



# Pharmacologic and Nonpharmacologic Therapies in Adult Patients With Exacerbation of COPD: A Systematic Review

## *Evidence Summary*

### Background and Objectives

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease characterized by airflow limitation and chronic respiratory symptoms. The global prevalence is estimated to be greater than 10 percent, impacting approximately 380 million people worldwide.<sup>1</sup> In the United States, COPD affects approximately 15 million people; chronic lower respiratory diseases, of which COPD is the largest contributing condition, are the fourth leading cause of death;<sup>2</sup> and COPD costs more than \$32 billion annually.<sup>3,4</sup> Patients with COPD experience chronic respiratory symptoms (including shortness of breath and cough), and have decreased quality of life, and premature mortality.

Patients with COPD are at risk of experiencing exacerbations of COPD (ECOPD). There have been various definitions of what constitutes an ECOPD. The Global Initiative for chronic obstructive lung disease (GOLD) defines ECOPD in its 2019 report as “acute worsening of respiratory symptoms that result in additional therapy.”<sup>5</sup> ECOPD is generally characterized by increased dyspnea, increased frequency and severity of cough, and/or increased sputum production.<sup>6</sup> ECOPD is a leading independent cause of increased mortality

### Purpose of Review

To evaluate the effectiveness and harms of pharmacologic and nonpharmacologic treatments for exacerbations of chronic obstructive pulmonary disease.

### Key Messages

- Antibiotic therapy increases the clinical cure rate and reduces the clinical failure rate.
- Oral and intravenous corticosteroids improve dyspnea and reduce the clinical failure rate.
- Antibiotics and corticosteroids are not associated with increase in serious adverse events.
- The evidence is insufficient to support the effect of aminophyllines, magnesium sulfate, mucolytics, inhaled corticosteroids, inhaled antibiotics, 5-lipoxygenase inhibitor, and statins on mortality, dyspnea, need for intubation, clinical failure, or hospital admission.
- Titrated oxygen reduces mortality compared with high flow oxygen.
- The evidence suggests benefits of some nonpharmacologic interventions such as chest physiotherapy using vibration/percussion/massage or using breathing technique (on dyspnea), resistance training (on dyspnea and quality of life), early pulmonary rehabilitation commenced before hospital discharge during the initial most acute phase of exacerbation rather than the convalescence period (on dyspnea), and whole body vibration training (on quality of life).
- Vitamin D supplementation may improve quality of life.
- Serious adverse events were not found to be different between most evaluated interventions.



and morbidity among patients with COPD. ECOPD is associated with a higher risk of dying during or shortly after the exacerbation, lower quality of life, more hospital admission, depletion of financial resources, and a progressive decline in lung function.<sup>7-14</sup> Hospitalizations for ECOPD account for more than half of all costs associated with COPD.<sup>10, 15</sup>

In recent years, a number of clinical trials of treatments to prevent ECOPD have shown promising results, but the evidence for acute treatments during an episode of ECOPD appears to be surprisingly scarce, given how relatively common the condition is.<sup>16, 17</sup>

Goals of management of ECOPD include relieving symptoms and hastening the recovery from ECOPD by addressing precipitating factors (e.g. antibiotic treatment for infections), improving expiratory airflow and gas exchange (and thus improving breathing) by using inhaled bronchodilators, and reducing lung inflammation with corticosteroids. Nonpharmacologic treatments include supplemental oxygen, nutritional support, and others.<sup>18-20</sup> In addition, several new pharmacologic agents with novel mechanisms of action in early stages of development may be of potential benefit to COPD patients including those in acute exacerbation.<sup>21</sup>

The area of ECOPD management has several uncertainties and necessitates an up to date evidence synthesis. These uncertainties include the benefits and harms of emerging pharmacologic and nonpharmacologic treatments, the benefits and harms of treatments for ECOPD that have been found efficacious in stable COPD, the benefits and harms of antibiotics and systemic corticosteroids in mild ECOPD, the benefits and harms of combinations of treatments that have been found to be individually effective, and—for antibiotics and systemic corticosteroids—the comparative effectiveness of different types of agents (e.g. broad-spectrum versus narrow-

spectrum antibiotics), delivery modes (e.g. intravenous, oral), and durations of treatment.

Examples of potentially emerging treatments for ECOPD, include immune-modulatory drugs and novel applications of treatments primarily used in stable COPD including mucolytics, aminophyllines, long-acting bronchodilators, inhaled corticosteroids, and others. Mucolytics may have a small effect on reducing the frequency of ECOPD.<sup>22, 23</sup> In clinical practice, they are also used during an ECOPD, where the evidence for their effectiveness appears less clear.

For nonpharmacological treatments, there are a number of areas in which an update of the evidence is required to inform best practice management of ECOPD. There is increasing recognition that too much oxygen might do more harm than good, and not just in patients with chronic hypercapnic respiratory who are at risk of iatrogenic worsening of respiratory failure due to oversupply of oxygen.<sup>24, 25</sup> Titrated oxygen with a target saturation rate as opposed to high flow oxygen has therefore been used in patients with ECOPD.<sup>26</sup> Historically, pulmonary rehabilitation programs have focused on enrolling patients with stable COPD or patients who had stabilized after an episode of ECOPD, but in more recent times, a number of trials have explored the role of exercise/early pulmonary rehabilitation during an episode of ECOPD.<sup>27, 28</sup> Chest physiotherapy using airway clearance techniques (including breathing technique, vibration/percussion, and autogenic drainage) are used routinely in many patients hospitalized with ECOPD. A Cochrane review published in 2012 found evidence that airway clearance techniques may reduce the need for hospital admission and improve health-related quality of life based on single studies with small study populations.<sup>29</sup> An update of this evidence is indicated. Furthermore, many patients with COPD are in a state of hyper-metabolism in which their body consumes more calories per kilogram on calorimetric measures compared with a person

without COPD, likely because of the increased work of breathing.<sup>30</sup> This hyper-metabolic state is even more pronounced during episodes of ECOPD, posing questions about the optimal nutritional support for patients with ECOPD.<sup>31, 32</sup>

Established treatments for ECOPD, such as antibiotics and systemic corticosteroids, may not be indicated in every single episode of an ECOPD. One uncertainty relates to the need for antibiotics in mild and moderately severe ECOPD, especially in an outpatient setting.<sup>33</sup> While antibiotics for treatment of severe ECOPD have been shown to be beneficial in some studies, the need for antibiotics in less severe forms of COPD is unclear.<sup>34</sup> Uncertainty remains regarding the use of systemic (oral, intravenous) corticosteroids relate to whether all patients stand to benefit from this treatment of ECOPD.<sup>34</sup> These questions are important to address in view of trying to reduce prescriptions of antibiotics, where safely possible, to reduce potential adverse events including development of antibiotic resistance, and to reduce potentially significant adverse events from systemic corticosteroids, in particular hyperglycemia, in patients with glucose intolerance and diabetes.<sup>35</sup>

Short-acting beta adrenergic agonists (SABAs) and short-acting muscarinic antagonists (SAMAs) are established treatments to relieve dyspnea and improve airflow obstruction during ECOPD, but the benefits of combining SABAs and SAMAs compared with using SABAs or SAMAs alone are unclear.<sup>36</sup> Long-acting bronchodilators and inhaled corticosteroids have historically only be used in stable COPD, but there is emerging evidence that an increase in dosage of inhalation therapy with inhaled corticosteroids and long-acting beta agonists (LABAs) may be beneficial in early treatment of ECOPD when patients experience mild to moderate dyspnea and may result in no requirement of systemic corticosteroids in a large proportion of patients presenting with mild-to-moderate worsening of dyspnea.<sup>37</sup> The benefit

of using LABAs and long-acting muscarinic antagonists (LAMAs) in the treatment of manifest ECOPD is unclear. For antibiotics and systemic corticosteroids, the comparative effectiveness of different agents (e.g. broad-spectrum versus narrow-spectrum antibiotics), delivery modes and durations of treatment needs to be established.<sup>38-41</sup>

In summary, determining the optimal treatment plan for patients with ECOPD requires 1) a synthesis of existing knowledge regarding the effectiveness of treatment options and 2) a synthesis of existing knowledge regarding the harms of treatment options. Currently, the comparative benefits and harms of these varied treatment approaches including the optimal combination of these treatments to mitigate COPD exacerbation are unclear. A systematic review of current evidence assists clinicians in understanding and determining optimal management for ECOPD. This review focuses on evidence from randomized controlled trials (RCTs) as the gold standard design for evaluating a therapeutic intervention. In terms of adverse events, they are also likely to be captured in RCTs because of the acute nature of condition being studied.

## Scope and Key Questions

### Scope of Review

The systematic review assessed the effectiveness of systemic antibiotics, systemic corticosteroids and other pharmacologic and nonpharmacologic therapies stratified by severity of ECOPD. The study also evaluated the effectiveness of combinations of treatments, and compared different regimens (different agents, routes of administration, and duration of treatment) of antibiotics and corticosteroids. Health service interventions (e.g. hospital in the home as alternative to hospitalization) and interventions during the convalescence period were not included.

## Key Questions

**Key Question (KQ) 1. In adult patients with exacerbation of COPD, what are the benefits and harms of systemic corticosteroids and antibiotics compared with placebo or standard care?**

**KQ2. In adult patients with exacerbation of COPD, what are the benefits and harms of emerging and other pharmacologic and nonpharmacologic therapies compared with placebo or standard care?**

**KQ3. In adult patients with exacerbation of COPD, what are the benefits and harms of combinations of treatments that are individually effective (based on empirical evidence in stable COPD)?**

**KQ4. In adult patients with exacerbation of COPD, what is the comparative effectiveness of different regimens of antibiotics and systemic corticosteroids based on type of agents (e.g., broad-spectrum vs. narrow-spectrum antibiotics), delivery modes (e.g., intravenous, oral), and durations of treatment?**

## Methods

We developed an analytic framework to guide the process of the systematic review. We followed the established methodologies of systematic reviews as outlined in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Comparative Effectiveness Reviews.<sup>42</sup> The reporting complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.<sup>43</sup> The study protocol is registered in the international prospective register of systematic reviews (PROSPERO #: 42018111609) and published on the AHRQ website (<https://effectivehealthcare.ahrq.gov/topics/copd/protocol>). The full report details our literature search strategy, inclusion and exclusion criteria, data synthesis, assessments of risk of bias, and strength of evidence (SOE). We graded SOE for final health outcomes deemed to be most

important or critical, including mortality, dyspnea, quality of life (QoL), need for intubation, repeat exacerbation and/or hospital readmissions and ECOPD resolution (clinical cure, failure). SOE was rated as high when we were very confident that the estimate of effect lies close to the true effect (the body of evidence has few or no deficiencies and is judged to be stable). SOE was rated as moderate when we were moderately confident that the estimate of effect lies close to the true effect (the body of evidence has some deficiencies and is judged to be likely stable). SOE was rated as low when we had limited confidence that the estimate of effect lies close to the true effect (the body of evidence has major or numerous deficiencies and is likely unstable). SOE was rated as insufficient when we had no evidence, were unable to estimate an effect, or had no confidence in the estimate of effect.

## Results

The literature search identified 8,916 citations. An additional 36 references were identified through reference mining, grey literature search; and from Key Informants and Technical Experts. There were 98 original studies with a total of 13,401 patients that met inclusion criteria and were included in the systematic review. Most studies were conducted in hospitalized patients with moderate to severe COPD. The mean treatment duration was 9.9 days and there was a mean 3.7 months of reported followup.

**KQ1. In adult patients with exacerbation of COPD, what are the benefits and harms of systemic corticosteroids and antibiotics compared with placebo or standard care?**

### Systemic Antibiotics Versus Placebo or Management Without Systemic Antibiotics

Antibiotics increased clinical cure of ECOPD compared with placebo or management without antibiotics at the end of the intervention and at the longest followup (moderate SOE).

Antibiotics reduced clinical failure rate compared with placebo at the end of the intervention (moderate SOE), but not at the longest followup (Low SOE).

Antibiotics did not change 30-day hospital readmission, repeat exacerbation, and quality of life, compared with placebo (low SOE).

No statistically significant difference in adverse events (AEs) was observed between antibiotics and placebo or management without antibiotics.

Systemic Corticosteroids Versus Placebo or Management Without Systemic Corticosteroids

### **Systemic corticosteroids improved dyspnea (Low SOE) and reduced clinical failure rate (low SOE) at the end of the intervention, compared with placebo.**

No statistically significant difference in serious adverse events was found between systemic corticosteroids and placebo or management without systemic corticosteroids. Systemic corticosteroids were associated with fewer withdrawals but more endocrine related adverse events.

KQ2. In adult patients with exacerbation of COPD, what are the benefits and harms of emerging and other pharmacologic and nonpharmacologic therapies compared with placebo or standard care?

### **Pharmacologic Therapies Versus Placebo or Management Without Pharmacologic Therapies**

The evidence was insufficient for the effect of aminophyllines, magnesium sulfate, mucolytics, inhaled corticosteroids, inhaled antibiotics, 5-lipoxygenase inhibitor and statins on mortality, dyspnea, need for intubation, clinical failure, or hospital admission.

Aminophyllines were associated with more gastrointestinal adverse events than placebo. No other statistically significant difference was

found in adverse events between the remaining pharmacologic therapies and placebo or management without pharmacologic therapies.

### **Nonpharmacologic Therapies Versus Management Without Nonpharmacologic Therapies**

Chest physiotherapy using vibration/percussion, breathing technique, or positive expiratory pressure did not improve dyspnea and other symptoms, quality of life, 6-minute walking distance, repeat exacerbations, or mortality (low SOE).

Resistance training improved dyspnea, and quality of life, compared with management without nonpharmacological therapies (low SOE).

Early pulmonary rehabilitation, commenced before hospital discharge during the initial most acute phase of exacerbation rather than the convalescence period, improved dyspnea, compared with management without rehabilitation (low SOE).

Whole body vibration training improved QoL compared with management without nonpharmacologic therapies (low SOE).

Titrated oxygen reduced mortality compared with high flow oxygen at the longest followup (low SOE).

Vitamin D supplementation improved quality of life compared with placebo (low SOE).

Omega-3 fatty acid enriched diet did not change quality of life, need for intubation, and dyspnea at the end of intervention compared with usual diet (low SOE).

Few adverse events were reported in studies of nonpharmacologic therapies. There was no statistically significant difference found in adverse events between nonpharmacologic therapies and management without nonpharmacologic therapies.

**KQ3. In adult patients with exacerbation of COPD, what are the benefits and harms of combinations of treatments that are individually effective (based on empirical evidence in stable COPD)?**

No statistically significant difference in adverse events was found between any of the combined treatments and individual treatments.

**KQ4. In adult patients with exacerbation of COPD, what is the comparative effectiveness of different regimens of antibiotics and systemic corticosteroids based on type of agents (e.g., broad-spectrum vs. narrow-spectrum antibiotics), delivery modes (e.g., intravenous, oral), and durations of treatment?**

#### **Comparative Effectiveness of Different Antibiotics**

Numerous antibiotics, given as empirical initial therapy for ECOPD (in the absence of pneumonia), were compared against each other, but the evidence was insufficient to estimate an effect on final health outcomes; except that levofloxacin reduced repeat exacerbations at 3 months of followup, compared with prulifloxacin (low SOE).

The only differences in adverse events that were statistically significant were for higher rates of adverse events with amoxicillin plus clavulanic acid compared with telithromycin; and for higher rate of adverse events with imipenem plus cilastatin compared with meropenem.

#### **Comparative Effectiveness of Different Dosages of the Same Antibiotic**

The evidence comparing different dosages of the same antibiotic was insufficient for mortality, clinical cure and clinical failure.

No statistically significant difference in adverse events was found between trovafloxacin 200 milligrams (mg) and trovafloxacin 100 mg.

#### **Comparative Effectiveness of Different Application Routes for Antibiotics**

No studies were found.

#### **Comparative Effectiveness of Different Durations of Treatment With Antibiotics**

The evidence was insufficient when comparing 3 day versus 10 day regimens of amoxicillin plus clavulanic acid.

No statistically significant difference of AEs was found between 3 day and 10 day regimens of amoxicillin plus clavulanic acid.

#### **Comparative Effectiveness of Different Corticosteroids**

The evidence was insufficient when comparing the different corticosteroids for mortality, need for intubation, clinical failures, and dyspnea.

There was no statistically significant difference in AEs found between the different systemic corticosteroids.

#### **Comparative Effectiveness of Different Routes of Application for Corticosteroids**

No difference between intravenous methylprednisolone and inhaled budesonide 40 mg was found in quality of life and repeat exacerbations (low SOE). The evidence was insufficient when comparing the different routes of administration of corticosteroids for mortality, dyspnea, quality of life, repeat exacerbation, clinical failures, hospital admission, and intensive care unit (ICU) admission.

Inhaled Budesonide 40 mg was associated with statistically significantly less endocrine-related AEs than methylprednisolone.

### **Comparative Effectiveness of Different Durations of Treatment With Corticosteroids**

The evidence was insufficient when comparing the different durations of corticosteroid treatment for mortality, hospital admission, need for intubation, clinical failure, quality of life, repeat exacerbation, and dyspnea.

There was no statistically significant difference found in AEs between the different systemic corticosteroid durations.

### **Discussion**

We conducted a systematic review to assess the effectiveness of pharmacologic and nonpharmacologic therapies in adults with ECOPD. We assessed the effectiveness of systemic antibiotics, systemic corticosteroids and emerging and other pharmacologic and nonpharmacologic therapies stratified by severity of ECOPD. Further, we assessed the effectiveness of combinations of treatments, and we compared different regimens (different agents, routes of administration, and duration of treatment) of antibiotics and corticosteroids.

The majority of studies were conducted in hospitalized patients with moderate or severe ECOPD with only a small number of studies conducted in outpatients with mild or mild to moderate ECOPD.

Lung function was the most frequently assessed outcome, and often studies did not measure final health outcomes, such as mortality, resolution of exacerbation, hospital readmission etc., to allow for assessment of the correlation between this

physiological surrogate outcome and final health outcome.

The findings of the systematic review highlight that in addition to standard therapy with antibiotics, systemic steroids and bronchodilators, some nonpharmacologic interventions hold promise for improving clinically important outcomes, in particular they might improve functional capacity and thus mitigate the deconditioning associated with ECOPD.

### **Findings in Relation to What Is Known**

This review provides a comprehensive overview of pharmacologic and nonpharmacologic interventions in ECOPD. The literature on interventions for COPD and ECOPD has proliferated substantially in recent years with numerous published systematic reviews on different interventions for the management of COPD. For clinicians, health policy makers and other end users of the evidence it has become an almost impossible task to keep up with the ever increasing body of evidence on the management of ECOPD. This review therefore addresses an urgent need to provide an up-to-date summary of the current state of evidence for the management of ECOPD.

One of the main findings of this systematic review is that despite a proliferation of the COPD literature, the evidence base for most interventions in ECOPD remains low. While significant progress has been made in recent years in assessing interventions to prevent ECOPD (during stable COPD), the same cannot be said for acute interventions used during ECOPD.

For the standard therapy of ECOPD with systemic antibiotics, corticosteroids and bronchodilators, many questions remain unanswered, based on the findings of our review. While the discussion of COPD phenotypes (and ECOPD phenotypes) has

taken center stage on the COPD research agenda, very limited information on ECOPD phenotypes (e.g. infective versus non-infective, high versus low eosinophil count) has been included in trials of intervention for ECOPD. In particular, whether a response to systemic corticosteroid treatment of ECOPD depends on the blood eosinophil level remains unexplored. Studies on inhaled corticosteroid (ICS) for prevention of ECOPD in stable COPD suggest that patients with higher blood eosinophil levels might be more likely to benefit from ICS treatment in terms of reducing the risk of ECOPD.<sup>44</sup>

Despite the ubiquitous use of SABAs and SAMAs in ECOPD, we found only two studies (KQ3) that studied their effectiveness. The role of LABAs and LAMAs in ECOPD remains largely unexplored with only one crossover trial identified in our review that assessed a LAMA versus placebo.

An important insight from our systemic review is that some nonpharmacologic interventions (resistance training, early pulmonary rehabilitation, whole body vibration training transcutaneous

electrical nerve stimulation, caloric supplementation, and vitamin D) show promise, but the current evidence is largely based on single, relatively small RCTs. In stable COPD, pulmonary rehabilitation is one of the most effective (though underused) interventions. In recent years, there has been a significant interest in exploring the effects of pulmonary rehabilitation in patients who have recently experienced an ECOPD or even in patients who are in the acute phase of ECOPD (e.g. before hospital discharge).

Our review indicated that pulmonary rehabilitation during ECOPD may increase functional capacity (based on 6-minute walking distance). A potential risk for increased mortality associated with pulmonary rehabilitation commenced during hospitalization for ECOPD has previously been flagged in the guidelines on management of

COPD exacerbations by the European Respiratory Society and the American Thoracic Society, published in 2017.<sup>45</sup> We did not find a significant association with increased mortality for pulmonary rehabilitation or any form of exercise commenced during hospitalization. Our review did not include studies conducted in an ICU, chronic ventilator unit, or respiratory care unit, which might have contributed to the discrepancy in the findings. Also, a trial of rehabilitation commenced within 48 hours of hospital admission in 389 patients with exacerbations of different chronic respiratory conditions found an increase in mortality in the intervention group at one year (odds ratio: 1.74, 95% confidence interval: 1.05 to 2.88).<sup>46</sup> Mortality was, however, not reported in the subgroup of patients with COPD and is therefore not included in our review. Given the potential of exercise programs during hospitalization for ECOPD to ameliorate deconditioning and improve functional status, further research in this area is urgently needed. Other nonpharmacologic interventions during ECOPD that may improve functional capacity included resistance training, whole body vibration training and transcutaneous electrical nerve stimulation. As these findings were based on single, relatively small studies, evidence from well-conducted large RCTs will be required to confirm these findings. Similarly, caloric supplementation and vitamin D may improve quality of life in patients with ECOPD, but confirmation from well-conducted large RCTs is required before any definite conclusions can be drawn.

## Limitations

For most interventions, only one RCT was available per outcome (KQ1-4), which limits inferences from the quantitative synthesis. Failure to detect statistical significance for most of the outcomes may have resulted from type II error. There was some heterogeneity in the definition of the severity of ECOPD, although in general mild ECOPD referred to patients that could be treated in an

outpatient setting, whereas moderate to severe ECOPD was used for hospitalized patients. A number of studies included patients assessed in an emergency department with a broad range of severity of ECOPD. We used the definition of serious AEs listed by the original studies, which could have varied between studies.

Defining resolution of ECOPD and differentiating poor resolution from re-exacerbation can be challenging. We used outcomes as described in the original studies, which might have resulted in heterogeneity of definitions of ECOPD resolution and overlap between clinical failure and re-exacerbation between studies.

Very limited information on ECOPD phenotypes (e.g. infective versus non-infective, high versus low eosinophil count) has been included in trials of intervention. We could therefore not draw any conclusions about interventions for different ECOPD phenotypes. In particular, whether a response to systemic corticosteroids depends on the blood eosinophil levels remains unexplored.

Studies were overall at high risk of bias. This, together with the low number of studies per intervention/outcome, makes interpretation of the body of evidence challenging. We were unable to statistically evaluate publication bias and only included studies published in English. An evaluation of completed clinical trials registered in [clinicaltrials.gov](https://clinicaltrials.gov) showed that 62 percent (24 out of 39) studies were not published.

## Applicability

Most studies were conducted in hospitalized patients with moderate to severe ECOPD, and the results of these studies may not be applicable to patients with milder forms of ECOPD treated in an outpatient setting. KQ1 and KQ2 were stratified by severity of ECOPD, which allows determination of the generalizability of the results based on the severity of ECOPD. For KQ2, almost all studies were conducted in hospitalized patients. As we

excluded studies conducted in an ICU setting, some of our findings may not be extrapolated to the most severely sick patients who require ICU admission for ECOPD.

The results of comparisons of different antibiotic agents/classes are context-specific, as the optimal antibiotic choice depends on local antimicrobial resistance patterns, which can change over time. The results of these comparisons (KQ4) are therefore not necessarily applicable to patients in different geographic locations and at different points in time.

COPD terminology has not been used consistently in the past with some older studies referring to chronic bronchitis without airflow obstruction as COPD. We excluded studies in patients with chronic bronchitis but no evidence of chronic airflow obstruction to increase applicability of the results to patients with chronic airflow obstruction.

Not all studies explicitly excluded patients with potential asthma or asthma-COPD overlap syndrome (ACOS), and there is therefore a potential for misclassification.

Pulmonary rehabilitation is a complex (multi-component) intervention, which consists of exercise training, patient education and behavior change. The detailed interventions for pulmonary rehabilitation were reported in the included studies, which should facilitate reproducibility and applicability. While there are published standards for pulmonary rehabilitation programs,<sup>47</sup> these have been developed in the context of pulmonary rehabilitation in patients with stable COPD (as opposed to patients with ECOPD).

## Suggestions for Future Research

Lung function (forced expiratory volume in 1 second) was the most commonly assessed outcome in studies of interventions to manage ECOPD, while final health outcomes, such as resolution of ECOPD (clinical cure, clinical failure) and repeat

exacerbation (with or without hospital admission), were rarely assessed. Future studies in ECOPD should focus on final health outcomes and include clinical resolution of ECOPD and risk of repeat exacerbation in addition to other final health outcomes, such as dyspnea and quality of life.

The response to antibiotic therapy as well as corticosteroid therapy in ECOPD likely differs based on the phenotype of the exacerbation episode. A number of studies that used pro-calcitonin-guided treatment algorithms have been conducted on antibiotic therapy versus placebo in ECOPD,<sup>48</sup> but identification of responders to systemic corticosteroid treatment of ECOPD based on blood eosinophils remains unexplored. This contrasts with the increasing recognition of eosinophilic phenotypes in stable COPD patients who appear to be more likely to benefit from long-term ICS.<sup>44</sup> Future studies on systemic corticosteroids in ECOPD should assess the treatment effect stratified by blood eosinophil count.

Chest physiotherapy using breathing technique and/or vibration/percussions and/or positive expiratory pressure is commonly prescribed in patients hospitalized for ECOPD, but there was insufficient evidence (from relatively small, low quality trials) that these interventions improve outcomes. As these are resource-intensive interventions, large well-designed trials with final health outcomes including clinical resolution of ECOPD and repeat exacerbations should be conducted to assess the role of chest physiotherapy for airway clearance in ECOPD and inform clinical practice.

It is currently unclear whether pulmonary rehabilitation commenced during hospitalization for ECOPD is associated with increased mortality. An increased mortality was found in the review conducted for the guidelines on management of COPD exacerbations by the European Respiratory Society and the American Thoracic Society but was not found in our systematic review. Given the potential benefit of pulmonary rehabilitation

to counteract the deconditioning associated with ECOPD, we believe that conducting high-quality RCTs to answer this question should be a priority.

The relatively new treatment options of whole body vibration, transcutaneous electrical nerve stimulation (TENS), dietary interventions with caloric supplements and vitamin D need to be assessed in large high quality RCTs to inform recommendations about these treatments. Such literature (e.g., on vitamin D) is notorious for contradictory findings over time.

Further research is required to determine the optimal route of administration for systemic corticosteroids, i.e. to determine whether oral corticosteroids are generally not inferior to intravenous corticosteroids and to determine a potential role of inhaled corticosteroids (possibly as alternative to systemic corticosteroids) in ECOPD.

Patients hospitalized with COPD exacerbations are at high risk for hospital readmissions and death after hospital discharge, which emphasizes the importance of improving the hospital-to-home continuum of care. Our systematic review only focused on the acute episode of an exacerbation and did not include health service interventions, but there is an urgent need for research that assesses interventions to reduce the risk of adverse outcomes following hospital discharge. Much of the recent debate on adverse outcomes following hospital discharge has focused on reducing 30-day hospital readmissions in ECOPD, as the Medicare's Hospital Readmissions Reduction Program (HRRP) lowered payments to Inpatient Prospective Payment System hospitals with too many readmissions within 30 days. Recent evidence, however, showed that implementation of the HRRP was associated with a significant increase in trends in 30-day post-discharge mortality among patients hospitalized for heart failure and pneumonia.<sup>49</sup> It is therefore evident that future research that aims to improve post-hospital discharge for any disease with frequent hospital readmissions including ECOPD should not

focus on reducing 30-day hospital admissions in isolation but only in conjunction with final health outcomes such as QoL and mortality.

## Conclusion

Despite a proliferation of the COPD literature, the evidence base for most interventions in ECOPD remains limited. Systemic antibiotics and corticosteroids are associated with improved outcomes in mild and moderate to severe ECOPD. Titrated oxygen reduces mortality. Future research is required to assess the effectiveness of several emerging nonpharmacologic and dietary treatments.

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## Full Report

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