>4</sup>

<sup>1</sup> Department of Veterans' Affairs, Health Services Research and Development, Center of Innovation for Veteran-Centered and Value-Driven Care, Seattle, Washington

<sup>2</sup> Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Washington Medical Center, Seattle, Washington

<sup>3</sup> Division of Pulmonary and Critical Care Medicine, Christus St. Vincent Regional Medical Center, Santa Fe, New Mexico

<sup>4</sup> Division of Pulmonary and Critical Care Medicine, Department of Medicine, Mount Auburn Hospital, Harvard Medical School, Boston, Massachusetts

<sup>5</sup> Department of Internal Medicine, Mount Auburn Hospital, Harvard Medical School, Boston, Massachusetts

<sup>6</sup> Breathe Chicago Center, Division of Pulmonary, Critical Care, Sleep & Allergy, University of Illinois at Chicago, Chicago, Illinois

<sup>7</sup> Department of Pneumology, Hospital Universitari Vall d'Hebron, Barcelona, Spain

<sup>8</sup> National Heart and Lung Institute, Imperial College, London, United Kingdom

<sup>9</sup> Division of Allergy, Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, Boston University, Boston, Massachusetts

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*Summary of: Wedzicha JA, Miravittles M, Hurst JR, Calverley PMA, Albert RK, Anzueto A, Criner GJ, Papi A, Rabe KF, Rigau D, Sliwinski P, Tonia T, Vestbo J, Wilson KC, Krishnan JA. Management of COPD exacerbations: A European Respiratory Society/American Thoracic Society (ERS/ATS) guideline. European Respiratory Journal 2017; 49: 1600791*

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## **Introduction**

The European Respiratory Society (ERS) and the American Thoracic Society (ATS) collaborated to create recommendations for the management of chronic obstructive pulmonary disease (COPD) exacerbations (1). Utilizing the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, a multidisciplinary task force of COPD experts performed a systematic evidence synthesis and rated the quality of the evidence (2). The panel identified *a priori* outcomes they deemed “important” or “critical” to making recommendations, and used an iterative consensus method to formulate “strong” or “conditional” recommendations in favor of, or against, specific interventions. Strong recommendations arise in situations where the guideline committee is confident that benefits outweigh the risks of following the recommendations based on the quality of the evidence, acceptability, and feasibility of implementing the intervention; otherwise, recommendations are framed as conditional. This report summarizes the task force’s recommendations for clinicians.

## **Treatment of Ambulatory Patients Experiencing an Exacerbation of COPD**

*“For ambulatory patients with an exacerbation of COPD, we suggest a short course (14 days or less) of oral corticosteroids (conditional recommendation, very low quality of evidence).”*

A meta-analysis of three placebo-controlled randomized trials guided the panel’s recommendation for the use of oral corticosteroids for outpatient exacerbations. Across studies, there were variations in corticosteroid dose, treatment duration (9-14 days), and length of follow-up (14-40 days). Corticosteroids were not convincingly superior to placebo for any of the *a priori* identified outcomes of “critical” importance. There was a trend towards reduced hospital admissions, no significant difference in the rates of treatment failure or mortality, and no information on time to subsequent COPD exacerbation. Corticosteroids improved lung function, as measured by forced expired volume in one second (FEV<sub>1</sub>), but they had no effect on quality

of life or occurrence of serious adverse events. While the task force acknowledged uncertainty about the estimated effects of corticosteroids, they thought the benefits were likely to exceed the risks. Future research is needed to determine steroid-responsive phenotypes, shortest possible courses of corticosteroid treatment, and the effectiveness of corticosteroids for treatment of outpatient exacerbations in clinical practice.

*“For ambulatory patients with an exacerbation of COPD, we suggest the administration of antibiotics (conditional recommendation, moderate quality of evidence). Antibiotic selection should be based upon local sensitivity patterns.”*

Meta-analysis of data from two randomized controlled trials informed the panel’s recommendation regarding the use of antibiotics for outpatient exacerbations. The included trials compared placebo to amoxicillin/clavulanate, doxycycline, trimethoprim/sulfamethoxazole, or amoxicillin. The range of treatment was between 7 and 10 days. Management of COPD exacerbations with antibiotics in the outpatient setting reduced the rate of treatment failure and increased the time to subsequent COPD exacerbation. There was a trend towards increased (mostly mild) adverse events in the antibiotic group. The studies did not report on other important outcomes, including need for hospitalization, length of hospitalization among patients subsequently admitted, or mortality. Overall, the benefits of using antibiotics in the ambulatory population experiencing exacerbations was thought to outweigh the risks, even though the trials also demonstrated a significant improvements (compared to baseline) in the placebo groups. This suggests a need for further research to identify which patients with an exacerbation would benefit most from antibiotic use.

### **Treatment of Patients Hospitalized for an Exacerbation of COPD**

*“For patients who are hospitalized with a COPD exacerbation, we suggest the administration of oral corticosteroids rather than intravenous corticosteroids if gastrointestinal access and function are intact (conditional recommendation, low quality of evidence).”*

The authors identified two randomized controlled trials hospitalized with COPD exacerbations that directly compared oral to intravenous steroids or, alternatively, compared each to placebo. Outcomes identified as “critical” to inform treatment guidelines included treatment failure, mortality, hospital readmission rates, total length of inpatient stay and change in time to subsequent exacerbation. There were no significant differences in these outcomes between patients receiving intravenous and oral corticosteroids; however, neither study assessed time to subsequent exacerbation. There were no serious adverse events, but there was an increase in mild adverse events (hypertension and hyperglycemia) in those patients receiving intravenous corticosteroids. Conclusions regarding mortality were limited and the task force stated a need for a non-inferiority trial to adequately assess the benefits and risks of the different routes of corticosteroid administration. In the presence of equivocal evidence and the potential increased cost effectiveness and ease of oral therapy, the guideline recommends oral rather than intravenous corticosteroids in patients admitted for COPD exacerbations. In cases where oral therapy is not tolerated, intravenous therapy is recommended.

*“For patients who are hospitalized with a COPD exacerbation associated with acute or acute-on-chronic hypercapnic respiratory failure, we recommend the use of non-invasive mechanical ventilation (strong recommendation, low quality of evidence).”*

A meta-analysis of 21 trials evaluating the role of non-invasive ventilation in patients with acute respiratory failure due to COPD exacerbation found that patients treated with non-invasive ventilation had a lower mortality rate, were less likely to require endotracheal intubation, had

shorter inpatient and ICU stays, and experienced fewer treatment-related complications. Most of these trials specifically studied patients with acute or acute-on-chronic hypercapnic respiratory failure. However, the included trials had a high risk of bias due to lack of blinding, low numbers of patients and events, and incomplete reporting of data, such as rates of nosocomial pneumonia. Despite these shortcomings, the possible benefits of non-invasive ventilation likely outweigh the minimal risk of harm. Most trials excluded patients who were unable to cooperate, protect the airway, or clear secretions, as well as those at high risk for aspiration and those with facial deformities. Future trials should address titration and weaning strategies, as well as the role of non-invasive ventilation in the outpatient setting among patients with COPD.

### **Home-Based Management Programs**

*“For patients with a COPD exacerbation presenting to the emergency department or hospital, we suggest a home-based management approach (i.e., “hospital-at-home”) (conditional recommendation, moderate quality of evidence).”*

Home-based management programs provide the potential for an earlier hospital discharge following an exacerbation or give patients who would otherwise be hospitalized an option for treatment at home. A meta-analysis of nine trials comparing home-based management to usual care in patients with COPD exacerbations found that home-based management reduced rates of hospital readmission and suggested a trend toward lower mortality among participants. There was no difference in the time to first hospital readmission between treatment groups. These effects did not differ between patients discharged directly from the emergency department and those discharged after hospitalization. Small patient numbers and few deaths limited the quality of the included trials, as did lack of data on hospital acquired infections, quality of life, and adverse events related to home-based management. Among the 4 trials that analyzed cost, 2 found lower costs with home-based management, 1 found a trend toward lower costs with

home-based management, and 1 showed no difference. No differences were found in “satisfaction” with care on the part of either patients or clinicians, although most patients indicated they would rather receive treatment at home if possible. Further research should evaluate which patients are most appropriate for home-based management and identify key elements of such programs.

### **Pulmonary Rehabilitation**

*“For patients who are hospitalized with a COPD exacerbation, we suggest the initiation of pulmonary rehabilitation within three weeks after hospital discharge (conditional recommendation, very low quality of evidence).”*

*“For patients who are hospitalized with a COPD exacerbation, we suggest NOT initiating pulmonary rehabilitation during hospitalization (conditional recommendation, very low quality of evidence).”*

Pulmonary rehabilitation consists of a suite of interventions including exercise training, patient education, and various support (e.g., smoking cessation interventions, nutritional counseling) to improve the capacity for self-management. The panel identified 13 studies assessing the benefit of pulmonary rehabilitation following hospitalization for an exacerbation of COPD. Across studies, there was large variation in the timing of pulmonary rehabilitation initiation (during the index hospitalization to up to 8 weeks following discharge), as well as in the components of the intervention. In the primary analysis, mortality was similar among patients participating in pulmonary rehabilitation compared to those who did not. The reliability of the estimated effects of the intervention on the other outcomes of interest (hospital readmission, quality of life and exercise capacity) was severely limited due to inconsistent results across trials. Differential effects were found in post-hoc analyses stratified by timing of pulmonary rehabilitation initiation.

Patients who initiated pulmonary rehabilitation during their hospitalization experienced increased mortality, although survivors demonstrated improved exercise capacity and no difference in rates of readmission. When rehabilitation was initiated within 3 weeks after discharge, patients experienced fewer readmissions and reported better quality of life. When rehabilitation was delayed to up to 8 weeks, patients had increased exercise capacity but there was significant variation in all other outcomes. Confidence in the estimated effects was reduced by persistent inconsistencies in the stratified analyses, as well as potential bias due to difficulties with allocation concealment, lack of blinding, and analyses that did not utilize “intention to treat principles.” Further studies are needed to determine the ideal components of a pulmonary rehabilitation program and how best to implement these programs.

## **Summary**

The task force strongly recommended non-invasive mechanical ventilation in patients with acute hypercapnic respiratory failure. The task force made conditional recommendations for the treatment of outpatient COPD exacerbations with oral corticosteroids and antibiotic therapy, as well as for home-based management of exacerbations for appropriate patients. Among hospitalized patients with a COPD exacerbation, the task force conditionally recommended oral over intravenous corticosteroids and initiation of pulmonary rehab following hospital discharge, but *NOT* during a hospitalization for an exacerbation.

## **References:**

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