Comparative Effectiveness Review
Number 221

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

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Key Messages

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.
- The evidence is insufficient for comparative effectiveness of different regimens of antibiotics and corticosteroids based on type of agents, delivery modes, and duration of treatments.
- The evidence is insufficient for effectiveness of combinations of treatments that are each individually effective.
- Serious adverse events were not found to be different between most evaluated interventions.

This report is based on research conducted by the Mayo Clinic Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00013-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program website at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new healthcare technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the healthcare system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who provided input to this report follows:

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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

Structured Abstract

Objectives. To synthesize existing knowledge about the effectiveness and harms of pharmacologic and nonpharmacologic treatments for exacerbations of chronic obstructive pulmonary disease (ECOPD).

Data sources. Embase®, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE® Daily, MEDLINE, Cochrane Central Registrar of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus from database inception to January 2, 2019.

Review methods. We included randomized controlled trials (RCTs) that evaluated pharmacologic intervention or nonpharmacologic interventions for ECOPD. The strength of evidence (SOE) was graded for critical final health outcomes.

Results. We included 98 RCTs (13,401 patients, mean treatment duration 9.9 days, mean followup 3.7 months). Final health outcomes, including mortality, resolution of exacerbation, hospital readmissions, repeat exacerbations, and need for intubation, were infrequently evaluated and often showed no statistically significant differences between groups. Antibiotic therapy increases the clinical cure rate and reduces the clinical failure rate regardless of the severity of ECOPD (moderate SOE). There is insufficient evidence to support a particular antibiotic regimen. Oral and intravenous corticosteroids improve dyspnea and reduce the clinical failure rate (low SOE). Despite the ubiquitous use of inhaled bronchodilators in ECOPD, we found only a small number of trials that assessed lung function tests, and not final health outcomes. The evidence is insufficient to support the effect of aminophyllines, magnesium sulfate, mucolytics, inhaled corticosteroids, inhaled antibiotics, 5-lipoxygenase inhibitor, and statins on final health outcomes. Titrated oxygen reduces mortality compared with high flow oxygen (low SOE). Low SOE suggested benefit from some nonpharmacologic interventions such as chest physiotherapy using vibration/percussion/massage or 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 (low SOE).

Conclusions. Although chronic obstructive pulmonary disease is a common condition, 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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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.[1] 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;[2] and COPD costs more than $32 billion annually.[3, 4] 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."[5] ECOPD is generally characterized by increased dyspnea, increased frequency and severity of cough, and/or increased sputum production.[6] ECOPD is a leading independent cause of increased mortality 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.[7-14] Hospitalizations for ECOPD account for more than half of all costs associated with COPD.[10, 15]

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.[16, 17]

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.[18-20] 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.[21]

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.[22, 23] 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.[24, 25] Titrated oxygen with a target saturation rate as opposed to high flow oxygen has therefore been used in patients with ECOPD. [26] 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.[27, 28] 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.[29] 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.[30] This hyper-metabolic state is even more pronounced during episodes of ECOPD, posing questions about the optimal nutritional support for patients with ECOPD.[31, 32]

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.[33] 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.[34] Uncertainty remains regarding the use of systemic (oral, intravenous) corticosteroids relate to whether all patients stand to benefit from this treatment of ECOPD.[34] 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.[35]

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.[36] 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.[37] 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.[38-41]

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.[42] The reporting complies with the Preferred Reporting Items for Systematic Reviews

and Meta-Analyses (PRISMA) statements.[43] 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 significantly 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.[44]

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.[45] 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).[46] 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 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, [47] 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, [48] 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.[44] 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.[49] 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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Introduction

Background

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.[1] 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;[2] and COPD costs more than $32 billion annually.[3, 4] Patients with COPD experience chronic respiratory symptoms (including shortness of breath and cough), 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."[5] ECOPD is generally characterized by increased dyspnea, increased frequency and severity of cough, and/or increased sputum production.[6] ECOPD is a leading independent cause of increased mortality 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, hospital admission, depletion of financial resources, and a progressive decline in lung function.[7-14] Hospitalizations for ECOPD account for more than half of all costs associated with COPD.[10, 15]

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.[16, 17]

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.[18-20] 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.[21]

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

appear to have a small effect on reducing the frequency of ECOPD.[22, 23] 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.[24, 25] Titrated oxygen with a target saturation rate as opposed to high flow oxygen has therefore been used in patients with ECOPD.[26] 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.[27, 28] Chest physiotherapy using airway clearance techniques (including breathing technique, vibration/percussion, and autogenic drainage) are used routinely in many hospitalized patients 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-center studies with small study populations.[29] 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.[30] This hyper-metabolic state is even more pronounced during episodes of ECOPD, posing questions about the optimal nutritional support for patients with ECOPD.[31, 32]

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.[33] 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.[34] Uncertainty remains regarding the use of systemic (oral, intravenous) corticosteroids relate to whether all patients stand to benefit from this treatment of ECOPD.[34] 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.[35]

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.[36] 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.[37] 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.[38-41]

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.

Key Questions

The following Key Questions (KQs) were determined based on input from multiple key informants, and the public (drafted KQs were posted for public comment from January 26, 2018,to February 16, 2018. The related PICOTS (population, interventions, comparisons, outcomes, timing, and setting) are listed in Table 1.

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?

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?

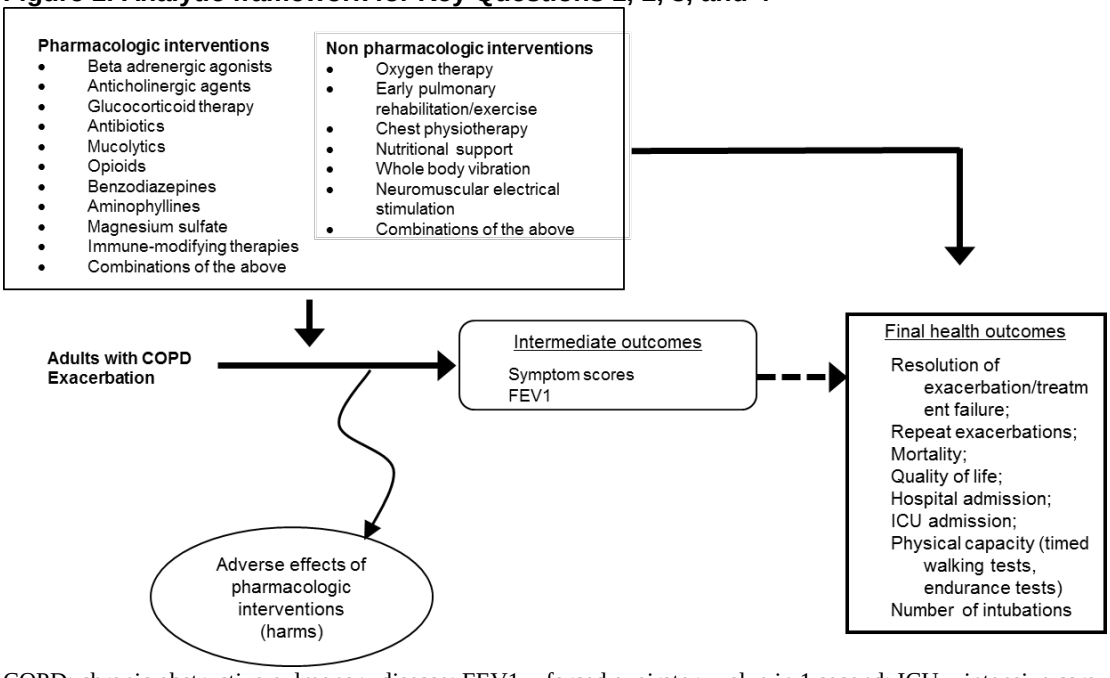
KQ3. In adult patients with exacerbation of COPD, what are the benefits and harms of combinations of treatments that are individually effective (based on empirical evidence in stable COPD)?

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 (Figure 1). 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.[42] The reporting complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.[43] 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).

Figure 1. Analytic framework for Key Questions 1, 2, 3, and 4



COPD: chronic obstructive pulmonary disease; FEV1 = forced expiratory value in 1 second; ICU = intensive care unit

Literature Search Strategy

Search Strategy

We conducted a comprehensive database search, including Embase, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, MEDLINE, Cochrane Central Registrar of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus from database inception to January 2, 2019. We searched Food and Drug Administration, ClinicalTrials.gov, Health Canada, Medicines and Healthcare Products Regulatory Agency (MHRA), AHRQ's Horizon Scanning System, conference proceedings, patient advocate group websites, and medical society websites. Reference mining of relevant publications, completed trials identified through ClinicalTrials.gov, relevant systematic reviews, and meta-analysis was used to identify additional existing and new literature. The search strategy was developed by an experienced medical librarian and further peer-reviewed by an independent information

specialist. The same librarian conducted the literature search. The detailed search strategy is listed in Appendix B.

Inclusion and Exclusion Criteria

The eligible studies had to meet all of the following criteria: 1) adult 18 years and older with exacerbations of chronic obstructive pulmonary disease (ECOPD); 2) received pharmacologic intervention or nonpharmacologic interventions; 3) compared with placebo, standard care, for antibiotics and systemic corticosteroids: different types of agents, different delivery modes, and different durations of treatments; 4) reported outcomes of interest; 5) conducted in outpatient, inpatients, and emergency department; 6) randomized controlled trials (RCTs); and 7) published in English. We excluded studies conducted in the intensive care unit, or chronic ventilator unit or respiratory care unit; studies of patients with exacerbation of chronic bronchitis if they did not have any evidence of airflow limitation on spirometry (at any time, including during a stable state); and studies of health service interventions (e.g. hospital in the home as alternative to hospitalization). We focused only on interventions during the initial acute phase of an exacerbation of COPD and not during the convalescence period. We did not restrict study location or sample size. The detailed inclusion and exclusion criteria are listed in Table 1.

All outcomes were final health outcomes except for the intermediate outcome, "forced expiratory volume in one second" (FEV1). FEV1 was included because it is a commonly used outcome in COPD studies and has been shown to be highly predictive of final health outcomes during ECOPD (including mortality, need for intubation, or hospital admission for COPD).[50]

Table 1. PICOTS (population, interventions, comparisons, outcomes, timing, and setting)

PICOTS Elements	Inclusion Criteria	Exclusion Criteria
Populations	Patients with exacerbation of COPD Adults 18 years and older	Animals Children (age < 18 years) Patients with stable COPD not in a current exacerbation
Interventions	KQ 1,4: Antibiotics Systemic corticosteroids KQ 2,3; Pharmacologic interventions include: Beta adrenergic agonists Anticholinergic agents Glucocorticoid therapy Antibiotics Mucolytics PDE4 Inhibitors Opioids Benzodiazepines Aminophyllines Magnesium sulfate Immune-modifying therapies Combinations of the above KQ 2,3; Nonpharmacologic interventions include: Oxygen therapy Early pulmonary rehabilitation/exercise Chest physiotherapy Nutritional support Whole body vibration Neuromuscular electrical stimulation Combinations of the above	Invasive and noninvasive mechanical ventilations Complementary and alternative medicine interventions Investigational drugs and drugs that are only available outside of the U.S. Interventions to prevent future COPD exacerbations
Comparators	KQ 1: Placebo or standard care KQ 2: Placebo or standard care KQ 3: Placebo, standard care or active individual intervention KQ 4: Different types of antibiotics and systemic corticosteroids, different delivery modes and durations of treatment	None
Outcomes	Intermediate outcomes • Symptom scores • FEV1 Final health outcomes • Resolution of exacerbation/treatment failure; • Repeat exacerbations; • Mortality; • Quality of life; • Hospital admission; • ICU admission; • Physical capacity (timed walking tests, endurance tests) • Number of intubations	None

PICOTS Elements	Inclusion Criteria	Exclusion Criteria
Timing	All	None
Settings	Outpatient, hospital, emergency department	ICU, chronic ventilator unit or respiratory care unit (RCU)
Study design	Original data Any sample size RCTs Relevant systematic reviews, or meta-analyses (used for identifying additional studies)	*In vitro* studies Non-original data (e.g. narrative reviews, editorials, letters, or erratum) Observational studies Case series Qualitative studies Cost-benefit analysis Cross-sectional (i.e., non-longitudinal) studies Before-after studies Survey
Publications	Studies published in English only.	Foreign language studies

Abbreviations: COPD = chronic obstructive pulmonary disease; FEV1 = Forced Expiratory Volume in One Second; ICU = intensive care unit; KQ = Key Question; PICOTS = population, interventions, comparators, outcomes, timing, and settings; RCT = randomized controlled trial

Study Selection

Independent reviewers, working in pairs, screened the titles and abstracts of all references. Studies included by either reviewer were retrieved for full-text screening. Independent reviewers, working in pairs, screened the full-text version of eligible references. Discrepancies between the reviewers were resolved through discussions and consensus.

Data Abstraction and Data Management

We developed a standardized data extraction form to extract study characteristics (author, study design, inclusion and exclusion criteria, patient characteristics, intervention, comparisons, outcomes, and related items for assessing study quality and applicability). The standardized form was pilot-tested by all study team members using five randomly selected studies. Reviewers worked independently to extract study details. A third reviewer reviewed data extraction, and resolve conflicts.

Assessment of the Risk of Bias of Individual Studies

We evaluated the risk of bias of the included study using the Cochrane Collaboration's Risk of Bias tool to assess sequence generation; allocation concealment; participant, personnel, and outcome assessor blinding; attrition bias; incomplete outcome data; selective outcome reporting; and other sources of bias.[51]

Data Synthesis

We summarized key features/characteristics (e.g. patient characteristics, intervention, comparison, outcomes, and conclusions) of the included studies and present in the tables by Key Questions (KQs). Table 2 presents the rules we used to categorize the severity of exacerbation.

Table 2. Categories of severity of exacerbation

Severity of Exacerbations	Rules
Mild	Outpatient treatment, possibly ED visit, but less likely than for moderate ECOPD OR classification as mild by the authors of the original study
Moderate	Requiring ED visit or hospitalization, but no mention of ventilatory failure (respiratory acidosis)/subsequent ICU admissions OR classification as moderate by the authors of the original study (including outpatients)
Severe	Requiring hospitalization, ventilatory failure (respiratory acidosis) and/or substantial rates of subsequent ICU admissions and deaths (studies with main location in ICU were, however, excluded) OR classification as severe by the authors of the original study

ECOPD = exacerbation of chronic obstructive pulmonary disease; ED = emergency department; ICU = intensive care unit

Table 3 lists the categories of adverse events and examples. Mortality was reported as a primary effectiveness outcome and not reported as serious adverse events in this review. We used the definition of serious adverse events listed by the original studies.

Table 3. Categories of adverse events

Type of Adverse Events	Example
Allergy and Immunology Adverse Event	Dermatitis
Cardiovascular Adverse Event	Paroxysmal atrial fibrillation, atrial fibrillation, palpitations, arrhythmia, symptomatic sinus, tachycardia
Dermatological Adverse event	Rash, urticaria, exanthema, pruritus
Ear, Nose and Throat Adverse Event	Transient episode of vocal cord dysfunction
Endocrine Adverse Event	Hyperglycemia, metabolism and nutrition disorders
Gastrointestinal Adverse Event	Gastrointestinal bleeding, diarrhea, nausea, stomachache, epigastric pain, heartburn, vomiting, constipation
General Internal Medicine Adverse Event	Facial puffiness, dizziness, new or worse hypertension, fatigue, chills, insomnia,, flushing, confusion, fever
Hepatic Adverse Event	Increased aspartate aminotransferase
Infectious (Non-Respiratory) Adverse Event	Vaginitis, urinary tract infection, influenza
Musculoskeletal Adverse Event	Muscle cramps, myalgia, tendonitis, rigors, musculoskeletal pain, muscle soreness
Neurological Adverse Event	Tremor, headache, seizure, rigors
Ocular Adverse Event	Blurred vision
Oncological Adverse Event	Classified as malignancy-related AEs by authors of the original study
Psychiatric Adverse Event	Mood change, psychosis, nervousness
Respiratory Adverse Event	Shortness of breath, respiratory acidosis, requiring noninvasive mechanical ventilation, dyspnea, bronchitis, wheezing, pneumothorax and pneumomediastinum, pneumonia, worsening exacerbation of COPD, bronchospasm
Urogenital Adverse Event	Hematuria

AEs = adverse events; COPD = chronic obstructive pulmonary disease

For outcome definitions, we defined as a resolution or clinical cure of ECOPD a complete improvement of clinical signs and symptoms, and as a clinical failure the lack of a significant improvement of clinical signs and symptoms and/or the requirement for additional or alternate treatment for an ECOPD. A repeat exacerbation (or repeat exacerbation) was defined as a new ECOPD following the initial ECOPD. For dyspnea, we differentiated between dyspnea measured with a numeric scale that represented different severity levels of breathlessness (e.g. visual

analogue scale or Borg scale) and dyspnea based on a questionnaire that assessed the functional limitation caused by dyspnea (e.g. medical research council dyspnea scale).

For crossover RCTs, we chose to qualitatively synthesize outcomes (i.e., not included in meta-analyses), as the included crossover RCTs suffered reporting and methodological issues, such as missing data, failure to control within-individual difference, and inhibited pooling with other studies.[52]

For other RCTs, we conducted meta-analyses to quantitatively summarize study findings. All statistical analyses were based on the intention-to-treat principle. Odds ratio and corresponding 95 percent confidence intervals were extracted or calculated for binary outcomes. For continuous outcomes, we calculated standardized mean difference when different measures for the same outcome were reported (e.g. St. George's Respiratory Questionnaire and 36-Item Short Form Survey (SF-36) for quality of life) and converted the direction of all measures (e.g. higher score represents better outcome). We calculated weighted mean difference when the included studies used the same outcome measure. For adverse events, we calculated rate ratio (i.e. ratio of the incidence rate of events within a given time between the intervention and the comparison).

For most of the outcomes, we extracted and pooled effect size by the end of the intervention and at the longest followup. For repeat exacerbation, we extracted at the end of intervention, 1-month, 3 month, 6-month, 12-month, and longest followup, which were commonly used followup time points in studies that measured exacerbations. For hospital admission, we extracted 30-day admission and at the longest followup. Thirty-day hospital admissions were chosen because hospital admissions within 30 days of an index hospitalization count as a readmission in Medicare's Hospital Readmissions Reduction Program, which lowers payments to Inpatient Prospective Payment System hospitals with too many readmissions.[53]

We used the DerSimonian and Laird (D-L) random effect method to combine direct comparisons between treatments if the number of studies included in the analysis was larger than 3.[54] The D-L method was chosen over alternative methods, such as the D-L with the Hartung-Knapp-Sidik-Jonkman variance correction (HKSJ) method and the profile likelihood (PL) method, because, when heterogeneity between the studies are low, the D-L method performs as well as alternative methods and the HKSJ method and PL method suffer methodological issues.[55-62] The HKSJ method and the PL method were used as sensitivity analyses for the D-L method (Appendix Table J.1.). When the number of studies was 3 or less, we used the fixed effect method based on the Mantel and Haenszel method due to instability of between-study variance.[63] We evaluated heterogeneity between studies using I^2 indicator. We were unable to use statistical methods to evaluate potential publication bias as the number of studies included in a direct comparison was small ($n<20$).[64] All statistical analyses were conducted using Stata/SE version 15.1 (StataCorp LLC, College Station, TX).

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

We graded the strength of evidence (SOE) as per the AHRQ Methods Guide on assessing SOE.[42] We graded SOE for most important or critical health outcomes, including mortality, dyspnea, quality of life (QoL), need for intubation, repeat exacerbation and/or hospital admissions and ECOPD resolution (clinical cure, failure). These outcomes were chosen because

they are clinically important from a patient's perspective and are highly relevant for decision making.

RCTs started as high SOE. The domains to be used for all KQs were: the methodological limitations of the studies (i.e., risk of bias); precision (based on the size of the body of evidence, number of events, and confidence intervals); directness of the evidence to the KQs (focusing on whether the outcomes were important to patients vs. surrogates); consistency of results (based on qualitative and statistical approaches to evaluate for heterogeneity); and the likelihood of reporting and publication bias. In most cases, sensitivity analyses based on risk of bias were not feasible due to the small number of studies per analysis.

Based on this assessment, we assigned SOE rating as high, moderate, low, or "insufficient evidence to estimate an effect". 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. We produced summary of evidence tables for each comparison and for each outcome: data source, effect size, SOE rating; and rationale for judgments made on each domain of evidence rating.

Assessing Applicability

We followed the procedures outlined in the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews to assess the applicability of the findings within and across studies.[42] We focused on whether the populations, interventions, and comparisons in existing studies were representative of current practice. For studies to have good applicability, the interventions used in research need to be available, accessible, acceptable and feasible to implement; and patients enrolled in the studies should be similar to typical patients with ECOPD, in particular in relation to underlying severity of COPD and co-morbidities. This congruence between research and practice as it relates to applicability was evaluated qualitatively and reported narratively. We reported limitations of applicability of the whole body of evidence in the discussion.

Peer Review and Public Commentary

A draft report was posted for peer review between March 29th and May 6th, 2019 and public comments between March 28th and May 6th, 2019. We revised and finalized the draft report in response to comments. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

Results

Literature Searches and Evidence Base

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 (Appendix Figure A.1.). Of the 98 studies, 4 were crossover randomized controlled trials (RCTs).[6, 65-67] 16 studies [6, 68-82] addressed Key Question (KQ)1(8[6, 68, 70-72, 74, 79, 82] had patients with mild exacerbation of chronic obstructive pulmonary disease (ECOPD) and 6[69, 73, 75-78], had patients with moderate to severe ECOPD, 1[80] had patients with mild to severe ECOPD, and 1[81] had severe ECOPD).51[25, 46, 65-67, 74-76, 83-125] addressed KQ2(4[74, 75, 89, 122]had patients with mild ECOPD, 47[25, 46, 65-67, 76, 83-88, 90-121, 123-125] had patients with moderate to severe ECOPD, 3 studies[126-128] addressed KQ 3 and 34 studies[75-77, 129-159] addressed KQ4. 59 trials were in a hospital setting,[46, 65, 69, 73, 75-78, 81, 83-91, 93-103, 105-112, 114-118, 120, 122-125, 127, 129, 130, 133, 140, 142, 144, 146, 149, 151, 155, 159] 10 in emergency departments,[80, 82, 92, 104, 119, 121, 126, 137, 141, 158] 19 in an outpatient setting[6, 66, 68, 70-72, 74, 79, 113, 132, 136, 138, 139, 143, 145, 148, 152-154] 1 was ambulance based[25], 2 were in both outpatients and hospitalized patients,[67, 156] and in 6 trials the setting was unclear.[128, 131, 134, 135, 150, 157] Studies were conducted in the US (11)[77, 79-81, 107, 119-121, 154, 156, 157], Canada (5) [6, 67, 82, 90, 118], Europe (44)[46, 65, 66, 68, 71-74, 76, 78, 83, 84, 86, 93, 99, 102, 106, 108, 110, 113-117, 124, 125, 127, 128, 130, 135, 138-144, 147, 148, 151-153, 155, 158], Australia (7), [25, 92, 97, 104, 105, 111, 126] Africa (2),[70, 101] Asia (26), [69, 75, 85, 87-89, 91, 94-96, 98, 103, 109, 112, 122, 123, 129, 131-134, 137, 146, 149, 150, 159] Africa (2),[70, 101] South America (2),[100, 145] and 1 study[136] was conducted in 30 countries. Most studies were conducted in hospitalized patients with moderate to severe chronic obstructive pulmonary disease (COPD). The mean treatment duration was 9.9 days and there was a mean 3.7 months of reported followup. A list of the studies excluded at the full-text review stage is in Appendix C. A search of ClinicalTrials.gov identified 33 ongoing clinical trials. We also found 102 studies published as conference abstracts.

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?

Key Points-KQ1

Systemic Antibiotics Versus Placebo or Management Without Systemic Antibiotics

- Antibiotics increased clinical cure of ECOPD compared with placebo or management without systemic antibiotics at the end of the intervention and at the longest followup (moderate Strength of Evidence (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 improved dyspnea compared with placebo at the end of the intervention (low 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 was observed, including serious adverse events, between antibiotics and placebo or management without antibiotics.

Systemic Corticosteroids Versus Placebo or Management Without Systemic Corticosteroids

- Systemic corticosteroids improved dyspnea (low SOE) at the end of the intervention 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. Systemic corticosteroids were associated with statistically significantly less withdrawals but more endocrine related adverse events.

KQ 1 Results

Sixteen studies with 2,762 patients were included for KQ1. The characteristics of the studies are listed in Appendix Table D.1. Eight[6, 68-73, 82] compared systemic antibiotics to placebo or management without systemic antibiotics and eight[74-81] compared systemic corticosteroids to placebo or management without systemic corticosteroids. Eight studies has patients with mild ECOPD,[6, 68, 70-72, 74, 79, 82] 6 studies[69, 73, 75-78] had patients with moderate to severe ECOPD 1[80] had patients with mild to severe ECOPD, and 1[81] had severe ECOPD. 7 trials were conducted in a hospital setting,[69, 73, 75-78, 81] 2 in the emergency department,[80, 82] and 7 were in outpatients.[6, 68, 70-72, 74, 79] Studies were conducted in the US(4),[77, 79-81]Canada(2) ,[6, 82] Europe (7), [68, 71-74, 76, 78]Africa (1) ,[70] and Asia (2).[69, 75] The average treatment length was 11.5 days and mean reported followup was 4.6 months. Details of the interventions used in each study can be found in Appendix Table F.1. Individual studies inclusion and exclusion criteria are in Appendix Table I.1.

The overall risk of bias is intermediate due to unclear allocation concealment (56.25%), unclear and random sequence generation (43.75%) (Appendix Table E.1.).

Systemic Antibiotics Versus Placebo or Management Without Systemic Antibiotics

Seven studies[6, 68-73, 82] evaluated the effectiveness of antibiotics versus placebo or management without systemic antibiotics, of which 2 studies were conducted in patients with mild,[68, 70] 4 mild to moderate[6, 71, 72, 82] ECOPD and 2 studies[69, 73] were conducted in patients with moderate to severe COPD. Table 4 and Table 5 provide an overview of all included studies. Tables stratified by the severity of ECOPD can be found in the Appendix (Appendix Table G.1: mild ECOPD, Appendix Table G.2: moderate to severe COPD).

Mortality

There was no statistically significant difference found between the antibiotics and placebo or management without antibiotics at the end of followup or at the end of the intervention.

When stratifying studies by severity of ECOPD, there were no statistically significant differences between groups in either mild or moderate to severe ECOPD. One study[68] in patients

with mild ECOPD did not show a statistically significant difference between antibiotics and placebo in mortality at the longest followup. In patients with moderate or severe ECOPD, there was no statistically significant difference observed between groups in mortality at the end of the intervention or at the end of followup.

Symptoms

One study showed statistically significantly less dyspnea (measured by numeric scale) at the end of the intervention in the antibiotics group compared with the placebo group[73] but not at the longest followup. Another study did not show a statistically significant difference in dyspnea[71](measured by questionnaire) at the longest followup.

In patients with mild ECOPD, there was no statistically significant difference observed in dyspnea between groups.

Cough was statistically significantly more reduced in the antibiotics groups compared with the placebo group at the end of the intervention but not at the longest followup.

Other symptoms were statistically significantly reduced in the antibiotics group compared with placebo or management without antibiotics at the end of treatment but not at the longest followup.

One study[71] was conducted in patients with mild ECOPD. The study did not find a statistically significant difference in dyspnea or other symptoms between intervention and placebo. Studies conducted in patients with moderate to severe COPD showed statistically significantly less dyspnea, cough and other symptoms at the end of the intervention but not at the longest followup in the antibiotics group compared with the placebo or management without antibiotics.[69, 73]

Quality of Life

Quality of life (QoL) was measured in one study (in patients with mild ECOPD, at the longest followup).[71] There was no statistically significant difference found between antibiotics and placebo.

Hospital Admission

Thirty-day hospital admissions were measured in one study[69] (including patients with moderate to severe ECOPD) with no statistically significant difference between antibiotics and management without antibiotics.

Repeat Exacerbations

Repeat exacerbations at the end of the intervention, at 30 days, 6 months, and longest followup did not show a statistically significant difference between the antibiotics and placebo or management without antibiotics. There was no statistically significant difference found in repeat exacerbations when stratifying studies by severity of ECOPD.

Intubations

The need for intubation at the end of the intervention was assessed in one study[69] (in patients with moderate to severe COPD).No statistically significantly difference was found between the antibiotics and management without antibiotics.

Clinical Resolution of Exacerbation

Statistically significantly more patients were clinically cured in the antibiotics group compared with placebo or management without antibiotics at the end of the intervention as well as at the longest followup.

In patients with mild ECOPD, statistically significantly more patients were clinically cured at the end of the intervention. Patients with mild ECOPD also had statistically significantly higher cure rates at the longest followup.

Statistically significantly less patients on antibiotics compared with patients in the placebo group had clinical failure at the end of the intervention but not at the longest followup.

In patients with mild ECOPD, statistically significantly less patients on antibiotics compared with patients in the placebo group had clinical failure at the end of the intervention but not at the longest followup.

A crossover RCT[6] compared antibiotics to placebo in mild to moderate ECOPD patients. After 3 weeks, patients in the antibiotic group were found to have statistically significantly more clinical cures (68% vs. 55%) and less clinical failures (10% vs. 19%) than those in the placebo group.

Table 4. Comparison of systemic antibiotics versus control, critical outcomes

Comparison	Outcome	Findings	Study Design and Sample size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Antibiotics vs. Management Without Antibiotics	Mortality End of Intervention	OR: 2.02; 95% CI: 0.18 to 22.66, I^2=N/A	1 RCT[69] with 194 patients	Severe imprecision	Low SOE supporting no difference
Antibiotics vs. Placebo or Management without Antibiotics	Mortality Longest Followup	OR: 1.78; 95% CI: 0.88 to 3.59, I^2= 0.00%	3 RCTs[68, 69 73] with 764 patients	Intermediate ROB and severe imprecision	Insufficient evidence
Antibiotics vs. Placebo	Dyspnea (Questionnaire: CRQ(dyspnea)) Longest Followup	WMD: 0.00; 95% CI: -0.97 to 0.97, I^2=N/A	1 RCT[71] with 35 patients	Severe imprecision	Low SOE supporting no difference
Antibiotics vs. Placebo	Dyspnea (Numeric Scale: VAS) End of Intervention	WMD: -0.80; 95% CI: -1.49 to -0.11, I^2=N/A	1 RCT[73] with 265 patients	High ROB and imprecision	Low SOE supporting improvement
Antibiotics vs. Placebo	Dyspnea (Numeric Scale: VAS) Longest Followup	WMD: -0.06; 95% CI: -1.27 to 0.07, I^2=N/A	1 RCT[73] with 265 patients	High ROB and imprecision	Low SOE supporting no difference
Antibiotics vs. Placebo	Quality of Life (CRQ) Longest Followup	WMD: 0.00; 95% CI: -1.80 to 1.79, I^2=N/A	1 RCT[71] with 35 patients	Severe imprecision	Low SOE supporting no difference
Antibiotics vs. Management Without Antibiotics	Hospital Admission 30 days	OR: 1.72; 95% CI: 0.68 to 4.36, I^2=N/A	1 RCT [69]with 194 patients	Severe imprecision	Low SOE supporting no difference

Comparison	Outcome	Findings	Study Design and Sample size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Antibiotics vs. Placebo or Management Without Antibiotics	Repeat Exacerbation End of Intervention	OR: 1.80; 95% CI: 0.89 to 3.62, I^2=0.00%	2 RCTs[69, 71] with 229 patients	Severe imprecision	Low SOE supporting no difference
		Rate Ratio; 1.01; 95% CI: 0.14 to 1.75, I^2=N/A	1 RCT[68] with 305 patients	Severe imprecision	Low SOE supporting no difference
Antibiotics vs. Placebo or Management Without Antibiotics	Repeat Exacerbation 30 days	OR: 1.69; 95% CI: 0.78 to 3.68, I^2=0.18%	2 RCTs[69, 71] with 229 patients	Severe imprecision	Low SOE supporting no difference
		Rate Ratio: 1.57; 95% CI: 0.76 to 3.24, I^2=0.00%	2 RCTs[69, 71] with 229 patients	Intermediate ROB and severe imprecision	Insufficient evidence
Antibiotics vs. Placebo	Repeat Exacerbation 6 months	OR: 2.24; 95% CI: 0.58 to 8.69, I^2=N/A	1 RCT[71] with 35 patients	Severe imprecision	Low SOE supporting no difference
Antibiotics vs. Placebo or Management Without Antibiotics	Repeat Exacerbation Longest Followup	OR: 1.80; 95% CI: 0.89 to 3.62, I^2=N/A	2 RCTs[69, 71] with 229 patients	Severe imprecision	Low SOE supporting no difference
Antibiotics vs. Management Without Antibiotics	Need for Intubation End of Intervention	OR: 0.49; 95% CI: 0.04 to 5.55, I^2=N/A	1 RCT[69] with 194 patients	Severe imprecision	Low SOE supporting no difference
Antibiotics vs. Placebo	Clinical Cure End of Intervention	OR: 2.03; 95% CI: 1.47 to 2.80, I^2=0.00%	3 RCTs[70, 72, 73] with 683 patients	High ROB	Moderate SOE supporting improvement
Antibiotics vs. Placebo or Management Without Antibiotics	Clinical Cure Longest Followup	OR: 1.50; 95% CI: 1.01 to 2.24, I^2=20.33%	4 RCTs[69, 71-73] with 812 patients	Intermediate ROB	Moderate SOE supporting improvement
Antibiotics vs. Placebo	Clinical Failure End of Intervention	OR: 0.54; 95% CI: 0.34 to 0.86, I^2=20.32%	2 RCTs[68, 70] with 405 patients	Intermediate ROB	Moderate SOE supporting improvement
Antibiotics vs. Placebo	Clinical Failure Longest Followup	OR: 0.82; 95% CI: 0.58 to 1.14, I^2=0.00%	2 RCTs[68, 73] with 570 patients	Intermediate ROB and imprecision	Low SOE supporting no difference

CI = confidence interval; CRQ = Chronic Respiratory Questionnaire; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; ROB = Risk of Bias; SOE = Strength of Evidence; VAS = visual analog scale; WMD = weighted mean difference

Lung Function

Forced expiratory volume in one second (FEV1) percent predicted and FEV1 absolute at the end of the intervention and at the longest followup were not statistically significantly different between the antibiotics and placebo or management without antibiotics. This finding was

independent of whether studies were conducted in patients with mild or moderate to severe ECOPD.

Table 5. Comparison of systemic antibiotics versus control, additional outcomes

Comparison	Outcome	Findings	Study Design and Sample Size
Antibiotics vs. Placebo	Cough (VAS) End of Intervention	WMD: -1.1; 95% CI: -1.80 to -0.40, I^2=N/A	1 RCT[73] with 265 patients
Antibiotics vs. Placebo	Cough (VAS) Longest Followup	WMD: -0.40; 95% CI: -1.33 to 0.33, I^2=N/A	1 RCT[73] with 265 patients
Antibiotics vs. Placebo/ Management Without Antibiotics	Other Symptoms(Total Symptom Score (Dyspnea, Fatigue, Cough, Sputum); VAS; CCQ Symptom Score) End of Intervention	SMD: 0.29; 95% CI: 0.11 to 0.47, I^2=41.0%	3 RCTs[69, 71, 73] with 494 patients
Antibiotics vs. Placebo	Other Symptoms(Total Symptom Score (Dyspnea, Fatigue, Cough, Sputum)) Longest Followup	WMD: -1.10; 95% CI: -3.31 to 1.11, I^2=N/A	1 RCT[73] with 265 patients
Antibiotics vs. Management Without Antibiotics	FEV1 % Predicted End of Intervention	WMD: -1.70; 95% CI: -7.31 to 3.91, I^2=N/A	1 RCT[69] with 194 patients
Antibiotics vs. Placebo	FEV1 % Predicted Longest Followup	WMD: -0.80; 95% CI: -6.67 to 5.07, I^2=N/A	1 RCT[71] with 35 patients
Antibiotics vs. Placebo	FEV1 Absolute End of Intervention	WMD: 0.05; 95% CI: -0.01 to 0.11, I^2=0.0%	2 RCTs[70, 73] with 365 patients
Antibiotics vs. Placebo	FEV1 Absolute Longest Followup	WMD: 0.05; 95% CI: -0.01 to 0.12, I^2=44.13%	2 RCTs[71, 73] with 300 patients

CCQ = Clinical COPD Questionnaire; CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; SMD = standardized mean difference; VAS = visual analog scale; WMD = weighted mean difference

Adverse Events

Appendix Table H.1. lists the rate ratio of adverse events(AEs) between antibiotics and placebo or management without antibiotics. There was no statistical difference between antibiotics and placebo on withdrawals, withdrawals due to AEs, total number of AEs, or any specific category of AEs (cardiovascular AE, dermatological AE, gastrointestinal AE, general internal medicine AE, musculoskeletal AE, or oncological AE). 2 studies[68, 73] reported serious AE in the antibiotics group, including pneumonia (1 case), urinary tract infection (1 case), cardiovascular (22 cases), hypoglycemia (1 case), malignancy-related (6 cases), and other unspecified (36 cases). There was no statistical difference on serious AEs.

Systemic Corticosteroids Versus Placebo or Management Without Systemic Corticosteroids

Nine studies compared the effectiveness of systemic corticosteroids versus placebo or management without systemic corticosteroids,[74-82] of which three studies were conducted in patients with mild ECOPD,[74, 79, 82] four studies in patients with moderate to severe ECOPD,[75-78, 100] one study in patients with severe ECOPD[81] and one in patients with mild to severe ECOPD.[80] Table 6 and Table 7 provide an overview of all included studies. Tables stratified by the severity

of ECOPD can be found in the Appendix (Appendix Table G.3: mild ECOPD, Appendix Table G.4: moderate to severe COPD).

Mortality

The pooled estimate of three studies (all conducted in patients with moderate to severe ECOPD) did not show any statistically significant difference between the systemic corticosteroids and the placebo or management without systemic corticosteroids group at the end of the intervention or at the end followup.

There were no studies measuring mortality in patients with mild ECOPD.

Symptoms

Dyspnea was statistically significantly better in the systemic corticosteroid group compared with the placebo group at the end of the intervention. There was no statistically significant difference in dyspnea at the end of the intervention when stratifying studies by severity of ECOPD.

Hospital Admission

Thirty-day hospital admissions were measured in two studies (including patients with moderate to severe ECOPD) with no statistically significant difference found between systemic corticosteroid and placebo group.

Repeat Exacerbations

Repeat exacerbations at the end of the intervention, at 1 month, 3 months, and longest followup did not show a statistically significant difference between systemic corticosteroid and placebo or management without systemic corticosteroids. There was no statistically significant difference observed in repeat exacerbations when stratifying studies by severity of ECOPD.

Intubations

The need for intubation at the end of the intervention and at the longest followup was found to be not statistically significantly different between the systemic corticosteroid and placebo group. There were no studies in mild ECOPD that assessed need for intubation as outcome.

Clinical Resolution of Exacerbation

Statistically significantly less patients on systemic corticosteroids compared with patients in the placebo group had clinical failure at the end of the intervention but not at the longest followup.

In patients with mild ECOPD, clinical failure in patients on systemic corticosteroids compared with patients in the placebo group was statistically significantly lower at the end of the intervention.

Table 6. Comparison of systemic corticosteroids versus control, critical outcomes

Comparison	Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Systemic Corticosteroids vs. Placebo	Mortality End of Intervention	OR: 1.61; 95% CI: 0.47 to 5.47, I^2= 0.00%	4 RCTs[76, 77, 82 81] with 510 patients	Intermediate ROB and severe imprecision	Insufficient evidence
Systemic Corticosteroids vs. Placebo or Management Aithout Systemic Corticosteroids	Mortality Longest Followup	OR: 0.89; 95% CI: 0.37 to 2.16, I^2= 0.00%	3 RCTs[75, 77, 78] with 353 patients	High ROB and severe imprecision	Insufficient evidence
Systemic Corticosteroids vs. Placebo	Dyspnea (Numeric Scale: Modified Borg, VAS) End of Intervention	SMD: 0.40; 95% CI:0.07 to 0.70, I^2=0.00%	2 RCTs[76, 79] with 154 patients	High ROB and imprecision	Low SOE supporting improvement
Systemic Corticosteroids vs. Placebo	Hospital Admission 30 days	OR: 0.54; 95% CI: 0.10 to 2.88, I^2=N/A	1 RCT[77] with 191 patients	High ROB and severe imprecision	Insufficient evidence
		Rate Ratio: 0.50; 95% CI: 0.15 to 1.66, I^2=N/A	1 RCT[75] with 106 patients	High ROB and severe imprecision	Insufficient evidence
Systemic Corticosteroids vs. Placebo or Management Aithout Systemic Corticosteroids	Repeat Exacerbation End of Intervention	OR: 0.97; 95% CI: 0.52 to 1.81, I^2=45.12%	3 RCTs[75, 78, 80] with 266 patients	High ROB and severe imprecision	Insufficient evidence
Systemic Corticosteroids vs. Management Aithout Systemic Corticosteroids	Repeat Exacerbation 1 Month	Rate Ratio: 0.52; 95% CI: 0.24 to 1.36, I^2=N/A	1 RCT[75] with 106 patients	High ROB and severe imprecision	Insufficient evidence
Systemic Corticosteroids vs. Placebo	Repeat Exacerbation 3 Months	OR: 1.29; 95% CI: 0.40 to 4.13, I^2=N/A	1 RCT[78] with 56 patients	Intermediate ROB and severe imprecision	Insufficient evidence
Systemic Corticosteroids vs. Placebo	Repeat Exacerbation Longest Followup	OR: 1.29; 95% CI: 0.40 to 4.13, I^2=N/A	1 RCT[78] with 56 patients	Intermediate ROB and severe imprecision	Insufficient evidence
Systemic Corticosteroids vs. Management without Systemic Corticosteroids	Repeat Exacerbation Longest Followup	Rate Ratio: 0.57, 95% CI: 0.24 to 1.36, I^2=N/A	1 RCT[75] with 106 patients	High ROB and severe imprecision	Insufficient evidence
Systemic Corticosteroids vs. Placebo	Need for Intubation End of Intervention	OR: 0.42; 95% CI: 0.06 to 2.68, I^2=0.00%	2 RCTs[76, 77] with 319 patients	High ROB and severe imprecision	Insufficient evidence

Comparison	Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Systemic Corticosteroids vs. Placebo	Need for Intubation Longest Followup	OR: 0.92; 95% CI: 0.15 to 5.66, I^2=N/A	1 RCT[77] with 191 patients	High ROB and severe imprecision	Insufficient evidence
Systemic Corticosteroids vs. Placebo	Clinical Failure End of Intervention	OR: 0.01; 95% CI: 0.00 to 0.13, I^2=0.00%	2 RCTs[77, 79] with 217 patients	High ROB and imprecision	Low SOE supporting improvement
Systemic Corticosteroids vs. Placebo	Clinical Failure Longest Followup	OR: 0.92; 95% CI: 0.58 to 1.45, I^2=81.42%	2 RCTs[77, 82] with 338 patients	Intermediate ROB and severe imprecision	Insufficient evidence

CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; ROB = risk of bias; SMD = standardized mean difference; SOE = strength of evidence

Lung Function

FEV1percent predicted was statistically significantly increased in the systemic corticosteroid group compared with placebo or management without systemic corticosteroids at the end of the intervention but not at the end of followup. FEV1percent absolute was statistically significantly increased in the systemic corticosteroid group compared with placebo or management without systemic corticosteroids at the end of the intervention.

Two stuides[74, 79] measured lung function in patients with mild ECOPD and found a statistically significantly increased FEV1 percent absolute in the systemic corticosteroid group compared with the placebo group at the end of the intervention.

Table 7. Comparison of systemic corticosteroids versus control, additional outcomes

Comparison	Outcome	Findings	Study Design and Sample Size
Systemic Corticosteroids vs. Placebo or Management Without Systemic Corticosteroids	FEV1 % Predicted End of Intervention	WMD: 4.64; 95% CI: 1.28 to 7.99, I^2=0.00%	4 RCTs[75, 80, 81] with 310 patients
Systemic Corticosteroids vs. Placebo	FEV1 % Predicted Longest Followup	WMD: 7.75; 95% CI: -0.30 to 15.80, I^2=0.62%	2 RCTs[78, 81] with 100 patients
Systemic Corticosteroids vs. Placebo	FEV1 Absolute End of Intervention	WMD: 0.36; 95% CI: 0.28 to 0.45, I^2=87.61%	3 RCTs[74, 78, 79] with 112 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Adverse Events

Appendix Table H.2. presents adverse events between systemic corticosteroids and placebo or management without systemic corticosteroids. The systemic corticosteroids group had statistically significant fewer withdrawals, and more endocrine AEs. One study[76] reported 5 cases of serious AEs (unspecified) in the systemic corticosteroids group. There was no statistical difference on serious AEs or other AEs.

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?

Key Points-KQ2

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 statistically significantly 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 Placebo or Management Without Nonpharmacologic Therapies

- Resistance training improved dyspnea, and quality of life compared with management without nonpharmacologic 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 nonpharmacologic therapies (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 usual diet (low SOE).
- Omega-3 fatty acid enriched diet did not change quality of life, need for intubation, or 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.

Results KQ2

There were 51studies [25, 46, 65-67, 74-76, 83-125], with 4,280 patients included for KQ2. The characteristics of the studies are listed in Appendix Table D.2. Four[66, 74, 113, 122] studies had patients with mild ECOPD, 6[25, 46, 65, 75, 76, 83-112, 114-121, 123-125] studies had patients with moderate to severe ECOPD, and1[67] study had patients with mild to severe ECOPD. Twenty [65, 66, 74-76, 89, 92, 93, 96, 98, 101, 104, 107, 112-114, 116, 119-121] evaluated pharmacologic therapies compared with management without pharmacologic therapies and 31[25, 46, 67, 83-88, 90, 91, 94, 95, 97, 99, 100, 102, 103, 105, 106, 108-111, 115, 117, 118, 122-125]evaluated nonpharmacologic therapies to management without nonpharmacologic

therapies. 41 were conducted in a hospital setting,[46, 65, 75, 76, 83-91, 93-103, 105-112, 114-118, 120, 123-125] 4 in the Emergency Department,[92, 104, 119, 121]3 in outpatients,[66, 74, 113] 1 in both outpatients and hospital settings,[67] one in an ambulance[25] and in one study the setting was unclear.[122] Studies were conducted in the US (4),[107, 119-121] Canada (3),[67, 90, 118] Europe (21), [46, 65, 66, 74, 76, 83, 84, 86, 93, 99, 102, 106, 108, 110, 113-117, 124, 125]Africa (1),[101], Asia (15),[75, 85, 87-89, 91, 94-96, 98, 103, 109, 112, 122, 123] Australia (6),[25, 92, 97, 104, 105, 111] and South America (1).[100] Average treatment length was 9.6 days and the mean reported followup was 3.6 months. Details of the interventions in each study can be found in Appendix Table F.2. Individual studies inclusion and exclusion criteria are in Appendix Table I.1.

The overall risk of bias is intermediate to high due to unclear sequence generation (49.02%), unclear allocation concealment (66.67%), and high risk or unclear risk of incomplete outcome data (56.86%) (Appendix Table E.1.).

Pharmacologic Therapies

Aminophyllines Versus Placebo

Three studies[114, 120, 121] evaluated the effectiveness of intravenous aminophyllines compared with placebo (Table 8 and Table 9). All studies were conducted in patients with moderate to severe ECOPD.

There were no statistically significant differences observed between groups in mortality, dyspnea, cough, other symptoms, FEV1 absolute, and need for intubation. Statistically significantly more patients in the aminophyllines group had total number of AEs and gastrointestinal AEs than those in the placebo group[114] (Appendix Table H.3.). No other statistically significant difference on withdrawals, other AEs (cardiovascular AE, neurological AE, withdrawals due to AEs) were found.

Table 8. Comparison of intravenous aminophyllines versus placebo, critical outcomes

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Mortality End of intervention	OR: 0.81; 95% CI: 0.29 to 2.28, I^2= 0.00%	2 RCT[114, 121] with 132 patients	Intermediate ROB and severe imprecision	Insufficient evidence
Dyspnea (Numeric Scale: Borg) End of Intervention	SMD: -0.01; 95% CI: -0.35 to 0.33, I^2= 0.00%	2 RCT[114, 121] with 132 patients	Intermediate ROB and severe imprecision	Insufficient evidence
Need for Intubation End of Intervention	OR: 0.87; 95% CI: 0.05 to 15.28, I^2=N/A	1 RCT[114, 120, 121]with 30 patients	Intermediate ROB and severe imprecision	Insufficient evidence

CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; ROB = risk of bias; SMD = standardized mean difference

Table 9. Comparison of intravenous aminophyllines versus placebo, additional outcomes

Outcome	Findings	Study Design and Sample Size
Cough (Scale no problem to severe problem) End of Intervention	WMD: -0.30; 95% CI: -0.94 to 0.34, I^2=N/A	1 RCT[121] with 52 patients

Outcome	Findings	Study Design and Sample Size
Other Symptoms (VAS) End of Intervention	WMD: -10.8; 95% CI: -21.59 to 0.00, I^2=N/A	1 RCT[114] with 80 patients
FEV1 Absolute End of Intervention	WMD: -0.02; 95% CI: -0.09 to 0.06, I^2=0.00%	3 RCT[114, 120, 121] with 162 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; VAS: visual analog scale; WMD = weighted mean difference

Magnesium Sulfate Versus Placebo

Four studies evaluated the effectiveness of intravenous magnesium sulfate,[65, 92, 98, 119] and one study[104] evaluated the effectiveness of nebulized magnesium sulfate (Table 10 and Table 11). All studies were conducted in patients with moderate to severe ECOPD.

There were no statistically significant differences observed in FEV1percent predicted at the longest followup and FEV1 absolute and dyspnea scores at the end of the intervention between intravenous magnesium and placebo. The intravenous magnesium sulfate group had a statistically significantly increased FEV1absolute at the longest followup. There was no statistically significant difference found in FEV1 absolute at the end of the intervention between nebulized magnesium sulfate and placebo. No adverse events were reported in the magnesium group. [119]

Table 10. Comparison of intravenous magnesium sulfate versus placebo, critical outcomes

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Dyspnea (Numeric Scale: Dyspnea 1-7) End of Intervention	No statistical difference	1 RCT[119] with 72 patients	High ROB and severe imprecision	Insufficient evidence

RCT = randomized controlled trial; ROB = risk of bias; SOE = strength of evidence

Table 11. Comparison of magnesium sulfate versus placebo, additional outcomes

Comparison	Outcome	Findings	Study Design and Sample Size
Intravenous Magnesium Sulfate vs. Placebo	FEV1 Absolute End of Intervention	WMD: 0.02; 95% CI: -0.02 to 0.05, I^2= N/A	1 RCT[98] with 30 patients
	FEV1 Absolute End of Intervention	No statistical difference	1 Crossover RCT[65] with 24 patients
	FEV1% Predicted End of intervention	No statistical difference	1 Crossover RCT[65] with 24 patients
	FEV1 Absolute Longest Followup	WMD: 0.09; 95% CI: 0.01 to 0.16, I^2= N/A	1 RCT[92] with 33 patients
	FEV1% predicted Longest Followup	WMD: 0.00; 95% CI: -48.08 to 48.08, I^2= N/A	1 RCT[98] with 30 patients
Nebulized Magnesium Sulfate vs. Placebo	FEV1 Absolute End of Intervention	WMD: -0.03; 95% CI: -0.15 to 0.09, I^2= N/A	1 RCT[104] with 116 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Mucolytics Versus Placebo or Management Without Mucolytics

The effectiveness of the oral mucolytics N-Acetylcysteine and Erdosteine compared with placebo or management without mucolytics was evaluated in 4[96, 101, 113, 116] studies and 1 study[93, 101] respectively. One N-Acetylcysteine study was in patients with mild ECOPD,[113] the remaining studies[93, 96, 101, 116] were in patients with moderate to severe ECOPD. Tables stratified by the severity of ECOPD can be found in the Appendix (Appendix Table G.5: mild ECOPD, Appendix Table G.6: moderate to severe COPD).

Erdosteine statistically significantly reduced repeat exacerbations at 3-month followup but not at 1-month followup compared with management without Erdosteine (low SOE). Erdosteine was associated with significantly reduced symptoms (based on the breathlessness, cough and sputum scale) at the end of the intervention but not at the longest followup. FEV1 percent predicted was statistically significantly increased in the erdosteine group compared with the management without Erdosteine group at the end of the intervention but not at the longest followup (Table 12 and Table 13). No AEs were reported in both groups.

Dyspnea and FEV1 absolute at the end of the intervention were not found to have a statistically significantly difference between the N-Acetylcysteine and the placebo group. There was no statistically significant difference found in FEV1 absolute at the end of the intervention between the N-Acetylcysteine and the placebo group in patients with mild or moderate to severe ECOPD (Table 12 and Table 13). There was no statistically significant difference observed on gastrointestinal AEs and total number of AEs (Appendix Table H.4.).[116]

Table 12. Comparison of oral mucolytics versus control, critical outcomes

Comparison	Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
N-Acetylcysteine (Mucolytic) vs. Placebo	Dyspnea (Numeric Scale: Dyspnea) End of intervention	SMD: -0.16; 95% CI: -0.57 to 0.25, I^2=50.36%	2 RCTs[96, 116] with 92 patients	High ROB and severe imprecision	Insufficient evidence
N-Acetylcysteine (Mucolytic) vs. Placebo	Hospital Admission Longest Followup	Rate Ratio: 1.70; 95% CI: 0.80 to 3.63, I^2=N/A	1 RCT[96] with 44 patients	High ROB and severe imprecision	Insufficient evidence
Erdosteine (Mucolytic) vs. Management Without Erdosteine	Repeat Exacerbation 1 month	OR: 0.05; 95% CI: 0.00 to 1.04, I^2=N/A	1 RCT[93] with 40 patients	High ROB and severe imprecision	Insufficient evidence
Erdosteine (Mucolytic) vs. Management Without Erdosteine	Repeat Exacerbation 3 months	OR: 0.14; 95% CI: 0.03 to 0.65, I^2=N/A	1 RCT[93] with 40 patients	High ROB and imprecision	Low SOE supporting reduction
Erdosteine (Mucolytic) vs. Management Without Erdosteine	Repeat Exacerbation Longest Followup	OR: 0.14; 95% CI: 0.03 to 0.65, I^2=N/A	1 RCT[93] with 40 patients	High ROB and imprecision	Low SOE supporting reduction

CI = confidence interval; OR = odds ratio; N/A = not applicable; RCT = randomized controlled trial; ROB = risk of bias; SMD = standardized mean difference; SOE = strength of evidence

Table 13. Comparison of oral mucolytics versus control, additional outcomes

Comparison	Outcome	Findings	Study Design and Sample Size
Erdosteine (Mucolytic) vs. Management Without Erdosteine	Symptoms BCSS End of Intervention	WMD: -1.00; 95% CI: -1.63 to -0.37, I^2=N/A	1 RCT[93] with 40 patients
Erdosteine (Mucolytic) vs. Management Without Erdosteine	Symptoms BCSS Longest Followup	WMD: -0.90; 95% CI: -1.82 to 0.02, I^2=N/A	1 RCT[93] with 40 patients
Mucolytics (Erdosteine, N-Acetylcysteine) vs. Placebo or Management Without Erdosteine	FEV1% Predicted End of Intervention	All mucolytics: WMD: 1.98; 95% CI: 0.51 to 3.44, I^2=89.12% Erdosteine: WMD: 9.00; 95% CI: 3.17 to 14.83, I^2= N/A; Acetylcysteine: WMD: 1.50; 95% CI: -0.02 to 3.02, I^2= N/A	All mucolytics: 2 RCT[93, 101] with 70 patients; Erdosteine: 1 RCT[93] with 40 patients; Acetylcysteine: 1 RCT[101] with 30 patients
Erdosteine (Mucolytic) vs. Management Without Erdosteine	FEV1% Predicted Longest Followup	WMD: 8.30; 95% CI: -0.69 to 17.29, I^2= N/A	1 RCT[93] with 40 patients
N-Acetylcysteine (Mucolytic) vs. Placebo	FEV1 Absolute End of Intervention	WMD: 0.07; 95% CI: -0.11 to 0.25, I^2=0.00%	2 RCT[96, 113] with 125 patients

BCSS = Breathlessness, Cough and Sputum Scale; CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Inhaled Corticosteroids With or Without Inhaled Short- and Long-Acting Bronchodilators Versus Placebo

Four studies[74-76, 112] evaluated the effectiveness of different inhaler treatments containing an inhaled corticosteroid (ICS) versus placebo, of which 3 were conducted in patients with moderate to severe ECOPD[75, 76, 112] and 1 in mild ECOPD[74] (Table 14 and Table 15).

In patients with moderate to severe ECOPD, ICS were associated with a statistically significantly higher FEV1percent predicted at the end of the intervention compared with placebo, but there was no statistically significant difference found in dyspnea, 30-day hospital admission, and need for intubation between groups (Appendix Table G.7).

In patients with moderate to severe ECOPD, a combination of ICS+SABA (budesonide+ terbutaline) was associated with a statistically significantly higher FEV1percent predicted and FEV1 absolute at the end of the intervention compared with placebo (Appendix Table G.8.).

In patients with mild ECOPD, a combination of ICS+ long-acting beta-2-agonists (LABA) (budesonide+formoterol) was not associated with a statistically significant difference in FEV1 absolute and clinical failure at the end of the intervention compared with placebo[74] (Appendix Table G.9).

No statistically significant difference was found on total number of AEs, number of withdrawals and number of withdrawals due to AEs (Appendix Table H.5). Eight unspecified serious AEs were reported in the ICS group (8 in the ICS group while 9 cases in the placebo group).

Table 14. Comparison of inhaled corticosteroids with or without inhaled short- and long-acting bronchodilators versus placebo, critical outcomes

Comparison	Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
ICS (Budesonide) vs. Placebo	Dyspnea (Numeric Scale: Modified Borg) End of Intervention	WMD: -0.10; 95% CI: -0.92 to 0.22, I^2= N/A	1 RCT[76] with 137 patients	High ROB and severe imprecision	Insufficient evidence
	Need for Intubation End of Intervention	OR: 0.31; 95% CI: 0.01 to 7.63, I^2= N/A	1 RCT[76] with 137 patients	High ROB and severe imprecision	Insufficient evidence
	Hospital Admission 30 Days	Rate Ratio: 0.63; 95% CI: 0.20 to 1.91, I^2= N/A	1 RCT[75] with 106 patients	High ROB and severe imprecision	Insufficient evidence
ICS+ LABA (Budesonide +Formoterol) vs. Placebo	Clinical failure End of Intervention	OR: 1.00; 95% CI: 0.06 to 17.62, I^2= N/A	1 RCT[74] with 30 patients	High ROB and severe imprecision	Insufficient evidence

CI = confidence interval; ICS = inhaled corticosteroid; LABA = Long-acting beta-agonist; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; ROB = risk of bias; SOE = strength of evidence; WMD = weighted mean difference

Table 15. Comparison of inhaled corticosteroids with or without inhaled short- and long-acting bronchodilators versus placebo, additional outcomes

Comparison	Outcome	Findings	Study Design and Sample Size
ICS (Budesonide) vs. Placebo	FEV1% Predicted End of Intervention	WMD: 10.10; 95% CI: 4.23 to 15.97, I^2= N/A	1 RCT[75] with 106 patients
ICS+SABA (Budesonide+ Terbutaline) vs. Placebo	FEV1% Predicted End of Intervention	WMD: 8.30; 95% CI: 2.92 to 13.68, I^2= N/A	1 RCT[112] with 40 patients
ICS+SABA (Budesonide +Terbutaline) vs. Placebo	FEV1 Absolute End of Intervention	WMD: 0.35; 95% CI: 0.05 to 0.65, I^2= N/A	1 RCT[112] with 40 patients
ICS+ LABA (Budesonide +Formoterol) vs. Placebo	FEV1 Absolute End of Intervention	WMD: 0.18; 95% CI: -0.17 to 0.53, I^2= N/A	1 RCT[74] with 30 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; ICS = inhaled corticosteroid; LABA = Long-acting beta-agonist; N/A = not applicable; RCT = randomized controlled trial; ROB = risk of bias; SABA = Short acting beta agonists; SOE = strength of evidence; WMD = weighted mean difference

Inhaled Antibiotics Versus Placebo

One study[89] evaluated the effectiveness of inhaled (nebulized) gentamicin compared with placebo in patients with moderate to severe ECOPD (Table 16). Inhaled gentamicin was associated with a statistically significantly higher FEV1 absolute at the end of the intervention compared with placebo.

Table 16. Comparison of inhaled antibiotics versus placebo

Outcome	Findings	Study Design and Sample Size
FEV1 Absolute End of Intervention	WMD: 3.49; 95% CI: 1.49 to 5.49, I^2= N/A	1 RCT[89] with 86 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Long-Acting Muscarinic Antagonists Versus Placebo

One crossover RCT[66] compared inhaled oxitropium, a long-acting muscarinic antagonist (LAMA) to placebo in 50 patients with ECOPD and heart disease (ischemic heart disease and/or arrhythmias). There was a statistically significant improvement of FEV1 absolute compared with placebo at the end of intervention ($p<0.05$) (Table 17).

Table 17. Long-acting muscarinic antagonists versus placebo

Outcome	Findings	Study Design and Sample Size
FEV1 Absolute End of Intervention	0.16 vs. 0.05, p<0.05	1 crossover RCT[66] with 50 patients

FEV1 = forced expiratory volume in one second; RCT = randomized controlled trial

5-Lipoxygenase Inhibitor Versus Placebo

The effectiveness of (oral) zileuton, a 5-lipoxygenase inhibitor, was evaluated in one study of patients with moderate to severe ECOPD.[107] 5-Lipoxygenase inhibitor was associated with a statistically significantly increased FEV1 absolute at the end of the intervention and at the longest followup compared with placebo. There were no statistically significant differences observed in FEV1 percent predicted, mortality, hospital admissions, clinical resolution and need for intubation between the zileuton and placebo group (Table 18 and Table 19). There was no statistically significant difference found on AEs between 5-lipoxygenase inhibitor and placebo (Appendix Table H.6.). 17 cases of unspecified serious AEs were reported in the 5-lipoxygenase inhibitor group while 21 cases in the placebo group (p=0.40).

Table 18. Comparison of 5-lipoxygenase inhibitor (zileuton) versus placebo, critical outcomes

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Mortality End of Intervention	OR: 0.48; 95% CI: 0.04 to 5.48, I^2=N/A	1 RCT[107] with 119 patients	High ROB and severe imprecision	Insufficient evidence
Hospital Admission Longest Followup	OR: 0.98; 95% CI: 0.32 to 2.99, I^2=N/A	1 RCT[107] with 119 patients	High ROB and severe imprecision	Insufficient evidence
Clinical Failure Longest Followup	OR: 0.82; 95% CI: 0.36 to 1.87, I^2=N/A	1 RCT[107] with 119 patients	High ROB and severe imprecision	Insufficient evidence
Need for Intubation End of Intervention	OR: 0.98; 95% CI: 0.06 to 16.09, I^2=N/A	1 RCT[107] with 119 patients	High ROB and severe imprecision	Insufficient evidence

CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; ROB = risk of bias; SOE = strength of evidence

Table 19. Comparison of 5-lipoxygenase inhibitor (zileuton) versus placebo, additional outcomes

Outcome	Findings	Study Design and Sample Size
FEV1% Predicted Longest Followup	WMD: 4:30; 95% CI: -2.28 to 10.88, I^2=N/A	1 RCT[107] with 119 patients
FEV1 Absolute End of Intervention	WMD: 0.17; 95% CI: 0.13 to 0.21, I^2=N/A	1 RCT[107] with 119 patients

Outcome	Findings	Study Design and Sample Size
FEV1 Absolute Longest Followup	WMD: 0.23; 95% CI: 0.02 to 0.44, I^2=N/A	1 RCT[107] with 119 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Statin (Simvastatin) Versus Management Without Statin

Statin therapy with simvastatin was compared with management without statin in one study,[122] which found a statistically significantly increased FEV1percent predicted at the end of the intervention in the statin group (Table 20).

Table 20. Comparison of statin versus management without statin

Outcome	Findings	Study Design and Sample Size
FEV1% Predicted End of Intervention	WMD: 0.68, 95% CI: 0.38 to 0.98, I^2= N/A	1 RCT[122] with 60 patients

CI = confidence interval; FEV1 = Forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Nonpharmacologic Therapies

Chest Physiotherapy (Breathing Technique; Vibration/Percussion; Positive Expiratory Pressure) Versus Management Without Chest Physiotherapy

Chest Physiotherapy Using Breathing Technique

Three studies[88, 106, 110] evaluated the effectiveness of chest physiotherapy using a specific breathing technique compared with management without chest physiotherapy in patients with moderate to severe ECOPD (Table 21 and Table 22).

Chest physiotherapy using a specific breathing technique significantly reduced hospital admission at the longest followup compared with management without chest physiotherapy (low SOE). There were no statistically significantly differences between the intervention and management without chest physiotherapy group for other outcomes, including: mortality at end of followup, mortality at the longest followup, dyspnea based on a questionnaire, dyspnea based on a numeric scale, other symptoms, quality of life, and FEV1 predicted. No statistically significant difference was found in withdrawals, and withdrawals due to AEs[106, 110] (Appendix Table H.7.). The intervention group[106] reported cardiovascular AEs (3 cases), respiratory AEs (7 cases), and general internal medicine AEs (5 cases).

Table 21. Comparison of chest physiotherapy using breathing technique versus management without chest physiotherapy, critical outcomes

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Mortality End of intervention	OR: 0.97; 95% CI: 0.06 to 16.20, I^2= N/A	1 RCT[110] with 59 patients	High ROB and severe imprecision	Insufficient evidence
Mortality Longest Followup	OR: 0.90; 95% CI: 0.54 to 1.49, I^2= N/A	1 RCT[106] with 522 patients	Intermediate ROB and imprecision	Low SOE supporting no difference

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Dyspnea (Questionnaire: MRC) End of Intervention	WMD: 0.40; 95% CI: -0.24 to 1.04, I^2= N/A	1 RCT[110] with 59 patients	High ROB and severe imprecision	Insufficient evidence
Dyspnea (Numeric Scale: VAS, Borg) End of Intervention	SMD: -0.42; 95% CI: -0.89 to 0.05, I^2=98.92%	2 RCT[88, 110] with 119 patients	High ROB, inconsistency and severe imprecision	Insufficient evidence
QoL(SGRQ) End of Intervention	SMD: -0.02; 95% CI: -0.18 to 0.14, I^2=0.00%	2 RCTs[106, 110] with 581 patients	High ROB and severe imprecision	Insufficient evidence
Hospital Admission Longest Followup	Rate Ratio: 0.91; 95% CI: 0.83 to 0.99, I^2=79.5%	2 RCTs[106, 110] with 581 patients	High ROB, and inconsistency	Low SOE supporting reduction

CI = confidence interval; MRC = Medical Research Council; N/A = not applicable; OR = odds ratio; QoL = quality of life; RCT = randomized controlled trial; ROB = risk of bias; SGRQ = St. George Respiratory Questionnaire; SMD = standardized mean difference; SOE = strength of evidence; VAS = visual analog scale; WMD = weighted mean difference

Table 22. Comparison of chest physiotherapy using breathing technique versus management without chest physiotherapy, additional outcomes

Outcome	Findings	Study Design and Sample Size
Other Symptoms (SGRQ, symptom score) End of Intervention	WMD: -0.02; 95% CI: -3.99 to 3.95, I^2= N/A	1 RCT[106] with 522 patients
Symptoms BCSS End of Intervention	WMD: -0.06; 95% CI: -0.56 to 0.44, I^2= N/A	1 RCT[106] with 522 patients
FEV1% Predicted End of Intervention	WMD: 6.50; 95% CI: -8.46 to 21.46, I^2= N/A	1 RCT[110] with 59 patients

BCSS = breathlessness, cough and sputum scale; CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; SGRQ = St. George respiratory questionnaire; SMD = standardized mean difference; WMD = weighted mean difference

Chest Physiotherapy Using Vibration, Percussion, or Massage

Three studies[67, 102, 103] evaluated the effectiveness of chest physiotherapy using vibration, percussion, or massage compared with management without chest physiotherapy in patients with moderate to severe ECOPD (Table 23 and Table 24).

There was no difference between the intervention and management without chest physiotherapy group for all evaluated outcomes including: dyspnea at the end of the intervention and at the longest followup, FEV1percent predicted at the end of the intervention and at the longest followup, FEV1 absolute at the end of the intervention, and 6-minute walking distance at the end of the intervention. No patient withdrew during the study (Appendix Table H.8.).

Table 23. Comparison of chest physiotherapy using vibration, percussion, or massage versus management without chest physiotherapy, critical outcomes

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Dyspnea (Questionnaire: MRC; MMRC) End of Intervention	SMD: 0.15; 95% CI: -0.29 to 0.60, I^2= 0.00%	2 RCTs[102, 103] with 80 patients	High ROB and severe imprecision	Insufficient evidence

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Dyspnea (Questionnaire: MMRC) Longest Followup	WMD: -0.24; 95% CI: -0.73 to 0.25, I^2= N/A	1 RCT[103] with 50 patients	High ROB and severe imprecision	Insufficient evidence

CI = confidence interval; MMRC = Modified Medical Research Council; MRC = Medical Research Council; N/A = not applicable; RCT = randomized controlled trial; ROB = risk of bias; SMD = standardized mean difference; SOE = strength of evidence; WMD = weighted mean difference

Table 24. Comparison of chest physiotherapy using vibration, percussion, or massage versus management without chest physiotherapy, additional outcomes

Outcome	Findings	Study Design and Sample Size
FEV1% Predicted End of Intervention	WMD: 4.88; 95% CI: -0.37 to 10.12, I^2= 87.37%	2 RCTs[102, 103] with 80 patients
FEV1% Predicted Longest Followup	WMD: 0.00; 95% CI: -5.98 to 5.98, I^2= N/A	1 RCT[103] with 50 patients
FEV1 Absolute End of Intervention	WMD: 0.00; 95% CI: -0.45 to 0.45, I^2= N/A	1 RCT[103] with 30 patients
	0.9 (SD: 0.5) vs. 0.9 (SD: 0.5), p=non-statistically significant	1 crossover RCT[67] with 24 patients
6MWD End of Intervention	WMD: 56.20; 95% CI: -8.18 to 120.58, I^2= N/A	1 RCT[102] with 30 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; SD = standard deviation; WMD = weighted mean difference

Chest Physiotherapy Using Positive Expiratory Pressure

One study[97] evaluated the effectiveness of chest physiotherapy using positive expiratory pressure compared with management without positive expiratory pressure in patients with moderate to severe ECOPD (Table 25 and Table 26).

There was no difference between the intervention and management without positive expiratory pressure group for all evaluated outcomes including: mortality at the end of the intervention and at the longest followup, dyspnea at the end of the intervention and at the longest followup, FEV1 predicted at the end of the intervention and at the longest followup, repeat exacerbations at the end of the intervention, 6-minute walking distance at the end of the intervention, and quality of life at the longest followup.

No statistically significant difference on withdrawals, withdrawals due to AEs, and total number of AEs was found (Appendix Table H.9.). Serious AEs (serious clinical deterioration) were reported in 9 patients in the chest physiotherapy compared with 6 patients in the management without positive expiratory pressure group (p=0.40).

Table 25. Comparison of chest physiotherapy using positive expiratory pressure versus management without positive expiratory pressure, critical outcomes

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Mortality End of Intervention	OR: 1.00; 95% CI: 0.06 to 16.48, I^2= N/A	1 RCT[97] with 92 patients	Severe imprecision	Low SOE supporting no difference
Mortality Longest Followup	OR: 1.58; 95% CI: 0.41 to 6.00, I^2= N/A	1 RCT[97] with 92 patients	Severe imprecision	Low SOE supporting no difference
Dyspnea (Questionnaire: MMRC) End of Intervention	WMD: 0.40; 95% CI: -0.16 to 0.96, I^2= N/A	1 RCT[97] with 92 patients	Severe imprecision	Low SOE supporting no difference

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Dyspnea (Questionnaire: MMRC) Longest Followup	WMD: 0.50; 95% CI: -0.06 to 1.06, I^2= N/A	1 RCT[97] with 92 patients	Severe imprecision	Low SOE supporting no difference
Repeat Exacerbation End of Intervention	OR: 1.00; 95% CI: 0.06 to 16.48, I^2= N/A	1 RCT[97] with 92 patients	Severe imprecision	Low SOE supporting no difference
Repeat Exacerbation Longest Followup	Rate Ratio: 1.05; 95% 0.69 to 1.59, I^2= N/A	1 RCT[97] with 92 patients	Severe imprecision	Low SOE supporting no difference
QoL(SGRQ) Longest Followup	WMD: -1.50; 95% CI: -5.99 to 8.99, I^2= N/A	1 RCT[97] with 92 patients	Severe imprecision	Low SOE supporting no difference

CI = confidence interval; MMRC: Modified Medical Research Council Scale N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; QoL = quality of life; ROB = risk of bias; SGRQ = St. George Respiratory Questionnaire; WMD = weighted mean difference

Table 26. Comparison of chest physiotherapy using positive expiratory pressure versus management without positive expiratory pressure, additional outcomes

Outcome	Findings	Study Design and Sample Size
FEV1% Predicted End of Intervention	WMD: -0.30; 95% CI: -4.18 to 3.58, I^2= N/A	1 RCT[97] with 92 patients
FEV1% Predicted Longest Followup	WMD: -1.30; 95% CI: -7.30 to 4.70, I^2= N/A	1 RCT[97] with 92 patients
6MWD End of Intervention	WMD: -26.00; 95% CI: -89.61 to 37.62, I^2= N/A	1 RCT[97] with 92 patients
6MWD Longest Followup	WMD: -4.00; 95% CI: -82.49 to 74.49, I^2= N/A	1 RCT[97] with 92 patients
Symptoms BCSS End of Intervention	WMD: 0.20; 95% CI: -0.91 to 1.31, I^2= N/A	1 RCT[97] with 92 patients
Symptoms BCSS Longest Followup	WMD: 0.10; 95% CI: -1.01 to 1.21, I^2= N/A	1 RCT[97] with 92 patients

6MWD = 6 minute walking distance; BCSS = Breathlessness, Cough and Sputum Scale; CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Exercise Versus Management Without Exercise

Exercise Using Resistance Training Versus Management Without Resistance Training

Three studies[84, 86, 100, 108] evaluated the effectiveness of exercise using resistance training compared with management without resistance training in patients with moderate to severe ECOPD (Table 27 and Table 28).

Exercise using resistance training was associated with statistically significantly better dyspnea, better QoL, and higher 6-minute walking distance at the end of the intervention, compared with management without resistance training.

There was no difference between the intervention and management without resistance training group for all other evaluated outcomes including: mortality at the longest followup, other symptoms at the end of the intervention and at the longest followup, FEV1percent predicted at the end of intervention, and hospital admissions at the longest followup. No statistically significant difference was found on number of withdrawals (Appendix Table H.10.).

Table 27. Comparison of exercise using resistance training versus management without resistance training, critical outcomes

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Mortality Longest Followup	OR: 0.22; 95% CI: 0.01 to 4.81, I^2= N/A	1 RCT[100] with 46 patients	Intermediate ROB and severe imprecision	Insufficient evidence
Dyspnea (Numeric Scale; Modified Borg) End of Intervention	WMD: -2.11; 95% CI: -3.50 to -0.72, I^2= N/A	1 RCT[84] with 60 patients	Intermediate ROB and imprecision	Low SOE supporting improvement
QoL(EQ-5D VAS) End of Intervention	WMD: 18.70; 95% CI: 5.06 to 32.34, I^2= N/A	1 RCT[84] with 60 patients	Intermediate ROB and imprecision	Low SOE supporting improvement
Hospital Admission Longest Followup	OR: 1.23; 95% CI: 0.35 to 4.31, I^2= N/A	1 RCT[108] with 40 patients	High ROB and severe imprecision	Insufficient evidence

CI = confidence interval; EQ-5d = EuroQol, 5 Dimensions; N/A = not applicable; OR = odds ratio; QoL = quality of life; RCT = randomized controlled trial; ROB = risk of bias; SOE = strength of evidence; VAS = visual analog scale; WMD = weighted mean difference

Table 28. Comparison of exercise using resistance training versus management without resistance training, additional outcomes

Outcome	Findings	Study Design and Sample Size
Other Symptoms (Health related Quality of Life, sub scale) End of Intervention	WMD: 5.90; 95% CI: -1.20 to 13.00, I^2= N/A	1 RCT[100] with 46 patients
Other Symptoms (Health related Quality of Life, sub scale) Longest Followup	WMD: 0.80; 95% CI: -10.31 to 11.90, I^2= N/A	1 RCT[100] with 46 patients
FEV1% Predicted End of Intervention	WMD: 2.37; 95% CI: -2.83 to 7.57, I^2=0.00%	2 RCTs[84, 100] with 106 patients
6MWD End of Intervention	WMD: 74.42; 95% CI: 46.85 to 101.99, I^2= 95.42%	2 RCTs[100, 108] with 86 patients

6MWD = 6-minute walking distance; CI = confidence interval; FEV1 = Forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Exercise Using Aerobic Training Versus Management Without Aerobic Training

Four studies reported relevant outcomes comparing aerobic training versus management without aerobic training.[83, 86, 124, 125] Aerobic exercise was associated with significantly improved dyspnea and quality of life at the end of intervention, worse dyspnea at the longest followup, statistically significant improvement in 6 minute walking distance, number of steps walked per day, and endurance based on a 30-second sit-to-stand test, compared with management without

aerobic exercise. There was no difference between the intervention and control group for mortality, hospital admissions and repeat exacerbations (Table 29 and Table 30).

Table 29. Comparison of exercise using aerobic training versus management without aerobic training, critical outcomes

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Mortality End of Intervention	OR: 1.00; 95% CI: 0.06 to 17.02, I^2= N/A	1 RCT [124] with 46 patients	High ROB and severe imprecision	Insufficient evidence
Dyspnea (Questionnaire: Transitional Dyspnea Index) End of Intervention	WMD: 7.20; 95% CI: 4.53 to 9.87, I^2= N/A	1 RCT [124] with 46 patients	High ROB and imprecision	Low SOE supporting better outcome
Dyspnea (Questionnaire: MRC) Longest Followup	WMD: 1.20; 95% CI: 0.33 to 2.07, I^2= N/A	1 RCT[83] with 29 patients	Intermediate ROB and imprecision	Low SOE supporting worse outcome
QoL (CRQ) End of Intervention	WMD: 38.00; 95% CI: 24.51 to 51.49, I^2= N/A	1 RCT [124] with 46 patients	High ROB and imprecision	Low SOE supporting better outcome
QoL(CAT) Longest Followup	WMD: -5.20; 95% CI: -2.99 to 13.39, I^2= N/A	1 RCT[83] with 29 patients	Intermediate ROB and severe imprecision	Insufficient evidence
Hospital Admission Longest Followup	OR: 1.50; 95% CI: 0.33 to 6.77, I^2= N/A	1 RCT[83] with 29 patients	Intermediate ROB and severe imprecision	Insufficient evidence
	Rate Ratio: 0.96; 95% CI: 0.39 to 2.37, I^2= N/A	1 RCT[83] with 29 patients	Intermediate ROB and severe imprecision	Insufficient evidence
Repeat Exacerbation End of Intervention	OR: 0.74; 95% CI: 0.22 to 2.49, I^2= 0.0%	2 RCTs[83] [124] with 75 patients	High ROB and severe imprecision	Insufficient evidence

CAT = COPD Assessment Test; CI = confidence interval; CRQ = Chronic Respiratory Disease Questionnaire; MRC = Medical Research Council Scale; OR = odds ratio; RCT = randomized controlled trial; ROB = risk of bias; SOE = strength of evidence; WMD = weighted mean difference

Table 30. Comparison of exercise using aerobic training versus management without aerobic training, additional outcomes

Outcome	Findings	Study Design and Sample Size
FEV1% Predicted End of Intervention	WMD: 0.10; 95% CI: -8.36 to 8.56, I^2= N/A	1 RCT [125] with 29 patients
FEV1 Absolute End of Intervention	WMD: 0.19; 95% CI: -0.08 to 0.46, I^2= N/A	1 RCT [124] with 46 patients
6MWD End of Intervention	WMD: 28.71; 95% CI: 10.91 to 46.50, I^2= 98.4%	2 RCTs [124] [125] with 75 patients
Number of steps walked per day End of Intervention	WMD: 663.03; 95% CI: 496.34 to 829.72, I^2= N/A	1 RCT[86] with 58 patients
30-second sit-to-stand test End of Intervention	WMD: 4.63; 95% CI: 2.54 to 6.72, I^2= N/A	1 RCT[86] with 58 patients

6MWD = 6 minute walking distance; CI = confidence interval; RCT = randomized controlled trial; WMD = weighted mean difference

Exercise Using Combined Aerobic + Resistance Training Versus Management Without Exercise Training

One study[105] evaluated the effectiveness of exercise using combined aerobic and resistance training compared with management without exercise training in patients with moderate to severe ECOPD (Table 31). The study had two active treatment arms: one low-intensity exercise arm and one moderate to high-intensity exercise arm, in addition to a management without exercise training arm.

Low-intensity and moderate-to-high intensity aerobic and resistance training was not associated with a statistical difference in FEV1 percent predicted, 3-minute walking distance test, and upper limb muscle strength at the end of the intervention compared with management without exercise training. There was no statistical difference in total number of AEs (Appendix Table H.11).

Table 31. Comparison of exercise using combined aerobic + resistance training versus management without exercise training

Comparison	Outcome	Findings	Study Design and Sample Size
Low Intensity Exercise Group vs. Management Without Exercise Training	FEV1% Predicted End of Intervention	WMD: -4.80; 95% CI: -13.23 to 3.63, I^2=N/A	1 RCT[105] with 22 patients
	3-minute Walking Distance Test End of Intervention	SMD: 0.40; 95% CI: -0.50 to 1.30, I^2=N/A	1 RCT[105] with 22 patients
	Upper Limb Muscle Strength	SMD: 0.20; 95% CI: -0.70 to 1.00, I^2=N/A	1 RCT[105] with 22 patients
Moderate-to-High Intensity Exercise Group vs. Management Without Exercise Training	3-minute Walking Distance Test End of Intervention	p=NS	1 RCT[105] with 22 patients
	Upper Limb Muscle Strength	p=NS	1 RCT[105] with 22 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; NS = not statistically significant; RCT = randomized controlled trial; SMD = standardized mean difference; WMD = weighted mean difference

Chest Physiotherapy + Exercise Combined Versus Management Without Exercise Training

One study[84] evaluated the effectiveness of chest physiotherapy and exercise (breathing technique and range of motion exercises) combined compared with management without exercise training in patients with moderate to severe ECOPD (Table 32 and Table 33).

The chest physiotherapy and exercise combination group was found to have statistically significantly more improvements in quality of life at the end of the intervention. No other statistically significant difference was found.

Table 32. Comparison of chest physiotherapy + exercise (breathing technique + range of motion exercises) combined versus management without exercise training, critical outcomes

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Dyspnea (Numeric Scale: Modified Borg Scale) End of Intervention	WMD: 1.15; 95% CI: -0.61 to 2.91, I^2= N/A	1 RCT[84] with 60 patients	Intermediate ROB and severe imprecision	Insufficient evidence
QoL (EQ-5D) End of Intervention	WMD: 14.89; 95% CI: 5.30 to 24.50, I^2= N/A	1 RCT[84] with 60 patients	Intermediate ROB and imprecision	Low SOE supporting improvement

CI = confidence interval; EQ-5D = EuroQol 5 Dimension Index; N/A = not applicable; RCT = randomized controlled trial; QoL = quality of life; ROB = risk of bias; SOE = strength of evidence; WMD = weighted mean difference

Table 33. Comparison of chest physiotherapy + exercise (breathing technique + range of motion exercises) combined versus management without exercise training, additional outcomes

Outcome	Findings	Study Design and Sample Size
FEV1% Predicted End of Intervention	WMD: 2.48; 95% CI: -1.81 to 6.77, I^2= N/A	1 RCT[84] with 60 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Early Pulmonary Rehabilitation (During ECOPD) Versus Management Without Early Pulmonary Rehabilitation

Four studies[46, 83, 94, 95, 111] evaluated the effectiveness of early pulmonary rehabilitation during ECOPD compared with management without early pulmonary rehabilitation in patients with moderate to severe ECOPD (Table 34 and Table 35).

Early pulmonary rehabilitation was associated with a statistically significantly longer 6-minute walking distance at the end of the intervention, compared with management without early pulmonary rehabilitation.

Dyspnea based on a numeric scale was statistically significantly improved at the end of the intervention, but not at the longest followup in the early pulmonary rehabilitation group compared with the management without early pulmonary rehabilitation group. Early pulmonary rehabilitation was also statistically significantly associated with decreased cough at the end of the intervention compared with management without early pulmonary rehabilitation.

There was no statistical difference between the intervention and management without early pulmonary rehabilitation for other outcomes including: dyspnea (based on questionnaire) at the end of the intervention and at the longest followup, hospital admissions at 30 days and 1 year.

Serious AEs were reported in 7 cases in the early pulmonary rehabilitation group, including worsening COPD exacerbations (5 cases), pneumonia (1 case), a not further specified respiratory, thoracic and mediastinal disorder (1 case), and vascular disorder (1 case). There was no statistically significant difference observed between the early pulmonary rehabilitation group and the management without early pulmonary rehabilitation in serious AEs, total number of AEs, withdrawals, and withdrawals due to AEs. (Appendix Table H.12.)

Table 34. Comparison of early pulmonary rehabilitation versus management without early pulmonary rehabilitation, critical outcomes

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Mortality End of Intervention	OR: 3.26; 95% CI: 0.13 to 81.98, I^2=N/A	1 RCT[111] with 97 patients	High ROB and severe imprecision	Insufficient evidence
Dyspnea (Questionnaire: MMRC) End of Intervention	WMD: -0.50; 95% CI: -3.01 to 2.06, I^2=N/A	1 RCT[95] with 94 patients	High ROB and severe imprecision	Insufficient evidence
Dyspnea (Questionnaire: MMRC) Longest Followup	WMD: 0.04; 95% CI: -0.48 to 0.56, I^2=N/A	1 RCT[95] with 94 patients	High ROB and severe imprecision	Insufficient evidence
Dyspnea (Numeric Scale: Modified Borg; Borg) End of Intervention	SMD: 0.66; 95% CI: 0.31 to 1.00, I^2=89.21%	2 RCT[94, 95] with 156 patients	High ROB and inconsistency	Low SOE supporting improvement
Dyspnea (Numeric Scale: Borg) Longest Followup	WMD: 0.20; 95% CI: -0.69 to 0.29, I^2= N/A	1 RCT[111] with 97 patients	High ROB and severe imprecision	Insufficient evidence
Hospital Admission At 30 days	OR: 0.65; 95% CI: 0.26 to 1.60, I^2= N/A	1 RCT[111] with 97 patients	High ROB and severe imprecision	Insufficient evidence
	Rate Ratio: 0.60; 95% CI: 0.31 to 1.15, I^2= N/A	1 RCT[111] with 97 patients	High ROB and severe imprecision	Insufficient evidence
Hospital Admission Longest Followup	Hazard ratio: 1.19, 95% CI: 0.90 to 1.60, I^2= N/A	1 RCT [46,] with 320 patients	High ROB and severe imprecision	Insufficient evidence

CAT = COPD Assessment Test; CI = confidence interval; MMRC = Modified Medical Research Council Scale; MRC = Medical Research Council Scale; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; QoL = quality of life; ROB = risk of bias; SMD = standardized mean difference; SOE = strength of evidence; WMD = weighted mean difference

Table 35. Comparison of early pulmonary rehabilitation versus management without early pulmonary rehabilitation, additional outcomes

Outcome	Findings	Study Design and Sample Size
Cough (VAS) End of Intervention	WMD: -2.00; 95% CI: -2.98 to -1.02, I^2= N/A	1 RCT[94] with 62 patients
6MWD End of Intervention	WMD: 20.02; 95% CI: 12.06 to 28.67, I^2=79.08%	3 RCTs[94, 95, 111] with 253 patients

6MWD = 6 minute walking distance; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial; SMD = standardized mean difference; WMD = weighted mean difference; VAS= visual analog score

Whole Body Vibration Training Versus Management Without Whole Body Vibration

One study[99] evaluated the effectiveness of whole body vibration training during ECOPD compared with management without whole body vibration in patients with moderate to severe ECOPD (Table 36 and Table 37).

There was a statistically significantly higher quality of life and a longer 6-minute walking distance at the end of the intervention in the intervention compared with the management without whole body vibration group. Whole body vibration training during ECOPD was not associated with statistically significant difference in FEV1 percent predicted.

No AEs were reported in the whole body vibration group. There was no statistical difference on withdrawals (Appendix Table H.13.).

Table 36. Comparison of whole body vibration training during ECOPD versus management without whole body vibration, critical outcomes

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
QoL(SGRQ) End of Intervention	WMD: -12.02; 95% CI: -21.41 to -2.63, I^2= N/A	1 RCT[99] with 49 patients	Intermediate ROB and imprecision	Low SOE supporting improvement

CI = confidence interval; N/A = not applicable; QoL = quality of life; RCT = randomized controlled trial; SGRQ = St. George Respiratory Questionnaire; WMD = weighted mean difference

Table 37. Comparison of whole body vibration training during ECOPD versus management without whole body vibration, additional outcomes

Outcome	Findings	Study Design and Sample Size
6MWD End of Intervention	WMD: 89.42; 95% CI: 45.18 to133.66, I^2= N/A	1 RCT[99] with 49 patients
FEV1% Predicted End of Intervention	WMD: -6.52; 95% CI: -16.96 to 3.92, I^2= N/A	1 RCT[99] with 49 patients

6MWD = 6 minute walking distance; CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Transcutaneous Electrical Nerve Stimulation (TENS) Versus Management Without TENS

One study[87] evaluated the effectiveness of transcutaneous electrical nerve stimulation (TENS) during ECOPD compared with management without TENS in patients with moderate to severe ECOPD (Table 38 and Table 39).

TENS during ECOPD was associated with a statistically significantly longer 6-minute walking distance at the end of the intervention, but no difference in dyspnea, FEV1 absolute, and number of withdrawals at the end of the intervention compared with management without TENS group (Appendix Table H.14.).

Table 38. Comparison of transcutaneous electrical nerve stimulation (TENS) during ECOPD versus management without TENS, critical outcomes

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Dyspnea (Questionnaire: MRC) End of Intervention	WMD: -0.23; 95% CI: -0.57 to 0.11, I^2= N/A	1 RCT[87] with 82 patients	High ROB and severe imprecision	Insufficient evidence

CI = confidence interval; ECPOD = Exacerbations of Chronic Obstructive Pulmonary Disease; MRC = Medical Research Council Scale N/A = not applicable; RCT = randomized controlled trial; ROB = risk of bias; WMD = weighted mean difference

Table 39. Comparison of transcutaneous electrical nerve stimulation (TENS) during ECOPD versus management without TENS, additional outcomes

Outcome	Findings	Study Design and Sample Size
6MWD End of Intervention	WMD: 64.54; 95% CI: 53.76 to 75.32, I^2= N/A	1 RCT[87] with 82 patients
FEV1 Absolute End of Intervention	WMD: -0.05; 95% CI: -0.33 to 0.23, I^2= N/A	1 RCT[87] with 82 patients

6MWD = 6 minute walking distance; CI = confidence interval; ECPOD = Exacerbations of Chronic Obstructive Pulmonary Disease; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Supplemental Oxygen Versus Supplemental Air During Mobilization With a Walking Aid

One study[117] randomized 120 patients with moderate to severe ECOPD to one of the four groups: gutter frame with supplemental oxygen; gutter frame with supplemental air; rollator with supplemental oxygen, or rollator with supplemental air (Table 40). The presence of hypoxemia at rest was not a requirement for study inclusion, and paO2 ranged from 72-80 mmHg in the different groups at baseline. Oxygen levels were not measured during mobilization. There was no statistically significant difference observed in dyspnea, mortality, and 30-day hospital admissions, AEs, withdrawals, and withdrawals due to AEs between groups (Appendix Tables H.15. and H.16.).

Table 40. Supplemental oxygen versus supplemental air

Comparison	Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Gutter Frame with Supplemental Oxygen vs. Gutter Frame with Supplemental Air	Dyspnea (Numeric: Borg Dyspnea Scale) End of intervention	WMD: 0.80; 95% CI: -0.90 to 2.50, I^2=N/A	1 RCT[117] with 60 patients	High ROB and severe imprecision	Insufficient evidence
	Mortality Longest Followup	OR:1.00; 95% CI: 0.06 to 16.76, I^2=N/A	1 RCT[117] with 60 patients	High ROB and severe imprecision	Insufficient evidence
	Hospital Admission 30 days	OR: 1.63; 95% CI: 0.41 to 6.47, I^2=N/A	1 RCT[117] with 60 patients	High ROB and severe imprecision	Insufficient evidence
Rollator with Supplemental Oxygen, vs. Rollator with Supplemental Air	Dyspnea (Numeric: Borg Dyspnea Scale) End of Intervention	WMD: -0.90; 95% CI: -2.35 to 0.58, I^2=N/A	1 RCT[117] with 60 patients	High ROB and severe imprecision	Insufficient evidence
	Mortality Longest Followup	0 case in both groups.	1 RCT[117] with 60 patients	High ROB and severe imprecision	Insufficient evidence
	Hospital Admission 30 days	OR: 1.63; 95% CI: 0.41 to 6.47, I^2=N/A	1 RCT[117] with 60 patients	High ROB and severe imprecision	Insufficient evidence

CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; ROB = risk of bias; WMD = weighted mean difference

Titrated Oxygen Versus High Flow Oxygen

A study[25] randomized 405 patients with a presumed moderate to severe ECOPD to titrated oxygen (with a target oxygen saturation between 88 percent and 92 percent delivered by nasal prongs) or high flow oxygen (8-10 liters/minute, administered by a non-rebreather face mask). In the subgroup analysis of confirmed ECOPD patients (117 in titrated oxygen vs. 97 in high flow oxygen), titrated oxygen was associated with statistically significantly reduced mortality compared with high flow oxygen at the longest followup (Table 41).

Table 41. Titrated oxygen versus high flow oxygen, critical outcomes

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Mortality Longest Followup	OR: 0.36; 95% CI: 0.14 to 0.88, I^2=N/A I^2	1 RCT[25] with 214 patients	High ROB and imprecision	Low SOE supporting improvement
Need for Intubation Longest Followup	OR: 0.13; 95% CI: 0.02 to 1.00, I^2=N/A	1 RCT[25] with 214 patients	High ROB and severe imprecision	Insufficient evidence

CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; ROB = risk of bias; SOE = strength of evidence

Automated Oxygen Titration Versus Manual Oxygen Titration

One RCT[90] compared automated oxygen titration with manual oxygen titration and found no statistically significant difference in mortality, need for intubation, ICU admission, and hospital admissions. The target oxygen saturation was determined by the attending physician before randomization (Table 42).

Table 42. Titrated oxygen versus free flow oxygen, critical outcomes

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Mortality End of Intervention	OR: 1.00; 95% CI: 0.06 to 16.93, I^2=N/A	1 RCT[90] with 50 patients	Intermediate ROB and severe imprecision	Insufficient evidence
Need for intubation End of intervention	OR: 3.12; 95% CI: 0.12 to 80.39, I^2=N/A	1 RCT[90] with 50 patients	Intermediate ROB and severe imprecision	Insufficient evidence
Hospital Admissions 30 days	OR: 1.00; 95% CI: 0.27 to 3.66, I^2=N/A	1 RCT[90] with 50 patients	Intermediate ROB and severe imprecision	Insufficient evidence
Hospital Admissions Longest Followup	OR: 1.63; 95% CI: 0.53 to 4.98, I^2=N/A	1 RCT[90] with 50 patients	Intermediate ROB and severe imprecision	Insufficient evidence
ICU Admission End of Intervention	OR: 3.12; 95% CI: 0.12 to 80.39, I^2=N/A	1 RCT[90] with 50 patients	Intermediate ROB and severe imprecision	Insufficient evidence

CI = confidence interval; ICU = intensive care unit; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; ROB = risk of bias; SOE = strength of evidence

Dietary Intervention Versus Usual Diet

Dietary Intervention Using a Caloric Supplement During ECOPD Versus Usual Diet

One study[118] evaluated the effectiveness of a dietary intervention using a caloric supplement during ECOPD compared with a usual diet in patients with moderate to severe ECOPD (Table 43 and Table 44). There were no statistically significant differences found between the intervention and usual diet for mortality, dyspnea, QoL, FEV1percent predicted, and number of withdrawals (Appendix Table H.17.).

Table 43. Comparison of a dietary intervention using a caloric supplement during ECOPD versus usual diet, critical outcomes

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Mortality End of Intervention	OR: 0.81; 95% CI: 0.05 to 14.28, I^2= N/A	1 RCT[118] with 31 patients	High ROB and severe imprecision	Insufficient evidence
Dyspnea (Questionnaire: Oxygen Cost Diagram) End of Intervention	WMD: 05.95; 95% CI: -5.74 to 17.64, I^2= N/A	1 RCT[118] with 31 patients	High ROB and imprecision	Insufficient evidence
QoL(General Well-Being) End of Intervention	WMD: 22.21; 95% CI: -6.99 to 151.40, I^2= N/A	1 RCT[118] with 31 patients	High ROB and imprecision	Insufficient evidence

CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; QoL = quality of life; ROB = risk of bias; SOE = strength of evidence; WMD = weighted mean difference

Table 44. Comparison of a dietary intervention using a caloric supplement during ECOPD versus usual diet, additional outcomes

Outcome	Findings	Study Design and Sample Size
FEV1% Predicted End of Intervention	WMD: 6.14; 95% CI: -0.76 to 13.04, I^2= N/A	1 RCT[118] with 31 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Dietary Intervention Using a Caloric and a Protein Supplement During ECOPD Versus Placebo (Non-Caloric Fluid, Vanilla Flavored Water)

One study[115] evaluated the effectiveness of a dietary intervention using a caloric and a protein supplement during ECOPD compared with placebo (non-caloric fluid, vanilla flavored water) in patients with moderate to severe ECOPD (Table 45 and Table 46).

A caloric and protein supplement during ECOPD was not associated with statistically significant differences in dyspnea and FEV1 percent predicted at the end of the intervention compared with placebo (non-caloric fluid, vanilla flavored water).

There was no statistically significant difference observed in withdrawals, withdrawals due to AEs, gastrointestinal AEs, and total number of AEs (Appendix Table H.18.).

Table 45. Comparison of a dietary intervention using a caloric and a protein supplement during ECOPD versus placebo (non-caloric fluid, vanilla flavored water), critical outcomes

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Dyspnea (Numeric Scale: VAS, dyspnea score while eating) End of Intervention	WMD: 0.5; 95% CI: -1.14 to 2.14, I^2= N/A	1 RCT[115] with 47 patients	High ROB and severe imprecision	Insufficient evidence

CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial; ROB = risk of bias; SMD = standardized mean difference; VAS = visual analog scale

Table 46. Comparison of a dietary intervention using a caloric and a protein supplement during ECOPD versus placebo (non-caloric fluid, vanilla flavored water), additional outcomes

Outcome	Findings	Study Design and Sample Size
FEV1% Predicted End of Intervention	WMD: 0.00; 95% CI: -4.36 to 4.36, I^2= N/A	1 RCT[115] with 47 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Dietary Intervention Using a High Fat Low Carbohydrate Diet During ECOPD Versus Usual Diet

One study[109] evaluated the effectiveness of a dietary intervention using a high fat low carbohydrate diet during ECOPD compared with a usual diet in patients with moderate to severe ECOPD (Table 47).

A high fat low carbohydrate diet during ECOPD was not found to have a statistically significant difference in FEV1 percent absolute at the end of the intervention compared with usual diet.

Table 47. Comparison of a dietary intervention using a high fat low carbohydrate diet during ECOPD versus usual diet

Outcome	Findings	Study Design and Sample Size
FEV1 Absolute End of Intervention	WMD: -0.01; 95% CI: -0.31 to 0.29, I^2= N/A	1 RCT[109] with 30 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Omega-3 Fatty Acid Enriched Diet Versus Usual Diet

One study compared omega-3 fatty acids to a usual diet in patients with moderate to severe ECOPD (Table 48 and Appendix table H.19).[123] There was no statistically significant difference observed in dyspnea, need for intubation, and quality of life between the two groups.

Table 48. Comparison of a dietary intervention using omega-3 fatty acid versus usual diet

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
QoL (CAT) End of Intervention	WMD: 0.00; 95% CI: -3.46 to 3.46, I^2= N/A	1 RCT[123] with 50 patients	Severe imprecision	Low SOE supporting no difference
Need for Intubation End of Intervention	OR: 0.18; 95% CI: 0.01 to 4.04, I^2= N/A	1 RCT[123] with 50 patients	Severe imprecision	Low SOE supporting no difference
Dyspnea (Questionnaire: MMRC) End of intervention	WMD: 0.00; 95% CI: -0.55 to 0.55, I^2= N/A	1 RCT[123] with 50 patients	Severe imprecision	Low SOE supporting no difference

CAT = COPD Assessment Test; CI = confidence interval; MMRC = Modified Medical Research Ccouncil Scale; N/A = not applicable; OR = odds ratio; QoL = quality of life; RCT = randomized controlled trial; SMD = standardized mean difference

Vitamin D Versus Placebo

Two studies[85, 91] evaluated the effectiveness of vitamin D during ECOPD compared with placebo in patients with moderate to severe ECOPD (Table 49 and Table 50). In one study,[91] vitamin D was given orally, in the other,[85] it was given as intermuscular injection.

Vitamin D during ECOPD was associated with a statistically significantly better quality of life and less symptoms at the end of the intervention and at the longest followup compared with placebo.

There was no statistically significant difference found in mortality at longest followup, dyspnea at the end of the intervention and at the longest followup, FEV1 percent predicted at the end of the intervention, and number of withdrawals (Appendix Table H.20.).

Table 49. Comparison of a dietary intervention using vitamin D during ECOPD versus placebo, critical outcomes

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Mortality Longest Followup	OR: 1.55; 95% CI: 0.24 to 9.88, I^2= N/A	1 RCT[85] with 70 patients	High ROB and severe imprecision	Insufficient evidence
Dyspnea (Questionnaire: MMRC) End of Intervention	SMD: -0.11; 95% CI: -0.42 to 0.20, I^2=0.00%	2 RCTs[85 91] with 160 patients	High ROB and severe imprecision	Insufficient evidence
Dyspnea (Questionnaire: MMRC) Longest Followup	SMD: 0.27; 95% CI: -0.09 to 0.63, I^2= N/A	1 RCT[85] with 70 patients	High ROB and severe imprecision	Insufficient evidence
QoL(SGRQ) End of Intervention	WMD: -1.96; 95% CI: -2.89 to -1.03, I^2= N/A	1 RCT[85] with 70 patients	High ROB and imprecision	Low SOE supporting improvement
QoL(SGRQ) Longest Followup	WMD: -4.67; 95% CI: -6.00 to -3.35, I^2= N/A	1 RCT[85] with 70 patients	High ROB and imprecision	Low SOE supporting improvement

CI = confidence interval; MMRC = Modified Medical Research Council Scale; N/A = not applicable; OR = odds ratio; QoL = quality of life; RCT = randomized controlled trial; ROB = risk of bias; SMD = standardized mean difference; SGRQ = St. George Respiratory Questionnaire; SOE = strength of evidence; WMD = weighted mean difference

Table 50. Comparison of a dietary intervention using vitamin D during ECOPD versus placebo, additional outcomes

Outcome	Findings	Study Design and Sample Size
Other Symptoms(SGRQ symptom score) End of Intervention	WMD: -4.47; 95% CI: -8.10 to -0.84, I^2= N/A	1 RCT[85] with 70 patients
Other Symptoms(SGRQ symptom score) Longest Followup	WMD: -7.19; 95% CI: -11.12 to -3.26, I^2= N/A	1 RCT[85] with 70 patients
FEV1% Predicted End of Intervention	WMD: 2.20; 95% CI: -7.24 to 11.64, I^2= N/A	1 RCT[91] with 90 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; SGRQ = St. George Respiratory Questionnaire; WMD = weighted mean difference

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)?

Key Point-KQ3

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

KQ3 Results

There were 3 studies[126-128] with 149 patients included for KQ3. The characteristics of the studies are listed in Appendix Table D.3. 1 trial was conducted in a hospital setting, [127] 1 in the emergency department,[126] and 1 in an unclear setting.[128] Studies were conducted in Europe (2),[127, 128] and in Australia (1).[126] The average length of treatment was 14.5 days. Followup was not reported in any study. Details of the interventions used in each study can be found in Appendix Table F.3. Individual studies inclusion and exclusion criteria are in Appendix Table I.1.

The overall risk of bias is moderate to high due to unclear risk of bias for most items, including sequence generation, allocation concealment, blinding of outcome assessors, and unknown risk of other bias (Appendix Table E.1.).

Three studies[126-128] assessed the comparative effectiveness of different inhalation treatments for ECOPD (Table 51 and Table 52).

Direct comparison of Ipratropium (short-acting muscarinic antagonists (SAMA) versus Salbutamol (SABA)[126] did not show any statistically significant difference in FEV1 absolute at the end of the intervention. Combination therapy with ipratropium + salbutamol (SAMA+SABA)[126, 127] did not result in a statistically significant change in FEV1 absolute at the end of the intervention compared with salbutamol (SABA) alone[126, 127] or ipratropium (SAMA)[126] alone.

Combination therapy of beclomethasone + salbutamol (ICS+SABA)[128] was not found to have a statistically significant difference in clinical cure, clinical failure and FEV1 percent predicted at the end of the intervention compared with fenoterol (SABA) only.

There was no statistically significant difference found on withdrawals, general internal medicine AEs, neurological AEs, and total number of AEs (Appendix Table H.21.).

Table 51. Comparative effectiveness of inhalation treatments, critical outcomes

Comparison	Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
ICS+ SABA (Beclomethasone+ Salbutamol) vs. SABA (Fenoterol)	Clinical Cure End of Intervention	OR: 1.00; 95% CI: 0.17 to 5.98, I^2= N/A	1 RCT[128] with 30 patients	High ROB and severe imprecision	Insufficient evidence

Comparison	Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
ICS+ SABA (Beclomethasone+ Salbutamol) vs. SABA (Fenoterol)	Clinical Failure End of Intervention	OR: 0.31; 95% CI: 0.01 to 8.28, I^2= N/A	1 RCT[128] with 30 patients	High ROB and severe imprecision	Insufficient evidence

CI = confidence interval; ICS = inhaled corticosteroid; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; SABA = short-acting beta adrenergic agonists; SOE = strength of evidence

Table 52. Comparative effectiveness of inhalation treatments, additional outcomes

Comparison	Outcome	Findings	Study Design and Sample Size
ICS + SABA (Beclomethasone + Salbutamol) vs. SABA (Fenoterol)	FEV1% Predicted End of Intervention	WMD: 7.60; 95% CI: -2.53 to 17.73, I^2=N/A	1 RCT[128] with 30 patients
SABA + SAMA (Salbutamol + Ipratropium) vs. SABA (Salbutamol)	FEV1 Absolute End of Intervention	WMD: -0.07; 95% CI: -0.17 to 0.02, I^2=0.00%	2 RCTs[126, 127] with 104 patients
SAMA (Ipratropium) vs. SABA (Salbutamol)	FEV1 Absolute End of Intervention	WMD: -0.11; 95% CI: -0.22 to 0.00, I^2=N/A	1 RCT[126] with 31 patients
SABA + SAMA (Ipratropium vs. Salbutamol) + SAMA (Ipratropium)	FEV1 Absolute End of Intervention	WMD: -0.04; 95% CI: -0.13 to 0.05, I^2=N/A	1 RCT[126] with 33 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; ICS = inhaled corticosteroid; N/A = not applicable; RCT = randomized controlled trial; SABA = short-acting beta adrenergic agonists; SAMA = short-acting muscarinic antagonists; WMD = weighted mean difference

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?

Key Points-KQ4

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 (;ow SOE).

- Amoxicillin plus clavulanic acid was associated with statistically significantly more adverse events than telithromycin. Imipenem plus cilastatin was associated with statistically significantly more adverse events than 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 difference in adverse events was found between trovafloxacin 200 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 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 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 Administration for Corticosteroids

- No difference between intravenous methylprednisolone and inhaled budesonide 40 mg was found in quality of life and repeat exacerbations (low SOE).
- Inhaled budesonide 40 mg was associated with statistically significantly less endocrine-related AEs than intravenous methylprednisolone.

Comparative Effectiveness of Different Durations of Treatment With Corticosteroids

- The evidence was insufficient 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 in AEs found between the different systemic corticosteroid durations.

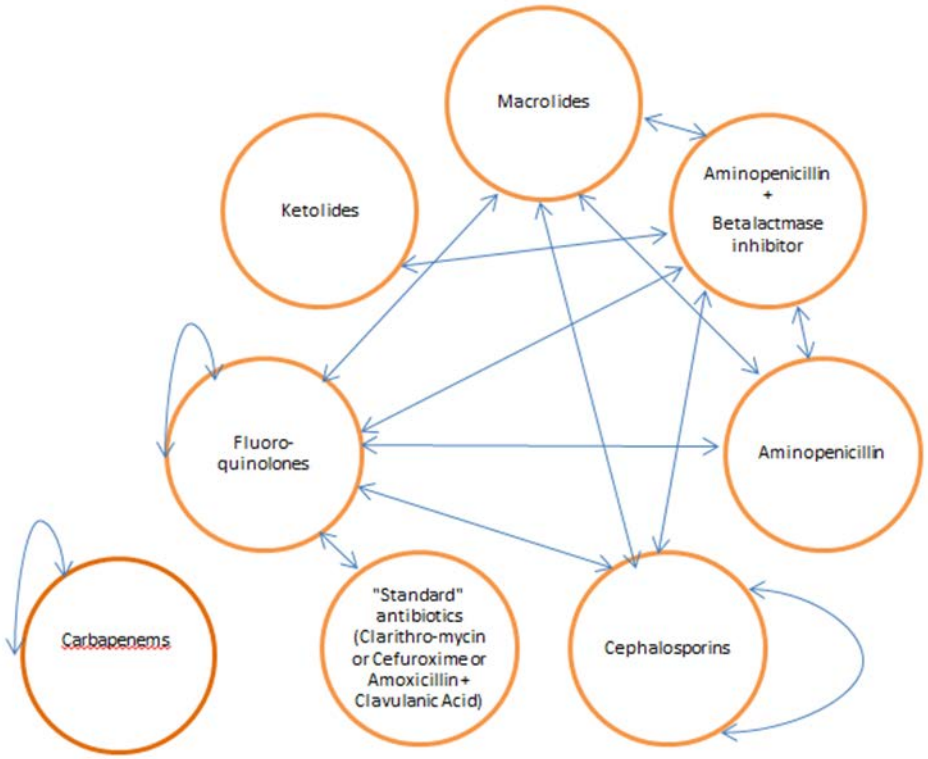
KQ 4 Results

There were 34 studies[75-77, 129-159] with 7,311 patients included for KQ4. The characteristics of the studies are listed in Appendix Table D.4. 14 trials were conducted in a hospital setting,[75-77, 129, 130, 133, 140, 142, 144, 146, 149, 151, 155, 159] 3 in the Emergency Department,[137, 141, 158] 10 in an outpatient setting,[132, 136, 138, 139, 143, 145, 148, 152-154] one in both outpatients and hospitalized patients,[156] and in 5 the setting was unclear.[131, 134, 135, 150, 157] Studies were conducted in the US (4),[77, 154, 156, 157] Europe (17),[76, 130, 135, 138-144, 147, 148, 151-153, 155, 158] Asia (11),[75, 129, 131-134, 137, 146, 149, 150, 159] South America (1),[145] and 1 study was conducted in 30 countries.[136] Mean treatment length was 10.6 days and mean reported followup was 3 months. Details of the interventions used in each study can be found in Appendix Table F.4. Individual studies inclusion and exclusion criteria are in Appendix Table I.1.

The overall risk of bias is high due to unclear sequence generation (50.00%), unclear allocation concealment (79.41%), high risk or unclear blinding of patients or care providers (58.82%), high risk or unclear blinding of outcome assessors (88.24%) and high risk or unclear risk of other bias (94.12%) (Appendix Table E.1.).

Figure 2 gives an overview of the different comparisons made in different studies.

Figure 2. Summary of comparisons between different antibiotic agents



Note: Each arrowed line represents a comparison between two treatments reported by the literature.

Fluoroquinolone Versus Aminopenicillin Plus Beta-Lactamase Inhibitor

Three studies[136, 150, 152] evaluated the effectiveness of a fluoroquinolone (either moxifloxacin, trovafloxacin, or ciprofloxacin) compared with an aminopenicillin (amoxicillin or ampicillin) plus a beta-lactamase inhibitor (clavulanic acid or sulbactam). There were no statistically significant differences observed between the groups in any of the outcomes (Table 53 and Table 54) and adverse events (Appendix Table H.22.). One study[136] compared moxifloxacin to amoxicillin + clavulanic acid and reported 97 cases of serious unspecified AEs (46 in the moxifloxacin group vs. 51 in the amoxicillin + clavulanic acid group). Four cases in the moxifloxacin group were considered as treatment related, including anaphylactic reaction, bronchitis, gastroenteritis, and tachyarrhythmia); while 2 cases (allergic dermatitis and radial nerve palsy) were reported in the amoxicillin + clavulanic acid group.

Table 53. Comparison of fluoroquinolone versus aminopenicillin plus beta-lactamase inhibitor, critical outcomes

Comparison	Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Fluoroquinolone vs. Amoxicillin + Clavulanic Acid Moxifloxacin vs. Amoxicillin + Clavulanic Acid Trovafloxacin vs. Amoxicillin + Clavulanic Acid	Mortality End of Intervention	OR: 1.28; 95% CI: 0.31 to 5.19, I^2=0.00% Moxifloxacin vs. Amoxicillin + Clavulanic Acid: OR: 1.00; 95% CI: 0.20 to 4.97, I^2=N/A Trovafloxacin vs. Amoxicillin + Clavulanic Acid: OR 2.94; 95% CI: 0.12 to 72.71, I^2=N/A	2 RCTs[136, 152] with 1656 patients Moxifloxacin vs. Amoxicillin + Clavulanic Acid: 1 RCT[136] with 1372 patients Trovafloxacin vs. Amoxicillin + Clavulanic Acid:1 RCT[152] with 284 patients	High ROB and severe imprecision	Insufficient evidence
Moxifloxacin vs. Amoxicillin + Clavulanic Acid	QoL(SGRQ) End of Intervention	WMD: -0.73; 95% CI: -2.04 to 0.58, I^2=N/A	1 RCT[136] with 1372 patients	High ROB and severe imprecision	Insufficient evidence
	QOL(SGRQ) Longest Followup	WMD: -0.05; 95% CI: -2.31 to 2.21, I^2=N/A	1 RCT[136] with 1372 patients	High ROB and severe imprecision	Insufficient evidence
	Hospital Admission Longest Followup	OR: 0.86; 95% CI: 0.56 to 1.33, I^2=N/A	1 RCT [136]with 1372 patients	High ROB and severe imprecision	Insufficient evidence

Comparison	Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Fluoroquinolone vs. Aminopenicillin plus Beta-lactamase inhibitor Ciprofloxacin vs. Ampicillin + Sulbactam Trovafloxacin vs. Amoxicillin + Clavulanic Acid	Clinical Cure End of Intervention	OR: 1.05; 95% CI: 0.61 to 1.81, I^2=64.80% OR: 11; 95% CI: 0.58 to 209.90, I^2=N/A OR: 0.87; 95% CI: 0.49 to 1.55, I^2=N/A	2 RCTs[150, 152] with 337 patients 1 RCT[150] with 53 patients 1 RCT with 284 patients	High ROB and severe imprecision	Insufficient evidence
Moxifloxacin vs. Amoxicillin + Clavulanic Acid	Clinical Failure Longest Followup	OR: 0.93; 95% CI: 0.72 to 1.21, I^2=N/A	1 RCT[136] with 1372 patients	High ROB and severe imprecision	Insufficient evidence

CI = confidence interval; N/A = not applicable; OR = odds ratio; QoL = quality of life; RCT = randomized controlled trial; ROB = risk of bias; SGRQ = St. George respiratory questionnaire; SOE = strength of the body of evidence; WMD = weighted mean difference

Table 54. Comparison of fluoroquinolone versus aminopenicillin plus beta-lactamase inhibitor, additional outcomes

Comparison	Outcome	Findings	Study Design and Sample Size
Moxifloxacin vs. Amoxicillin + Clavulanic Acid	FEV1% Predicted End of Intervention	WMD: 0.76; 95% CI: -0.94 to 2.46, I^2=N/A	1 RCT[136] with 1372 patients
Moxifloxacin vs. Amoxicillin + Clavulanic Acid	FEV1% Predicted Longest Followup	WMD:1.10; 95% CI: -0.61 to 2.81, I^2=N/A	1 RCT[136] with 1372 patients
Fluoroquinolone vs. Aminopenicillin + Beta-lactamase inhibitor Moxifloxacin vs. Amoxicillin + Clavulanic Acid Ciprofloxacin vs. Ampicillin + Sulbactam	FEV1 Absolute End of Intervention	WMD: 0.03; 95% CI: -0.02 to 0.08, I^2=0.56% WMD: 0.03; 95% CI: -0.02 to 0.08, I^2=N/A WMD: 0.13; 95% CI: -0.20 to 0.46, I^2=N/A	2 RCTs[136, 150] with 1425 patients 1 RCT[136] with 1372 patients 1 RCT[150] with 53 patients
Moxifloxacin vs. Amoxicillin + Clavulanic Acid	FEV1 Absolute Longest Followup	WMD: 0.04; 95% CI: -0.01 to 0.09, I^2=N/A	1 RCT[136] with 1372 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Ciprofloxacin (Fluoroquinolone) Versus Amoxicillin (Aminopenicillin)

One study[153] evaluated the effectiveness of ciprofloxacin, a fluoroquinolone, compared with amoxicillin, an aminopenicillin, and did not find a statistically significant difference between groups for FEV1 percent predicted at the end of the intervention (Table 55). Five patients in the ciprofloxacin group withdrew compared with 1 patient in the amoxicillin group (Appendix Table H.23.).

Table 55. Comparison of ciprofloxacin versus amoxicillin

Outcome	Findings	Study Design and Sample Size
FEV1% Predicted End of Intervention	WMD: 5.00; 95% CI: -7.52 to 17.52, I^2=N/A	1 RCT[153] with 12 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Levofloxacin (Fluoroquinolone) Versus "Standard" Antibiotic Therapy (Clarithromycin or Cefuroxime or Amoxicillin + Clavulanic Acid)

One study[141] evaluated the effectiveness of levofloxacin, a fluoroquinolone, compared with "standard" antibiotic therapy (defined as clarithromycin or cefuroxime or amoxicillin + clavulanic acid). Levofloxacin was associated with significantly lower risk of 30-day hospital admission than "standard" antibiotic therapy (low SOE). There were no statistically significant differences found in mortality, quality of life, repeat exacerbation, and FEV1 predicted between the two groups (Table 56 and Table 57).

There was no statistically significant difference observed in AEs (Appendix Table H.24.). Three patients in the levofloxacin group withdrew due to serious AEs (2 dizziness and 1 diarrhea), compared with 4 patients in the "standard" antibiotic therapy group (3 diarrhea cases and 1 urticaria).

Table 56. Comparison of levofloxacin versus "standard" antibiotic therapy (clarithromycin or cefuroxime or amoxicillin + clavulanic acid), critical outcomes

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Mortality Longest Followup	OR : 0.71; 95% CI: 0.26 to 1.96, I^2=N/A	1 RCT[141] with 102 patients	High ROB and severe imprecision	Insufficient evidence
QoL(HRQOL) End of Intervention	WMD : -0.73; 95% CI: -2.57 to 0.44, I^2=N/A	1 RCT[141] with 102 patients	High ROB and severe imprecision	Insufficient evidence
QoL(HRQOL) Longest Followup	WMD : -2.12; 95% CI: -1.97 to 6.21, I^2=N/A,	1 RCT[141] with 102 patients	High ROB and severe imprecision	Insufficient evidence
Hospital Admission 30 day	Rate Ratio: 0.46; 95% CI: 0.23 to 0.91, I^2=N/A	1 RCT[141] with 102 patients	High ROB and imprecision	Low SOE supporting reduction
Repeat Exacerbation 6 Month Followup	Rate Ratio: 0.84: 95% CI: 0.53 to 1.32, I^2=N/A	1 RCT[141] with 102 patients	High ROB and severe imprecision	Insufficient evidence
Repeat Exacerbation Longest Followup	Rate Ratio: 0.84: 95% CI: 0.53 to 1.32, I^2=N/A	1 RCT[141] with 102 patients	High ROB and severe imprecision	Insufficient evidence

CI = confidence interval; HRQL = health related quality of life; N/A = not applicable; OR = odds ratio; QoL = quality of life; RCT = randomized controlled trial; ROB = risk of bias; SOE = strength of evidence; WMD = weighted mean difference

Table 57. Comparison of levofloxacin versus "standard" antibiotic therapy (clarithromycin or cefuroxime or amoxicillin + clavulanic acid), additional outcomes

Outcome	Findings	Study Design and Sample Size
FEV1% Predicted End of Intervention	WMD: -0.95; 95% CI: -8.11 to 6.21, I^2=N/A	1 RCT[141] with 102 patients
FEV1% Predicted Longest Followup	WMD: 4.17; 95% CI:- 6.00 to 14.34, I^2=N/A	1 RCT[141] with 102 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Azithromycin (Macrolide) Versus Amoxicillin (Aminopenicillin)

Azithromycin was compared with amoxicillin in one study,[145] which showed that azithromycin was associated with a statistically significantly higher FEV1percent predicted at the end of the intervention but statistically significantly lower FEV1 percent predicted at the longest followup compared with amoxicillin. There were no statistically significant differences found in other outcomes (Table 58 and Table 59) and AEs (Appendix Table H.25.) between groups. 5 patients treated with azithromycin and 2 patients with amoxicillin t reported serious AEs, including respiratory conditions with bronchoconstriction (4 cases), convulsive seizure (1 case), and rib fracture (1 case).

Table 58. Comparison of azithromycin versus amoxicillin, critical outcomes

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Clinical Cure End of Intervention	OR: 1.60; 95% CI: 0.62 to 4.11, I^2=N/A	1 RCT[145] with 102 patients	High ROB and severe imprecision	Insufficient evidence
Clinical Cure Longest Followup	OR: 1.24; 95% CI: 0.50 to 3.07, I^2=N/A	1 RCT[145] with 102 patients	High ROB and severe imprecision	Insufficient evidence
Clinical Failure End of Intervention	OR: 0.64; 95% CI: 0.22 to 1.80, I^2=N/A	1 RCT[145] with 102 patients	High ROB and severe imprecision	Insufficient evidence
Clinical Failure Longest Followup	OR: 0.75; 95% CI: 0.27 to 2.04, I^2=N/A	1 RCT[145] with 102 patients	High ROB and severe imprecision	Insufficient evidence

CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; ROB = risk of bias; SOE = strength of evidence

Table 59. Comparison of azithromycin versus amoxicillin, additional outcomes

Outcome	Findings	Study Design and Sample Size
FEV1% Predicted End of Intervention	WMD: 3.35; 95% CI: 3.23 to 3.47, I^2=N/A	1 RCT[145] with 102 patients
FEV1% Predicted Longest Followup	WMD: -5.10; 95% CI: -5.24 to -4.96, I^2=N/A	1 RCT[145] with 102 patients
FEV1 Absolute End of Intervention	WMD: 0.10; 95% CI: -0.21 to 0.41, I^2=N/A	1 RCT[145] with 102 patients
FEV1 Absolute Longest Followup	WMD: -0.10; 95% CI: -0.43 to 0.23, I^2=N/A	1 RCT[145] with 102 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Cefaclor (Cephalosporin) Versus Ampicillin + Sulbactam (Aminopenicillin Plus Beta-Lactamase Inhibitor)

Cefaclor, a cephalosporin, was compared with ampicillin + sulbactam (aminopenicillin plus beta-lactamase inhibitor) in one study.[150] There was no statistically significant difference found in FEV1 absolute and clinical cure at the end of the intervention between the two groups (Table 60 and Table 61).

Table 60. Comparison of cefaclor versus ampicillin + sulbactam, critical outcomes

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Clinical Cure End of Intervention	OR: 0.96; 95% CI: 0.24 to 3.75, I^2=N/A	1 RCT[150] with 57 patients	High ROB and severe imprecision	Insufficient evidence

CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; SOE = strength of evidence

Table 61. Comparison of cefaclor versus ampicillin + sulbactam, additional outcomes

Outcome	Findings	Study Design and Sample Size
FEV1 Absolute End of Intervention	WMD: 0.05; 95% CI: -0.23 to 0.33, I^2=N/A	1 RCT[150] with 57 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Fluoroquinolone Versus Cephalosporin

Three studies[134, 143, 150] evaluated the effectiveness of a fluoroquinolone (ciprofloxacin or levofloxacin) compared with a cephalosporin (cefaclor or cefuroxime). There were no statistically significant differences found between the groups in any of the outcomes (Table 62 and Table 63). Two serious AEs were reported, including 1 case of hypersensitivity reaction in the levofloxacin group, and 1 case of bronchitis in the cefuroxime group. There was no statistically significant difference observed in AEs, serious AEs, withdrawals, and withdrawals due to AEs (Appendix Table H.26.).

Table 62. Comparison of fluoroquinolone versus cephalosporin, critical outcomes

Comparison	Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Fluoroquinolones, vs. Cephalosporin Ciprofloxacin vs. Cefaclor Levofloxacin vs. Cefuroxime	Clinical Cure End of Intervention	OR: 1.22; 95% CI: 0.85 to 1.75, I^2=57.69% OR: 11.47; 95% CI: 0.60 to 219.08, I^2=N/A OR: 1.13; 95% CI: 0.78 to 1.64, I^2=N/A	2 RCTs[143, 150] with 741 patients 1 RCT[150] with 52 patients 1 RCT[143] with 689 patients	High ROB and severe imprecision	Insufficient evidence
Levofloxacin vs. Cefuroxime	Clinical Cure Longest Followup	OR: 1.01; 95% CI: 0.49 to 2.09, I^2=N/A	1 RCT[134] with 137 patients	Intermediate ROB and severe imprecision	Insufficient evidence
Levofloxacin vs. Cefuroxime	Clinical Failure Longest Followup	OR: 0.92; 95% CI: 0.27 to 3.16, I^2=N/A	1 RCT[134] with 137 patients	Intermediate ROB and severe imprecision	Insufficient evidence

CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; ROB = risk of bias; SOE = strength of evidence

Table 63. Comparison of fluoroquinolone versus cephalosporin, additional outcomes

Comparison	Outcome	Findings	Study Design and Sample Size
Ciprofloxacin vs. Cefaclor	FEV1 Absolute End of Intervention	WMD: 0.08; 95% CI: -0.23 to 0.39, I^2=N/A	1 RCT[150] with 52 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Azithromycin (Macrolide) Versus Cefaclor (Cephalosporin)

Two studies[150, 157] compared azithromycin, a macrolide, with cefaclor, a cephalosporin. There were no statistically significant differences found between groups in FEV1 absolute, clinical cure and clinical failure at the end of the intervention (Table 64 and Table 65). No statistical difference was found in AEs, withdrawals and withdrawals due to AEs (Appendix Table H.27).

Table 64. Comparison of azithromycin versus cefaclor, critical outcomes

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Clinical Cure End of Intervention	OR: 2.26; 95% CI: 0.94 to 5.48, I^2=0.00%	2 RCTs[150, 157] with 254 patients	High ROB and severe imprecision	Insufficient evidence
Clinical Failure End of Intervention	OR: 0.09; 95% CI: 0.00 to 1.97, I^2=N/A	1 RCT[157] with 201 patients	High ROB and severe imprecision	Insufficient evidence

CI = confidence interval; OR = odds ratio; N/A = not applicable; RCT = randomized controlled trial; ROB = risk of bias; SOE = strength of evidence

Table 65. Comparison of azithromycin versus cefaclor, additional outcomes

Outcome	Findings	Study Design and Sample Size
FEV1 Absolute End of Intervention	WMD: -0.03; 95% CI: -0.30 to 0.23, I^2=N/A	1 RCT[150] with 53 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Azithromycin (Macrolide) Versus Ciprofloxacin (Fluoroquinolone)

One study[150] compared azithromycin, a macrolide, with ciprofloxacin, a fluoroquinolone. There were no statistically significant differences found between groups in FEV1 absolute and clinical cure at the end of the intervention (Table 66 and Table 67).

Table 66. Comparison of azithromycin versus ciprofloxacin, critical outcomes

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Clinical Cure End of Intervention	OR: 0.19; 95% CI: 0.01 to 4.21, I^2=N/A	1 RCT[150] with 49 patients	High ROB and severe imprecision	Insufficient evidence

CI = confidence interval; OR = odds ratio; N/A = not applicable; RCT = randomized controlled trial; ROB = risk of bias; SOE = strength of evidence

Table 67. Comparison of azithromycin versus ciprofloxacin, additional outcomes

Outcome	Findings	Study Design and Sample Size
FEV1 Absolute End of Intervention	WMD: -0.05; 95% CI: -0.37 to 0.28, I^2=N/A	1 RCT[150] with 49 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Amoxicillin (Aminopenicillin) Versus Amoxicillin Plus Clavulanic Acid

One study[139] compared amoxicillin with amoxicillin plus clavulanic acid. There were no statistically significant differences observed between groups in clinical cure and clinical failure at the end of the intervention and clinical cure at the longest followup (Table 68). No statistical difference was found in AEs and withdrawals (Appendix Table H.28.).

Table 68. Comparison of amoxicillin versus amoxicillin plus clavulanic acid

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Clinical Cure End of Intervention	OR: 0.68; 95% CI: 0.21 to 2.26, I^2=N/A	1 RCT[139] with 137 patients	High ROB and severe imprecision	Insufficient evidence
Clinical Cure Longest Followup	OR: 0.59; 95% CI: 0.21 to 1.61, I^2=N/A	1 RCT[139] with 137 patients	High ROB and severe imprecision	Insufficient evidence
Clinical Failure End of Intervention	OR: 2.13; 95% CI: 0.51 to 8.88, I^2=N/A	1 RCT[139] with 137 patients	High ROB and severe imprecision	Insufficient evidence

CI = confidence interval; OR = odds ratio; N/A = not applicable; RCT = randomized controlled trial; ROB = risk of bias; SOE = strength of evidence

Telithromycin (Ketolide) Versus Amoxicillin Plus Clavulanic Acid (Aminopenicillin Plus Beta-Lactamase Inhibitor)

One study[148] compared telithromycin, a ketolide, with amoxicillin plus clavulanic acid. There were no statistically significant differences found between groups in clinical cure at the end of the intervention and at the longest followup (Table 69). Statistically significantly more patients in the amoxicillin plus clavulanic acid group reported AEs and withdrew due to AEs than those in the telithromycin group (Appendix Table H.29.). 13 patients reported unspecified serious AEs: 7 in the telithromycin group and 6 in the amoxicillin plus clavulanic acid group.

Table 69. Comparison of telithromycin versus amoxicillin plus clavulanic acid

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Clinical Cure End of Intervention	OR: 1.13; 95% CI: 0.67 to 1.93, I^2=N/A	1 RCT[148] with 324 patients	High ROB and severe imprecision	Insufficient evidence
Clinical Cure Longest Followup	OR: 1.08; 95% CI: 0.67 to 1.75, I^2=N/A	1 RCT[148] with 324 patients	High ROB and severe imprecision	Insufficient evidence

CI = confidence interval; OR = odds ratio; N/A = not applicable; RCT = randomized controlled trial; ROB = risk of bias; SOE = strength of evidence

Azithromycin (Macrolide) Versus Aminopenicillin Plus Beta-Lactamase Inhibitor

Two studies[150, 154] evaluated the effectiveness of azithromycin, a macrolide, compared with an aminopenicillin plus beta-lactamase inhibitor (amoxicillin or ampicillin).There were no statistically significant differences observed between the groups in clinical cure, clinical failure, and FEV1 absolute at the end of the intervention (Table 70 and Table 71). No statistically significant difference in AEs and withdrawals was found (Appendix Tables H.30. and H.31).

Table 70. Comparison of macrolide versus aminopenicillin plus beta-lactamase inhibitor, critical outcomes

Comparison	Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Macrolides vs. Aminopenicillin plus Beta-lactamase inhibitor	Clinical Cure End of Intervention	OR: 1.46; 95% CI: 0.64 to 3.32, I^2=0.00%	2 RCTs[150, 154] with 124 patients	High ROB and severe imprecision	Insufficient evidence
Azithromycin vs. Ampicillin + Sulbactam		OR: 2.40; 95% CI: 0.42 to 13.60, I^2=N/A	1 RCT[150] with 54 patients		
Azithromycin vs. Amoxicillin + Clavulanic Acid		OR: 1.24; 95% CI: 0.48 to 3.20, I^2=N/A	1 RCT[154] with 70 patients		
Azithromycin vs. Amoxicillin + Clavulanic Acid	Clinical Failure End of Intervention	OR: 0.15; 95% CI: 0.01 to 3.23, I^2=N/A	1 RCT[154] with 70 patients	High ROB and severe imprecision	Insufficient evidence

CI = confidence interval; FEV1 = Forced expiratory volume in one second; OR = odds ratio; N/A = not applicable; RCT = randomized controlled trial; ROB = risk of bias; SOE = strength of evidence; WMD = weighted mean difference

Table 71. Comparison of macrolide versus aminopenicillin plus beta-lactamase inhibitor, additional outcomes

Comparison	Outcome	Findings	Study Design and Sample Size
Macrolides vs. Aminopenicillin plus Beta-lactamase inhibitor	FEV1 Absolute End of Intervention	WMD: 0.08; 95% CI: -0.21 to 0.38, I^2=N/A	1 RCT[150] with 54 patients

CI = confidence interval; FEV1 = Forced expiratory volume in one second; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Prulifloxacin (4th Generation Fluoroquinolone) Versus Levofloxacin (2nd Generation Fluoroquinolone)

Two studies[130, 135] evaluated the effectiveness of prulifloxacin, a 4th generation fluoroquinolone, compared with levofloxacin, a 2nd generation fluoroquinolone. The only statistically significant difference in outcomes between groups was repeat exacerbations at 3 months, which were statistically significantly higher with prulifloxacin compared with levofloxacin (Table 72 and Table 73). Unspecified serious AEs were reported in 5 patients in the prulifloxacin group and 6 patients in the levofloxacin group. There was no statistically significant difference found in AEs, withdrawals, and withdrawals due to AEs (Appendix Table H.32.).

Table 72. Comparison of prulifloxacin versus levofloxacin, critical outcomes

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Mortality Longest Followup	OR: 0.43; 95% CI: 0.14 to 1.23, I^2=N/A	1 RCT[130] with 258 patients	High ROB and severe imprecision	Insufficient evidence

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Dyspnea (Numeric Scale: Dyspnea Score) End of Intervention	WMD: -0.05; 95% CI: -0.21 to 0.11,I^2=N/A	1 RCT[135] with 357 patients	Intermediate ROB and severe imprecision	Insufficient evidence
Repeat Exacerbation End of Intervention	OR: 1.37; 95% CI: 0.84 to 2.24, I^2=7.10%	2 RCTs[130, 135] with patients	High ROB and severe imprecision	Insufficient evidence
Repeat Exacerbation 3 Months	OR: 2.26; 95% CI: 1.15 to 4.45, I^2=N/A	1 RCT[135] with 357 patients	Intermediate ROB and imprecision	Low SOE supporting worsening
	Rate Ratio: 0.77; 95% CI: 0.42 to 1.43, I^2=N/A	1 RCT[130] with 258 patients	High ROB and severe imprecision	Insufficient evidence
Repeat Exacerbation 6 Months	OR: 1.29; 95% CI: 0.72 to 2.31, I^2=N/A	1 RCT[135] with 357 patients	Intermediate ROB and severe imprecision	Insufficient evidence
Repeat Exacerbation 12 Months	Rate Ratio: 1.16; 95% CI: 0.76 to 1.76, I^2=N/A	1 RCT[130] with 258 patients	High ROB and severe imprecision	Insufficient evidence
Repeat Exacerbation Longest Followup	OR: 1.29; 95% CI: 0.72 to 2.31, I^2=N/A	1 RCT[135] with 357 patients	Intermediate ROB and severe imprecision	Insufficient evidence
	Rate Ratio: 1.16; 95% CI: 0.76 to 1.76, I^2=N/A	1 RCT[130] with 258 patients	High ROB and severe imprecision	Insufficient evidence
Clinical Cure End of Intervention	OR: 0.96; 95% CI: 0.52 to 1.78, I^2=68.97%	2 RCTs[130, 135] with 615 patients	High ROB and severe imprecision	Insufficient evidence
Clinical Cure Longest Followup	OR: 0.83; 95% CI: 0.51 to 1.37, I^2=N/A	1 RCT[135] with 357 Patients	Intermediate ROB and severe imprecision	Insufficient evidence
Clinical Failure End of Intervention	OR: 2.24; 95% CI: 0.83 to 6.05, I^2=N/A	1 RCT[135] with 357 patients	Intermediate ROB and severe imprecision	Insufficient evidence
Clinical Failure Longest Followup	OR: 3.05; 95% CI: 0.61 to 15.33, I^2=N/A	1 RCT[135] with 357 patients	Intermediate ROB and severe imprecision	Insufficient evidence

CI = confidence interval; OR = odds ratio; N/A = not applicable; RCT = randomized controlled trial; ROB = risk of bias; SOE = strength of the body of vidence; WMD = weighted mean difference

Table 73. Comparison of prulifloxacin versus levofloxacin, additional outcomes

Outcome	Findings	Study Design and Sample Size
Cough (Scale 0-4 from absent to severe) Longest Followup	WMD: -0.07; 95% CI: -0.19 to 0.05, I^2=N/A	1 RCT[135] with 357 patients
Other Symptoms (Total Symptom Score) End of Intervention	SMD: 0.05; 95% CI: -0.11 to 0.21, I^2=0.00%	2 RCTs[130, 135] with 615 patients
FEV1% Predicted End of Intervention	WMD: -1.50; 95% CI: -4.72 to 1.72, I^2=N/A	1 RCT[135] with 357 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; SMD = standardized mean difference; WMD = weighted mean difference

Zabofloxacin (Next Generation Fluoroquinolone) Versus Moxifloxacin (4th Generation Fluoroquinolone)

One study[132] evaluated the effectiveness of zabofloxacin, a next generation fluoroquinolone, compared with moxifloxacin, a 4th generation fluoroquinolone. There were no statistically significant differences observed in outcomes (Table 74), and AEs (Appendix Table H.33.). Serious AEs were reported in 15 cases: 7 cases in the zabofloxacin group (4 COPD exacerbations, 1 influenza like illness, 1 pneumonia, and 1 acute pyelonephritis); and 8 cases in the fluoroquinolone group (4 COPD exacerbations, 2 pneumonia, 1 variant angina, and 1 urethral stenosis).

Table 74. Comparison of zabofloxacin versus moxifloxacin

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Repeat Exacerbation 30 Days	OR: 0.82; 95% CI: 0.39 to 1.74, I^2=N/A	1 RCT[132] with 342 patients	High ROB and severe imprecision	Insufficient evidence
Repeat Exacerbation Longest Followup	OR: 0.82; 95% CI: 0.39 to 1.74, I^2=N/A	1 RCT[132] with 342 patients	High ROB and severe imprecision	Insufficient evidence
Clinical Cure End of Intervention	OR: 0.99; 95% CI: 0.60 to 1.65, I^2=N/A	1 RCT[132] with 342 patients	High ROB and severe imprecision	Insufficient evidence
Clinical Cure Longest Followup	OR: 1.19; 95% CI: 0.76 to 1.87, I^2=N/A	1 RCT[132] with 342 patients	High ROB and severe imprecision	Insufficient evidence
Clinical Failure End of Intervention	OR: 1.07; 95% CI: 0.54 to 2.10, I^2=N/A	1 RCT[132] with 342 patients	High ROB and severe imprecision	Insufficient evidence
Clinical Failure Longest Followup	OR: 0.94; 95% CI: 0.55 to 1.60, I^2=N/A	1 RCT[132] with 342 patients	High ROB and severe imprecision	Insufficient evidence

CI = confidence interval; OR = odds ratio; N/A = not applicable; RCT = randomized controlled trial; ROB = risk of bias

Cefpodoxime (3rd Generation Cephalosporin) Versus Cefaclor (2nd Generation Cephalosporin)

One study[156] evaluated the effectiveness of cefpodoxime, a 3rd generation cephalosporin, compared with cefaclor, a 2nd generation cephalosporin. There were no statistically significant differences in outcomes found (Table 75), AEs, and withdrawals (Appendix Table H.34.).

Table 75. Comparison of cefpodoxime versus cefaclor

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Repeat Exacerbation End of Intervention	OR: 1.51; 95% CI: 0.57 to 3.99, I^2=N/A	1 RCT[156] with 301 patients	High ROB and severe imprecision	Insufficient evidence
Repeat Exacerbation 30 Days	OR: 1.51; 95% CI: 0.57 to 3.99, I^2=N/A	1 RCT[156] with 301 patients	High ROB and severe imprecision	Insufficient evidence
Repeat Exacerbation Longest Followup	OR: 1.51; 95% CI: 0.57 to 3.99, I^2=N/A	1 RCT[156] with 301 patients	High ROB and severe imprecision	Insufficient evidence
Clinical Cure End of Intervention	OR: 1.42; 95% CI: 0.84 to 2.40, I^2=N/A	1 RCT[156] with 301 patients	High ROB and severe imprecision	Insufficient evidence
Clinical Failure End of Intervention	OR: 0.13; 95% CI: 0.01 to 1.21, I^2=N/A	1 RCT[156] with 301 patients	High ROB and severe imprecision	Insufficient evidence

CI = confidence interval; OR = odds ratio; N/A = not applicable; RCT = randomized controlled trial; ROB = risk of bias

Meropenem (Carbapenem) Versus Imipenem (Carbapenem)

One study[155] evaluated the effectiveness of meropenem, a carbapenem, compared with imipenem, a carbapenem (combined with cilastatin, which is an inhibitor of the enzyme dehydropeptidase and prolongs the antibacterial effect of imipenem). There were no statistically significant differences observed in outcomes between groups (Table 76). Statistically significantly more AEs cases were reported in the imipenem group than those in the meropenem group, though there is no statistically significant difference in specific AEs, withdrawals, and withdrawals due to AEs (Appendix Table H.35.).

Table 76. Comparison of meropenem versus imipenem

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Repeat Exacerbation 30 Days	OR: 1.01; 95% CI: 0.28 to 3.63, I^2=N/A	1 RCT[155] with 173 patients	High ROB and severe imprecision	Insufficient evidence
Repeat Exacerbation Longest Followup	OR: 1.01; 95% CI: 0.28 to 3.63, I^2=N/A	1 RCT[155] with 173 patients	High ROB and severe imprecision	Insufficient evidence
Clinical Cure End of Intervention	OR: 0.93; 95% CI: 0.48 to 1.81, I^2=N/A	1 RCT[155] with 173 patients	High ROB and severe imprecision	Insufficient evidence
Clinical Cure Longest Followup	OR: 0.85; 95% CI: 0.47 to 1.55, I^2=N/A	1 RCT[155] with 173 patients	High ROB and severe imprecision	Insufficient evidence
Clinical Failure End of Intervention	OR: 0.67; 95% CI: 0.11 to 4.09, I^2=N/A	1 RCT[155] with 173 patients	High ROB and severe imprecision	Insufficient evidence
Clinical Failure Longest Followup	OR: 1.01; 95% CI: 0.06 to 16.44, I^2=N/A	1 RCT[155] with 173 patients	High ROB and severe imprecision	Insufficient evidence

CI = confidence interval; OR = odds ratio; N/A = not applicable; RCT = randomized controlled trial; ROB = risk of bias

Comparative Effectiveness of Different Dosages of the Same Antibiotic

Trovafloxacin 200 Mg Versus Trovafloxacin 100 Mg

One study[152] evaluated the effectiveness of trovafloxacin 200 mg compared with trovafloxacin 100 mg. There were no statistically significant differences found in outcomes between groups (Table 77). Unspecified serious AEs were reported in 13 patients treated by trovafloxacin 200 mg and 8 patients in trovafloxacin 100 mg. No statistically significant difference was found in AEs, and withdrawals (Appendix Table H.36.).

Table 77. Comparison of trovafloxacin 200 mg versus trovafloxacin 100 mg

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Mortality End of Intervention	OR: 3.02; 95% CI: 0.12 to 74.78, I^2=N/A	1 RCT[152] with 288 patients	High ROB and severe imprecision	Insufficient evidence
Clinical Cure End of Intervention	OR: 1; 95% CI: 0.57 to 1.75, I^2=N/A	1 RCT[152] with 288 patients	High ROB and severe imprecision	Insufficient evidence
Clinical Cure Longest Followup	OR:1.34; 95% CI: 0.81 to 2.20, I^2=N/A	1 RCT[152] with 288 patients	High ROB and severe imprecision	Insufficient evidence

CI = confidence interval; OR = odds ratio; N/A = not applicable; RCT = randomized controlled trial; ROB = risk of bias

Intermittent Cefotaxime Versus Continuous Cefotaxime

One study[140] evaluated the effectiveness of intermittent compared with continuous intravenous dosing of cefotaxime, a 3rd generation cephalosporin.

There were no statistically significant differences observed in clinical cure, clinical failure, and number of withdrawals at the end of the intervention between groups (Table 78 and Appendix Table H.37.).

Table 78. Comparison of intermittent intravenous cefotaxime versus continuous intravenous cefotaxime

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Clinical Cure End of Intervention	OR: 1.80; 95% CI: 0.60 to 5.45, I^2=N/A	1 RCT[140] with 93 patients	High ROB and severe imprecision	Insufficient evidence
Clinical Failure End of Intervention	OR: 1.02; 95% CI: 0.20 to 5.35, I^2=N/A	1 RCT[140] with 93 patients	High ROB and severe imprecision	Insufficient evidence

CI = confidence interval; OR = odds ratio; N/A = not applicable; RCT = randomized controlled trial; ROB = risk of bias

Comparative Effectiveness of Different Application Routes for Antibiotics

No eligible studies were identified that compared different routes of application (for example oral, intravenous) for the same antibiotic (class).

Comparative Effectiveness of Different Durations of Treatment With Antibiotics

Amoxicillin + Clavulanic for 3 Days Versus Amoxicillin + Clavulanic for 10 Days

One study[142] compared amoxicillin + clavulanic for 3 days with amoxicillin + clavulanic for 10 days. There was no statistically significant difference found in outcomes and adverse events between the two groups (Table 79). Only mild gastrointestinal AEs were reported: 1 patient in the 3-day group and 5 patients in the 10-day group (p=0.11) (Appendix Table H. 38.).

Table 79. Comparison of amoxicillin + clavulanic for 3 days versus 10 days

Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Mortality Longest Followup	OR: 0.35; 95% CI: 0.01 to 8.96, I^2=N/A	1 RCT[142] with 48 patients	Intermediate ROB and severe imprecision	Insufficient evidence
Hospital Admission 30 Days	OR: 0.14; 95% CI: 0.01 to 2.80, I^2=N/A	1 RCT[142] with 48 patients	Intermediate ROB and severe imprecision	Insufficient evidence
Repeat Exacerbation End of Intervention	OR: 0.38; 95% CI: 0.07 to 2.19, I^2=N/A	1 RCT[142]with 48 patients	Intermediate ROB and severe imprecision	Insufficient evidence
Repeat Exacerbation 30 Days	OR: 0.71; 95% CI: 0.19 to 2.68, I^2=N/A	1 RCT[142] with 48 patients	Intermediate ROB and severe imprecision	Insufficient evidence
Repeat Exacerbation Longest Followup	OR: 0.71; 95% CI: 0.19 to 2.68, I^2=N/A	1 RCT[142] with 48 patients	Intermediate ROB and severe imprecision	Insufficient evidence
Clinical Cure End of Intervention	OR: 0.57; 95% CI: 0.15 to 2.14, I^2=N/A	1 RCT[142] with 48 patients	Intermediate ROB and severe imprecision	Insufficient evidence
Clinical Cure Longest Followup	OR: 1.02; 95% CI: 0.33 to 3.20, I^2=N/A	1 RCT[142] with 48 patients	Intermediate ROB and severe imprecision	Insufficient evidence
Resolution Clinical Failure End of Intervention	OR: 1.10; 95% CI: 0.20 to 6.09, I^2=N/A	1 RCT[142] with 48 patients	Intermediate ROB and severe imprecision	Insufficient evidence

CI = confidence interval; OR = odds ratio; N/A = not applicable; RCT = randomized controlled trial; ROB = risk of bias

Corticosteroids-Comparative Effectiveness Studies

Comparative Effectiveness of Different Systemic Corticosteroid Agents

One study[151] compared intravenous methylprednisolone with intravenous deflazacort hemisuccinate for 7 days. There were no statistically significant differences found in mortality and FEV1 absolute at the end of the intervention between groups (Table 80 and Table 81). No statistically significant difference was observed in AEs, withdrawals and withdrawals due to AEs (Appendix Table H.39.).

One study[137] compared intravenous methylprednisolone, followed by oral methylprednisone with intravenous hydrocortisone, followed by oral prednisolone. The total treatment duration was 14 days. FEV1 absolute at the end of treatment was statistically significantly higher in the methylprednisolone group compared with the hydrocortisone/prednisolone group, but there were no statistically significant differences observed in the other evaluated outcomes between groups (Table 80 and Table 81). No statistically significant difference in AEs, withdrawals and withdrawals due to AEs was found (Appendix Table H.40).

Table 80. Comparison of different systemic corticosteroid agents, critical outcomes

Comparison	Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
iv Methyl-prednisolone vs. iv Deflazacort Hemisuccinate	Mortality End of Intervention	OR : 0.32; 95% CI: 0.01 to 8.24, I2=N/A	1 RCT[151] with 60 patients	High ROB and severe imprecision	Insufficient evidence
iv Methyl-prednisolone, followed by oral Methylprednisone vs. iv Hydro-cortisone, followed by oral Prednisolone	Mortality Longest Followup	OR: 1.07; 95% CI: 0.06 to 17.53, I2=N/A	1 RCT[137] with 97 patients	Intermediate ROB and severe imprecision	Insufficient evidence
iv Methyl-prednisolone, followed by oral Methylprednisone vs. iv Hydro-cortisone, followed by oral Prednisolone	Need for Intubation Longest Followup	OR: 1.07; 95% CI: 0.06 to 17.53, I2=N/A	1 RCT[137] with 97 patients	Intermediate ROB and severe imprecision	Insufficient evidence
iv Methyl-prednisolone, followed by oral Methylprednisone vs. iv Hydro-cortisone, followed by oral Prednisolone	Clinical Failure End of Intervention	OR: 1.37; 95% CI: 0.34 to 5.44, I2=N/A	1 RCT[137] with 97 patients	Intermediate ROB and severe imprecision	Insufficient evidence

Comparison	Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
iv Methyl-prednisolone, followed by oral Methylprednisone vs. iv Hydro-cortisone, followed by oral Prednisolone	Dyspnea (Questionnaire: MRC) Longest Followup	WMD: -01; 95% CI: -0.29 to 0.09, I^2=N/A	1 RCT[137] with 97 patients	Intermediate ROB and severe imprecision	Insufficient evidence

CI = confidence interval; N/A = not applicable; MRC = Medical Research Council Scale; OR = odds ratio; RCT = randomized controlled trial; ROB = risk of bias; WMD = weighted mean difference

Table 81. Comparison of different systemic corticosteroid agents, additional outcomes

Comparison	Outcome	Findings	Study Design and Sample Size
iv Methyl-prednisolone vs. iv Deflazacort Hemisuccinate	FEV1 Absolute End of Intervention	WMD: 0.12; 95% CI: -0.06 to 0.30, I^2=N/A	1 RCT[151] with 60 patients
iv Methyl-prednisolone, followed by oral Methylprednisone vs iv Hydro-cortisone, followed by oral Prednisolone	FEV1 Absolute Longest Followup	WMD: 0.20; 95% CI: 0.06 to 0.34, I^2=N/A	1 RCT[137] with 97 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; I.V. = intravenous; OR = odds ratio; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Comparative Effectiveness of Different Routes of Application for Corticosteroids

Systemic Corticosteroids Versus Inhaled Corticosteroids

One study[75] compared subcutaneous prednisolone with nebulized budesonide given for at least 10 days. FEV1 percent predicted at the end of treatment was statistically significantly lower with subcutaneous prednisolone compared with nebulized budesonide (Table 82 and Table 83).

Oral prednisolone versus nebulized budesonide given for 10 days was compared in one study.[76] There were no statistically significant differences found between groups in mortality and dyspnea at the end of the intervention (Table 82 and Table 83). Unspecified serious AEs were reported in 8 patients treated by nebulized budesonide and 5 treated by oral prednisolone. No statistical difference in AEs, withdrawals, and withdrawals due to AEs were found (Appendix Table H.41.).

Intravenous prednisolone versus nebulized budesonide[146] given for 10 days was compared in one study. No AEs were reported in any of the two groups.

Another study[138] evaluated the effectiveness of oral prednisolone + inhaled formoterol (in a metered dose inhaler) compared with inhaled budesonide + formoterol (in a single metered dose inhaler) for 14 days. There were no statistically significant differences observed between groups in any of the evaluated outcomes (Table 82 and Table 83) and AEs (Appendix Table H.42.).

One study[131] compared methylprednisolone (initially intravenous, then oral) versus inhaled budesonide. Patients in the inhaled budesonide group had significantly lower incidence of adverse events than those in the systemic methylprednisolone group. There was no statistically significant difference in FEV1 percent predicted. Another study[159] compared intravenous methylprednisolone versus inhaled budesonide. There was no statistically significantly difference found in quality of life, FEV1 absolute values, and repeat exacerbation between the groups (Table 82 and Table 83). However, budesonide was associated with statistically significantly less endocrine-related AEs (Appendix Tables H.43 and H.44). Another study[133] compared methylprednisolone (intravenous) to inhaled budesonide 4mg or inhaled budesonide 8mg. There was no statistically significant difference found in FEV1 percent predicted, FEV1 absolute, dyspnea (Table 82 and Table 83) and AEs (Appendix Tables H. 45 and H.46.) between groups.

Table 82. Systemic corticosteroids versus inhaled corticosteroids, critical outcomes

Comparison	Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Oral Prednisolone vs. Nebulized Budesonide	Mortality End of Intervention	OR: 3.49; 95% CI: 0.14 to 87.18, I^2=N/A	1 RCT[76] with 133 patients	High ROB and severe imprecision	Insufficient evidence
	Dyspnea (Numeric Scale: Modified Borg Scale)End of Intervention	WMD: -0.70; 95% CI: -1.48 to 0.08, I^2=N/A	1 RCT[76] with 133 patients	High ROB and severe imprecision	Insufficient evidence
Subcutaneous Prednisolone vs. Nebulized Budesonide	Hospital Admission 30 days	Rate Ratio: 0.80; 95% CI: 0.21 to 2.98, I^2=N/A	1 RCT[75] with 106 patients	High ROB and severe imprecision	Insufficient evidence
	Repeat Exacerbation 1 Month Followup	Rate Ratio: 0.88; 95% CI: 0.34 to 2.33, I^2=N/A	1 RCT[75] with 106 patients	High ROB and severe imprecision	Insufficient evidence
Oral Prednisolone (+ Inhaled Formoterol) vs Inhaled Budesonide (+Inhaled Formoterol)	QoL(CCQ) End of Intervention	WMD: -0.09; 95% CI: -0.53 to 0.35, I^2=N/A	1 RCT[138] with 109 patients	Intermediate ROB and severe imprecision	Insufficient evidence
	QoL(CCQ) Longest Followup	WMD: -0.20; 95% CI: -0.63 to 0.23, I^2=N/A	1 RCT[138] with 109 patients	Intermediate ROB and severe imprecision	Insufficient evidence
	Repeat Exacerbation End of Intervention	Rate Ratio: 1.02; 95% CI; 0.49 to 2.14, I^2=N/A	1 RCT[138] with 109 patients	Intermediate ROB and severe imprecision	Insufficient evidence
	Repeat Exacerbation End of Intervention	OR: 0.91; 95% CI: 0.35 to 2.36, I^2=N/A	1 RCT[138] with 109 patients	Intermediate ROB and severe imprecision	Insufficient evidence
	Clinical Failure End of Intervention	OR: 0.2; 95% CI: 0.01 to 4.19, I^2=N/A	1 RCT[138] with 109 patients	Intermediate ROB and severe imprecision	Insufficient evidence

Comparison	Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Intravenous Methylprednisolone vs. inhaled Budesonide	QoL(CAT) End of Intervention	WMD: -0.27, 95% CI: -1.28 to 1.26, I^2=N/A	1 RCT[159] with 471 patients	Intermediate ROB and imprecision	Low SOE supporting no difference
	Repeat Exacerbations End of Intervention	Rate Ratio: 0.90; 95% CI: 0.76 to 1.06, I^2=N/A	1 RCT[159] with 471 patients	Intermediate ROB and imprecision	Low SOE supporting no difference
Intravenous Methylprednisolone vs. inhaled Budesonide 4 mg	Dyspnea (Numeric Scale) End of Intervention	P=NS	1 RCT[133] with 60 patients	High ROB and severe imprecision	Insufficient evidence
Intravenous Methylprednisolone vs. inhaled Budesonide 8 mg	Dyspnea (Numeric Scale) End of Intervention	P=NS	1 RCT[133] with 59 patients	High ROB and severe imprecision	Insufficient evidence

CAT = COPD Assessment Test; CCQ = Clinical COPD Questionnaire; CI = confidence interval; FEV1 = forced expiratory volume in one second; OR = odds ratio; N/A = not applicable; NS = not statistically significant; QoL = quality of life; RCT = randomized controlled trial; ROB = risk of bias; WMD = weighted mean difference

Table 83. Systemic corticosteroids versus inhaled corticosteroids, additional outcomes

Comparison	Outcome	Findings	Study Design and Sample Size
Subcutaneous Prednisolone vs. Nebulized Budesonide	FEV1% Predicted End of Intervention	WMD: -6.60; 95% CI: -12.39 to -0.81, I^2=N/A	1 RCT[75] with 106 patients
Oral Prednisolone (+ inhaled Formoterol) vs. inhaled Budesonide (+inhaled Formoterol)	FEV1% Predicted End of Intervention	WMD: -1.40; 95% CI: -5.79 to 2.99, I^2=N/A	1 RCT[138] with 109 patients
	FEV1% Predicted Longest Followup	WMD: -0.40; 95% CI: -4.98 to 4.18, I^2=N/A	1 RCT[138] with 109 patients
	FEV1 Absolute End of Intervention	WMD: -0.02; 95% CI: -0.17 to 0.13, I^2=N/A	1 RCT[138] with 109 patients
	FEV1 Absolute Longest Followup	WMD: 0.02; 95% CI: -0.14 to 0.18, I^2=N/A	1 RCT[138] with 109 patients
Intravenous Methylprednisolone vs. inhaled Budesonide	FEV1% Predicted End of Intervention	WMD: -0.48; 95% CI: -10.18 to 9.22, I^2=N/A	1 RCT[131] with 30 patients
	FEV1 Absolute End of Intervention	WMD: -0.04, 95% CI: -0.12 to 0.04, I^2=N/A	1 RCT[159] with 471 patients
Intravenous Methylprednisolone vs. Inhaled Budesonide 4 mg	FEV1 % Predicted End of Intervention	50.7 vs. 44.5; p=NS	1 RCT[133] with 60 patients
Intravenous Methylprednisolone vs. Inhaled Budesonide 8 mg	FEV1 % Predicted End of Intervention	54.8 vs. 44.5; p=NS	1 RCT[133] with 59 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; mg = milligram; N/A = not applicable; NS = not statistically significant; QoL = quality of life; RCT = randomized controlled trial; ROB = risk of bias; WMD = weighted mean difference

Oral Corticosteroids Versus Intravenous Corticosteroids

One study[144] compared oral prednisolone with intravenous prednisolone for 5 days. There were no statistically significant differences observed between groups in any of the evaluated outcomes (Table 84 and Table 85) and number of withdrawals (Appendix Table H.47).

Intravenous methylprednisolone, (+nebulized salbutamol and ipratropium bromide) was compared with oral methylprednisolone (+fenoterol and ipratropium bromide via metered dose inhaler) in one study.[147] There were no statistically significant differences observed in any of the evaluated outcomes and withdrawals between groups (Table 84 and Table 85 and Appendix Table H.48.).

Table 84. Comparison of oral corticosteroids versus intravenous corticosteroids, critical outcomes

Comparison	Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Oral Prednisolone vs. iv Prednisolone	Mortality End of Intervention	OR: 0.14; 95% CI: 0.01 to 2.83, I^2=N/A	1 RCT[144] with 210 patients	High ROB and severe imprecision	Insufficient evidence
	Mortality Longest Followup	OR: 0.40; 95% CI: 0.08 to 2.13, I^2=N/A	1 RCT[144] with 210 patients	High ROB and severe imprecision	Insufficient evidence
	QoL(SGRQ) End of Intervention	WMD: -0.07; 95% CI: -4.33 to 2.92, I^2=N/A	1 RCT[144] with 210 patients	High ROB and severe imprecision	Insufficient evidence
	Hospital Admission Longest Followup	OR: 0.86; 95% CI: 0.37 to 2.03, I^2=N/A	1 RCT[144] with 210 patients	High ROB and severe imprecision	Insufficient evidence
	Clinical Failure End of Intervention	OR: 1.05; 95% CI: 0.52 to 2.12, I^2=N/A	1 RCT[144]with 210 patients	High ROB and severe imprecision	Insufficient evidence
	Clinical Failure Longest Followup	OR: 0.78; 95% CI: 0.45 to 1.35, I^2=N/A	1 RCT [144]with 210 patients	High ROB and severe imprecision	Insufficient evidence
iv Methyl-prednisolone vs. Oral Methyl-Prednisolone	Mortality Longest Followup	OR: 3.45; 95% CI: 0.13 to100, I^2=N/A	1 RCT [147] with 48 patients	High ROB and severe imprecision	Insufficient evidence
	Dyspnea (Numeric Scale: VAS(1-10)) End of Intervention	WMD: 1.4; 95% CI: -0.07 to 2.87, I^2=N/A	1 RCT[147] with 48 patients	High ROB and severe imprecision	Insufficient evidence
	QoL(CRQ) Longest Followup	WMD:4.00; 95% CI: -8.56 to 16.56, I^2=N/A	1 RCT[147] with 48 patients	High ROB and severe imprecision	Insufficient evidence
	Hospital Admission Longest Followup	OR: 0.36; 95% CI: 0.11 to 1.18, I^2=N/A	1 RCT[147] with 48 patients	High ROB and severe imprecision	Insufficient evidence
	ICU Admission End of Intervention	OR: 0.28; 95% CI: 0.03 to 2.89, I^2=N/A	1 RCT[147] with 48 patients	High ROB and severe imprecision	Insufficient evidence

CI = confidence interval; I.V. = intravenous; N/A = not applicable; OR = odds ratio; QoL = quality of life; RCT = randomized controlled trial; ROB = risk of bias; SGRQ = St. George Respiratory Questionnaire; WMD = weighted mean difference

Table 85. Comparison of oral corticosteroids versus intravenous corticosteroids, additional outcomes

Comparison	Outcome	Findings	Study Design and Sample Size
Oral Prednisolone vs. iv Prednisolone	FEV1 Absolute End of Intervention	WMD: 0.02; 95% CI: -0.04 to 0.08, I^2=N/A	1 RCT[144] with 210 patients
iv Methyl-prednisolone vs. Oral Methyl-Prednisolone	FEV1% Predicted End of Intervention	WMD: 0.00; 95% CI: -7.98 to 7.98, I^2=N/A	RCT[147] with 48 patients
	FEV1 Absolute End of Intervention	WMD: 0.01; 95% CI: -0.21 to 0.23, I^2=N/A	RCT[147] with 48 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; I.V. = intravenous; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Comparative Effectiveness of Different Durations of Treatment With Corticosteroids

One study[77] compared systemic corticosteroid treatment for 8 weeks versus 2 weeks. Treatment in both groups started with intravenous methylprednisolone, followed by oral prednisone. There were no statistically significant differences found in any of the outcomes (Table 86 and Table 87) and AEs (Appendix Table H.49.) between groups.

Another study[158] compared systemic corticosteroid treatment for 5 days versus 14 days. Intravenous methylprednisolone was given on day 1 in both treatment groups, followed by prednisone for days 2-5 and placebo on days 6-14 in the shorter active treatment group, and prednisone for days 2-14 in the longer active treatment group. There were no statistically significant differences observed in any of the outcomes (Table 86 and Table 87), AEs, and number of withdrawals (Appendix Table H.50.) between groups.

Intravenous methylprednisolone for 3 days versus 10 days was assessed in one study.[149] FEV1 absolute at the end of intervention was statistically significantly lower in the group treated with methylprednisolone for 3 days compared with the group treated for 10 days, but all other outcomes, AEs, and withdrawals were not found to be statistically significantly different between groups (Table 86, Table 87 and Appendix Table H.51.).

Table 86. Comparison of different durations of treatment with corticosteroids, critical outcomes

Comparison	Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
Systemic Corticosteroids for 8 Weeks vs. 2 Weeks	Mortality End of Intervention	OR: 5.13; 95% CI: 0.24 to 108.51, I^2=N/A	1 RCT[77] with 160 patients	High ROB and severe imprecision	Insufficient evidence
	Mortality Longest Followup	OR: 1.82; 95% CI: 0.51 to 6.49, I^2=N/A	1 RCT[77] with 160 patients	High ROB and severe imprecision	Insufficient evidence

Comparison	Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
	Hospital Admission 30 Days	OR: 0.49; 95% CI: 0.09 to 2.74, I^2=N/A	1 RCT[77] with 160 patients	High ROB and severe imprecision	Insufficient evidence
	Hospital Admission Longest Followup	OR: 1.10; 95% CI: 0.47 to 2.58, I^2=N/A	1 RCT[77] with 160 patients	High ROB and severe imprecision	Insufficient evidence
	Need for Intubation End of Intervention	OR: 0.49; 95% CI: 0.04 to 5.59, I^2=N/A	1 RCT[77] with 160 patients	High ROB and severe imprecision	Insufficient evidence
	Need for Intubation Longest Followup	OR: 0.66; 95% CI: 0.11 to 4.05, I^2=N/A	1 RCT[77] with 160 patients	High ROB and severe imprecision	Insufficient evidence
	Clinical Failure Longest Followup	OR: 0.94; 95% CI: 0.46 to 1.90, I^2=N/A	1 RCT[77] with 160 patients	High ROB and severe imprecision	Insufficient evidence
Systemic Corticosteroids for 5 Days vs. 14 Days	Dyspnea (Questionnaire: MRC) Longest Followup	WMD: -0.08; 95% CI: -0.33 to 0.17, I^2=N/A	1 RCT[158] with 313 patients	Severe imprecision	Low SOE supporting no difference
	Mortality Longest Followup	OR: 0.91; 95% CI: 0.40 to 2.06, I^2=N/A	1 RCT[158] with 313 patients	Severe imprecision	Low SOE supporting no difference
	QoL(Bronchitis-Associated Quality of Life) End of Intervention	WMD: 0.05; 95% CI: -0.12 to 0.22, I^2=N/A	1 RCT[158] with 313 patients	Severe imprecision	Low SOE supporting no difference
	QoL(Bronchitis-Associated Quality of Life) Longest Followup	WMD: -0.02; 95% CI: -0.18 to 0.14, I^2=N/A	1 RCT[158] with 313 patients	Severe imprecision	Low SOE supporting no difference
	Repeat Exacerbation End of Intervention	OR: 0.96; 95% CI: 0.61 to 1.53, I^2=N/A	1 RCT[158] with 313 patients	Severe imprecision	Low SOE supporting no difference
	Need for Intubation Longest Followup	OR: 0.78; 95% CI: 0.39 to 1.54, I^2=N/A	1 RCT[158] with 313 patients	Severe imprecision	Low SOE supporting no difference

Comparison	Outcome	Findings	Study Design and Sample Size	Rationale for Strength of Evidence (SOE)	Overall Strength of Evidence
iv Methyl-prednisolone for 3 Days vs. 10 Days	Dyspnea (Numeric Scale: Dyspnea Score) End of Intervention	WMD: 0.20; 95% CI: -0.35 to 0.75, I^2=N/A	1 RCT[149] with 34 patients	Intermediate ROB and severe imprecision	Insufficient evidence
	Dyspnea (Numeric Scale: Dyspnea Score) Longest Followup	WMD: -0.10; 95% CI: -0.81 to 0.61, I^2=N/A	1 RCT[149] with 34 patients	Intermediate ROB and severe imprecision	Insufficient evidence
	Repeat Exacerbation End of Intervention	OR: 1.31; 95% CI: 0.31 to 5.53, I^2=N/A	1 RCT[149] with 34 patients	Intermediate ROB and severe imprecision	Insufficient evidence
		Rate Ratio: 1.60; 95% CI: 0.52 to 4.89, I^2=N/A	1 RCT[149] with 34 patients	Intermediate ROB and severe imprecision	Insufficient evidence

CI = confidence interval; I.V. = intravenous; MRQ = Medical Research Council Scale; N/A = not applicable; OR = odds ratio; QoL = quality of life; RCT = randomized controlled trial; ROB = risk of bias; WMD = weighted mean difference

Table 87. Comparison of different durations of treatment with corticosteroids, additional outcomes

Comparison	Outcome	Findings	Study Design and Sample Size
Systemic Corticosteroids for 5 Days vs. 14 Days	FEV1% Predicted End of Intervention	WMD: -1.16; 95% CI: -4.63 to 2.31, I^2=N/A	1 RCT[158] with 313 patients
	FEV1% Predicted Longest Followup	WMD: 0.80; 95% CI: -2.91 to 4.51, I^2=N/A	1 RCT[158] with 313 patients
iv Methyl-prednisolone for 3 Days vs. 10 Days	Cough(Cough Scale) End of Intervention	WMD: 0.00; 95% CI: -0.83 to 0.83, I^2=N/A	1 RCT[149] with 34 patients
	Cough(Cough Scale) Longest Followup	WMD: 0.30; 95% CI: -0.41 to 1.00, I^2=N/A	1 RCT[149] with 34 patients
	FEV1 Absolute End of Intervention	WMD: -0.23; 95% CI: -0.41 to -0.04, I^2=N/A	1 RCT[149] with 34 patients

CI = confidence interval; FEV1 = forced expiratory volume in one second; I.V. = intravenous; N/A = not applicable; RCT = randomized controlled trial; WMD = weighted mean difference

Discussion

Overview

We conducted a systematic review to assess the effectiveness of pharmacologic and nonpharmacologic therapies in adults with exacerbations of chronic obstructive pulmonary disease (ECOPD). We assessed the effectiveness of systemic antibiotics, systemic corticosteroids and potentially emerging 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. Figures 3 and 4 are evidence maps that summarize the distribution of evidence for the effectiveness of interventions compared with placebo or management without intervention treatment. Lung function (forced expiratory volume in one second (FEV1) absolute or FEV % predicted) was the most commonly evaluated outcome. For most interventions there was only one randomized controlled trial (RCT) per outcome available.

Figure 3. Evidence map showing distribution of trials in mild (or mild/moderate) ECOPD (Key Questions 1 and 2)

	Mortality	Dyspnea	QoL	FEV1 (absolute or % predicted)	6MWD or shuttle walk	Need for intubation	Repeat exacerbation and/or hospital admissions	ECOPD resolution (clinical cure, failure)
Key Question 1								
Systemic Antibiotics	1 RCT	1 RCT	1 RCT	2 RCTs			1 RCT	4 RCTs
Systemic Corticosteroids	1 RCT	1 RCT	1RCT	2 RCTs			1 RCT	2 RCTs
Key Question 2								
Oral Mucolytics				1 RCT				
ICS+LABA				1 RCT				1 RCT
Statin				1 RCT				

6MWD = 6 minute walking distance; ECPOD = exacerbations of chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in one second; ICS = inhaled corticosteroids; LABA = long-acting beta-agonist; RCT = randomized controlled trial

White cells = no RCTS; Grey cells = 1 RCT; Black cells = 2 or more RCTs

Figure 4. Evidence map showing distribution of trials in moderate to severe ECOPD (Key Questions 1 and 2)

Key Question 1

	Mortality	Dyspnea	QoL	FEV1 (absolute or % predicted)	6MWD or shuttle walk	Need for intubation	Repeat exacerbation and/or hospital admissions	Resolution of ECOPD (clinical cure, failure)
Key Question 1								
Systemic Antibiotics	2 RCTs	1 RCT		2 RCTs		1 RCT	1 RCT	2 RCTs
Systemic Corticosteroids	4 RCTs	1 RCT		3 RCTs		2 RCTs	3 RCTs	1 RCT

6MWD = 6 minute walking distance; ECPOD = exacerbations of chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in one second; QoL = quality of life; RCT = randomized controlled trial

White cells = no RCTS; grey cells = 1 RCT; black cells = 2 or more RCTs

Key Question 2 – pharmacologic interventions

	Mortality	Dyspnea	QoL	FEV1 (absolute or % predicted)	6MWD or shuttle walk	Need for intubation	Repeat exacerbation and/or hospital admissions	Resolution of ECOPD (clinical cure, failure)
Key Question 2								
Pharmacologic interventions								
i.v. Aminophyllines	2 RCTs	2 RCTs		3 RCTs		1 RCT		
i.v. Magnesium Sulfate		1 RCT		3 RCTs				
Nebulized Magnesium Sulfate				1 RCT				
Oral Mucolytics		2 RCTs		3 RCTs			2 RCTs	
ICS		1 RCT		1 RCT		1RCT	1 RCT	
ICS+SABA				1RCT				
Inhaled Antibiotics				1 RCT				
5-lipogygenase inhibitor	1 RCT			1 RCT		1 RCT	1 RCT	1 RCT

6MWD = 6 minute walking distance; ECPOD = exacerbations of chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in one second; ICS = inhaled corticosteroids; i.v. = intravenous; SABA = short-acting beta-agonist; QoL = quality of life; RCT = randomized controlled trial

White cells = no RCTS; grey cells = 1 RCT; black cells = 2 or more RCTs

Key Question 2 – nonpharmacologic interventions

	Mortality	Dyspnea	QoL	FEV1 (absolute or % predicted)	6MWD or shuttle walk	Need for intubation	Repeat exacerbation and/or hospital admissions	Resolution of ECOPD (clinical cure, failure)
Key Question 2								
Nonpharmacologic interventions								
Chest Physio, Breathing Technique	2 RCTs	2 RCTs	2 RCTs	1 RCT			2 RCTs	
Chest Physio, Vibration/Percussion		2 RCTs		3 RCTs	1 RCT			
Chest Physio, Positive Expiratory Pressure	1 RCT	1 RCT	1 RCT	1 RCT	1 RCT		1 RCT	
Resistance Training	1 RCT	1 RCT	1 RCT	2 RCTs	2 RCTs		1 RCT	
Aerobic Training		1 RCT	1 RCT				1 RCT	
Aerobic + Resistance Training				1 RCT				
Chest Physio + Exercise		1 RCT	1 RCT	1 RCT				
Early Pulmonary Rehab		3 RCTs	1 RCT		3 RCTs		1 RCT	
Whole Body Vibration Training			1 RCT	1RCT	1 RCT			
Transcutaneous Electrical Nerve Stimulation		1 RCT		1 RCT	1 RCT			
Dietary Intervention, Caloric Supplement	1 RCT	1 RCT	1 RCT	1 RCT				
Dietary Intervention, Caloric and Protein supplement		1 RCT		1 RCT				
Dietary Intervention, High Fat Low Carbohydrate				1 RCT				
Dietary Intervention, Vitamin D	1 RCT	2 RCTs	1 RCT	1 RCT				
Dietary Intervention, Omega-3 Fatty Acid		1 RCT	1 RCT			1 RCT		

6MWD = 6 minute walking distance; ECPOD = exacerbations of chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in one second; RCT = randomized controlled trial

White cells = no RCTS; grey cells = 1 RCT; black cells = 2 or more RCTs

We found moderate strength of evidence for antibiotics to improve clinical cure and reduce clinical failure in ECOPD compared with placebo. The finding was independent of the severity of an exacerbation episode including in patients with only mild ECOPD treated as outpatients. The review did not identify any antibiotic (group) that was clearly outperforming another.

There was low strength of evidence for the effectiveness of systemic corticosteroids (oral and intravenous) to reduce clinical failure at the end of the intervention. No significant differences were found between different systemic corticosteroid agents or routes of administration. A 5-day course of systemic corticosteroids was not statistically different to a 14-day course based on the final health outcomes mortality, quality of life, repeat exacerbation, and need for intubation.

Additional nonpharmacologic treatments showed in general more promising results than pharmacologic treatments. Some pharmacologic interventions had only been assessed for intermediate outcomes (lung function, symptoms) including magnesium sulfate, mucolytics, inhaled corticosteroid (ICS) and ICS+ short-acting beta adrenergic agonists (SABA), and inhaled antibiotics. None of the pharmacological interventions that were assessed for final health outcomes (aminophyllines, ICS+ long-acting beta-agonist (LABA) and the 5-lipoxygenase inhibitor zileuton) showed a significant improvement in any final health outcomes compared with placebo. In addition to intermediate outcomes, many studies on nonpharmacologic interventions assessed exercise capacity (e.g. 6-minute walking distance) and/or quality of life. For nonpharmacologic interventions, a significant improvement in exercise capacity compared with management without nonpharmacologic was found for resistance training, early pulmonary rehabilitation, whole body vibration training, and transcutaneous electrical nerve stimulation. This suggests that these interventions can potentially successfully address ECOPD-associated deconditioning. An improvement in quality of life was observed for combined chest physiotherapy (using breathing technique) and motion exercises, whole body vibration training, caloric supplements and vitamin D. Evidence from one study indicated that oxygen titration in ECOPD compared with high flow oxygen may reduce mortality.

Chest physiotherapy is commonly prescribed in patients hospitalized for ECOPD; however, the evidence-base for chest physiotherapy, as shown in our review, is weak. There was no evidence of improved final health outcomes, other than reduced hospital admission, from relatively small, low quality trials in our review.

Inhaled salbutamol (SABA) and inhaled ipratropium (short-acting muscarinic antagonists (SAMA)) had comparable effects on lung function and combining the SABA and SAMA did not result in better lung function than either medication alone.

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 chronic obstructive pulmonary disease (COPD) and ECOPD has proliferated substantially in recent years with numerous published systematic reviews on different interventions for the management of ECOPD. 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. 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 noninfective, 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 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.[44]

Despite the ubiquitous use of SABAs and SAMAs in ECOPD, we found only two studies (Key Question [KQ]3) that studied their effectiveness. The role of LABAs and long-acting muscarinic antagonists (LAMAs) in ECOPD remains largely unexplored with only one crossover trial identified in our review that assessed a LAMA versus placebo.

Another 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.[45] 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 intensive care unit (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) .[46] 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 ECOP 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 noninfective, 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 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 with patients who had 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,[47] 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 (FEV1) 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,[48] 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 which appear to be more likely to benefit from long-term inhaled corticosteroids.[44] 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 (PEP) is commonly prescribed in patients hospitalized for ECOPD, but there was insufficient evidence 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 and transcutaneous electrical nerve stimulation (TENS) and 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.[49] It is therefore evident that future research that aims to improve outcomes 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 nonpharmacological and dietary treatments.

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Abbreviations and Acronyms

ACOS	Asthma-COPD overlap syndrome
AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality
ATS	American Thoracic Society
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
D-L	DerSimonian and Laird
ECOPD	Exacerbations of Chronic Obstructive Pulmonary Disease
ED	Emergency Department
EPC	Evidence-based Practice Center
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in One Second
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HKSJ	Hartung-Knapp-Sidik-Jonkman
ICS	Inhaled Corticosteroid
ICU	Intensive Care Unit
KQ	Key Question
LABA	Long-acting beta-agonist
LAMA	Long-acting muscarinic antagonists
Mg	Milligram
OR	Odds Ratio
PICOTS	Population, Interventions, Comparisons, Outcomes, Timing, and Setting
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL	Quality of Life
RCTs	Randomized Controlled Trials
RCU	Respiratory Care Unit
SABAs	Short-acting Beta Adrenergic Agonists
SAMAs	Short-acting Muscarinic Antagonists
SMD	Standardized Mean Difference
SOE	Strength of Evidence
TENS	Transcutaneous Electrical Nerve Stimulation
US	United States of America
WMD	Weighted Mean Difference

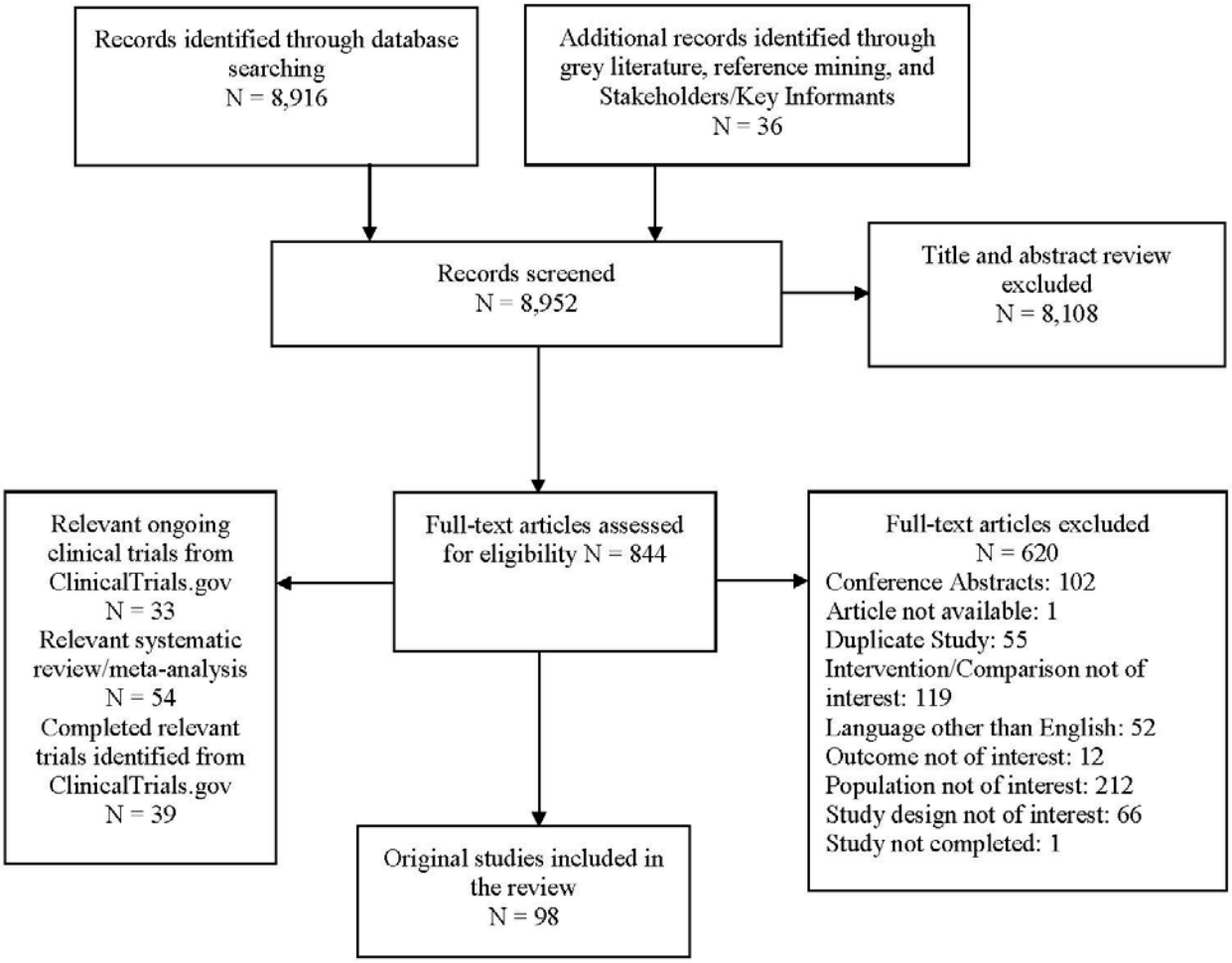
Appendixes

Tables

Figures

Appendix A. Flow Chart

Figure A.1. Flow chart



Appendix B. Search Strategy

Ovid

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials November 2018, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to December 28, 2018, Embase 1974 to 2018 January 02, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to January 02, 2019

Search Strategy:

Searches

1 exp Pulmonary Disease, Chronic Obstructive/dh, dt, px, rh, th or exp Lung Diseases, Obstructive/dh, dt, px, rh, th

2 exp chronic obstructive lung disease/dm, dt, rh, th

3 ((chronic* adj3 bronchiti*) or (obstruct* adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) or aecb or "chronic airflow disease*" or "chronic airflow disorder*" or "chronic airflow limitation*" or "chronic airflow obstruction*" or "chronic airway disease*" or "chronic airway disorder*" or "chronic airway limitation*" or "chronic airway obstruction*" or "chronic bronchitis" or "chronic obstructive airflow disease*" or "chronic obstructive airflow disorder*" or "chronic obstructive airway disease*" or "chronic obstructive airway disorder*" or "chronic obstructive bronchitis" or "chronic obstructive bronchopulmonary disease*" or "chronic obstructive broncho-pulmonary disease*" or "chronic obstructive bronchopulmonary disorder*" or "chronic obstructive broncho-pulmonary disorder*" or "chronic obstructive lung disease*" or "chronic obstructive lung disorder*" or "chronic obstructive pulmonary disease*" or "chronic obstructive pulmonary disorder*" or "chronic obstructive respiratory disease*" or "chronic obstructive respiratory disorder*" or coad or cobd or copd or emphysema* or "obstructive lung disease" or "obstructive lung disorder*" or "obstructive pulmonary disease*" or "obstructive pulmonary disorder*" or "obstructive pulmonary tract disease*" or "obstructive pulmonary tract disorder*" or "obstructive respiratory disease*" or "obstructive respiratory disorder*" or "obstructive respiratory tract disease*" or "obstructive respiratory tract disorder*").ti,ab,hw,kw.

4 ((increas* adj3 (severity or seriousness)) or exacerbation* or worsen*).ti,ab,hw,kw.

5 (1 or 2 or 3) and 4

6 exp Bronchodilator Agents/ or exp Adrenergic beta-2 Receptor Agonists/ or exp Cholinergic Antagonists/ or exp Phosphodiesterase 4 Inhibitors/ or exp Antibiotic Prophylaxis/ or exp Anti-Bacterial Agents/ or exp antibiotic agent/ or exp Benzodiazepines/ or exp Respiration, Artificial/ or exp Adrenal Cortex Hormones/ or exp corticosteroid/ or exp corticosteroid therapy/ or exp Expectorants/ or exp narcotic analgesic agent/ or exp Analgesics, Opioid/ or exp Smoking Cessation/ or exp Respiratory Therapy/ or exp exercise/ or exp Exercise Therapy/ or exp Breathing Exercises/ or exp Exercise Movement Techniques/ or exp Nutrition Therapy/ or exp Influenza Vaccines/ or exp Pneumococcal Vaccines/ or exp vaccination/ or exp Psychotherapy/ or exp Cognitive Therapy/ or exp Cognitive Behavior Therapy/ or exp Mindfulness/ or exp Mind-Body Therapies/ or exp Self Care/ or exp Acupuncture exp Complementary Therapies/ or exp Electric Stimulation Therapy/

7 ((action adj3 plan*) or (disease adj2 manag*) or (management adj1 program*) or Acupuncture or "Adrenal Cortex Hormone*" or "Adrenergic beta-2 Receptor Agonist*" or "Adrenergic beta-2 Receptor Antagonist*" or "alternative medicine*" or antibacterial* or "Anti-Bacterial*" or antibiotic* or Anticholinergic* or "artificial respiration" or behavior* or behaviour* or Benzodiazepine* or "Beta adrenergic agonist*" or "Beta adrenergic Antagonist*"

or "Breathing Exercise*" or Bronchodilator* or chemotherap* or "Chest physiotherap*" or "Cholinergic agonist*" or "Cholinergic Antagonist*" or "Cognitive Behavior Therap*" or "Cognitive Therap*" or "Complementary Therap*" or corticosteroid* or diet or drug* or educat* or "Electric Stimulation*" or empower* or exercise* or Expectorant* or Glucocorticoid* or instruct* or "management plan*" or "Mind-Body" or Mindfulnes* or narcotic* or Nutrition* or opioid* or "Oxygen therap*" or "patient cent*" or "patient educat*" or "patient focus*" or pharmacotherap* or "Phosphodiesterase 4 Inhibitor*" or Psychotherap* or respirator* or "Respiratory Therap*" or "Self Car*" or "self-efficac*" or "self-manag*" or "Smoking Cessation" or steroid* or train* or Vaccin* or ventilation or ventilator*).ti,ab,hw,kw.
8 6 or 7
9 5 and 8
10 limit 9 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") [Limit not valid in CCTR,CDSR,Embase; records were retained]
11 limit 10 to (adult <18 to 64 years> or aged <65+ years>) [Limit not valid in CCTR,CDSR,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]
12 limit 9 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)") [Limit not valid in CCTR,CDSR,Embase; records were retained]
13 limit 12 to (embryo or infant or child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) [Limit not valid in CCTR,CDSR,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]
14 13 not 11
15 9 not 14
16 limit 15 to (editorial or erratum or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in CCTR,CDSR,Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]
17 from 16 keep 8-93
18 (15 not 16) or 17
19 limit 18 to yr="2017 -Current"
20 limit 19 to yr="2018 -Current"
21 remove duplicates from 20
22 19 not 20
23 remove duplicates from 22
24 21 or 23
25 exp meta analysis/
26 exp Meta-Analysis as Topic/
27 exp "systematic review"/
28 ((meta adj analys*) or (systematic* adj3 review*)).mp,pt.

29 25 or 26 or 27 or 28
30 24 and 29
31 exp controlled study/
32 exp Randomized Controlled Trial/
33 exp triple blind procedure/
34 exp Double-Blind Method/
35 exp Single-Blind Method/
36 exp latin square design/
37 ((control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or "pragmatic clinical trial" or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square").mp,pt.
38 or/31-37
39 (24 not 30) and 38

Scopus

1 TITLE-ABS-KEY((chronic* W/3 bronchiti*) or (obstruct* W/3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)) or aecb or "chronic airflow disease*" or "chronic airflow disorder*" or "chronic airflow limitation*" or "chronic airflow obstruction*" or "chronic airway disease*" or "chronic airway disorder*" or "chronic airway limitation*" or "chronic airway obstruction*" or "chronic bronchitis" or "chronic obstructive airflow disease*" or "chronic obstructive airflow disorder*" or "chronic obstructive airway disease*" or "chronic obstructive airway disorder*" or "chronic obstructive bronchitis" or "chronic obstructive bronchopulmonary disease*" or "chronic obstructive broncho-pulmonary disease*" or "chronic obstructive bronchopulmonary disorder*" or "chronic obstructive broncho-pulmonary disorder*" or "chronic obstructive lung disease*" or "chronic obstructive lung disorder*" or "chronic obstructive pulmonary disease*" or "chronic obstructive pulmonary disorder*" or "chronic obstructive respiratory disease*" or "chronic obstructive respiratory disorder*" or coad or cobd or copd or emphysema* or "obstructive lung disease" or "obstructive lung disorder*" or "obstructive pulmonary disease*" or "obstructive pulmonary disorder*" or "obstructive pulmonary tract disease*" or "obstructive pulmonary tract disorder*" or "obstructive respiratory disease*" or "obstructive respiratory disorder*" or "obstructive respiratory tract disease*" or "obstructive respiratory tract disorder*")
2 TITLE-ABS-KEY((increas* W/3 (severity or seriousness)) or exacerbation* or worsen*)
3 TITLE-ABS-KEY((action W/3 plan*) or (disease W/2 manag*) or (management W/1 program*) or Acupuncture or "Adrenal Cortex Hormone*" or "Adrenergic beta-2 Receptor Agonist*" or "Adrenergic beta-2 Receptor Antagonist*" or "alternative medicine*" or antibacterial* or "Anti-Bacterial*" or antibiotic* or Anticholinergic* or "artificial respiration" or behavior* or behaviour* or Benzodiazepine* or "Beta adrenergic agonist*" or "Beta adrenergic Antagonist*" or "Breathing Exercise*" or Bronchodilator* or chemotherap* or "Chest physiotherap*" or "Cholinergic agonist*" or "Cholinergic Antagonist*" or "Cognitive Behavior Therap*" or "Cognitive Therap*" or "Complementary Therap*" or corticosteroid* or diet or drug* or educat* or "Electric Stimulation*" or empower* or exercise* or Expectorant* or Glucocorticoid* or instruct* or "management plan*" or "Mind-Body" or Mindfulnes* or narcotic* or Nutrition* or opioid* or "Oxygen therap*" or "patient cent*" or "patient educat*" or

"patient focus*" or pharmacotherap* or "Phosphodiesterase 4 Inhibitor*" or Psychotherap* or respirator* or "Respiratory Therap*" or "Self Car*" or "self-efficac*" or "self-manag*" or "Smoking Cessation" or steroid* or train* or Vaccin* or ventilation or ventilator*)
4 1 and 2 and 3
5 TITLE-ABS-KEY(newborn* or neonat* or infant* or toddler* or child* or adolescent* or paediatric* or pediatric* or girl or girls or boy or boys or teen or teens or teenager* or preschooler* or "pre-schooler*" or preteen or preteens or "pre-teen" or "pre-teens" or youth or youths) AND NOT TITLE-ABS-KEY(adult or adults or "middle age" or "middle aged" OR elderly OR geriatric* OR "old people" OR "old person*" OR "older people" OR "older person*" OR "very old")
6 4 and not 5
7 DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
8 6 and not 7
9 PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
10 8 and not 9
11 TITLE-ABS-KEY("consensus development" or guideline* or "position statement*")
12 10 and not 11
13 TITLE-ABS-KEY((meta W/1 analys*) or (systematic* W/3 review*))
14 12 and 13
15 12 and not 14
16 TITLE-ABS-KEY((control* W/3 study) or (control* W/3 trial) or (randomized W/3 study) or (randomized W/3 trial) or (randomised W/3 study) or (randomised W/3 trial) or "pragmatic clinical trial" or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or "latin square")
17 15 and 16

ClnicalTrials.Gov

(aecb OR "airflow obstruction" OR "airway obstruction" OR "bronchial obstruction" OR "bronchus obstruction" OR "chronic airflow disease") AND ("increased severity" OR "increasing severity"
OR "increased seriousness" OR "increasing seriousness" OR exacerbation OR worsening)

("chronic airflow disorder" OR "chronic airflow limitation" OR "chronic airflow obstruction" OR "chronic airway disease" OR "chronic airway disorder" OR "chronic airway limitation") AND ("increased severity" OR "increasing severity" OR "increased seriousness" OR "increasing seriousness" OR exacerbation OR worsening)

("chronic airway obstruction" OR "chronic bronchitis" OR "chronic obstructive airflow disease" OR "chronic obstructive airflow disorder" OR "chronic obstructive airway disease" OR "chronic obstructive airway disorder") AND ("increased severity" OR "increasing severity" OR "increased seriousness" OR "increasing seriousness" OR exacerbation OR worsening)

("chronic obstructive bronchitis" OR "chronic obstructive bronchopulmonary disease" OR "chronic obstructive broncho-pulmonary disease" OR "chronic obstructive bronchopulmonary disorder") AND ("increased severity" OR "increasing severity" OR "increased seriousness" OR "increasing seriousness" OR exacerbation OR worsening)

("chronic obstructive broncho-pulmonary disorder" OR "chronic obstructive lung disease" OR "chronic obstructive lung disorder" OR "chronic obstructive pulmonary disease" OR "chronic obstructive pulmonary disorder") AND ("increased severity" OR "increasing severity" OR "increased seriousness" OR "increasing seriousness" OR exacerbation OR worsening)

("chronic obstructive respiratory disease" OR "chronic obstructive respiratory disorder" OR coad OR cobd OR copd OR emphysema OR "lung obstruction" OR "obstructive lung disease" OR "obstructive lung disorder") AND ("increased severity" OR "increasing severity" OR "increased seriousness" OR "increasing seriousness" OR exacerbation OR worsening)

("obstructive pulmonary disease" OR "obstructive pulmonary disorder" OR "obstructive pulmonary tract disease" OR "obstructive pulmonary tract disorder" OR "obstructive respiratory disease") AND ("increased severity" OR "increasing severity" OR "increased seriousness" OR "increasing seriousness" OR exacerbation OR worsening)

("obstructive respiratory disorder" OR "obstructive respiratory tract disease" OR "obstructive respiratory tract disorder" OR "pulmonary obstruction" OR "respiratory obstruction") AND ("increased severity" OR "increasing severity" OR "increased seriousness" OR "increasing seriousness" OR exacerbation OR worsening)

All limited to adults.

Appendix C. Excluded Studies

1. 1-year Study to Assess the Efficacy, Safety, and Tolerability of Glycopyrronium Bromide (NVA237) in Chronic Obstructive Pulmonary Disease (COPD). 2009 June. PMID: NCT00929110. [Population not of interest].
2. A 24-week Study to Compare Umeclidinium/Vilanterol (UMEC/VI), UMEC and Salmeterol in Subjects With Chronic Obstructive Pulmonary Disease (COPD). Https://clinicaltrials.gov/show/nct03034915. 2017. PMID: CN-01561596. [Duplicate Study].
3. A 52-Week, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Safety and Tolerability of GSK573719/GW642444 and GSK573719 in Subjects With Chronic Obstructive Pulmonary Disease (COPD). 2011 January 1. PMID: NCT01316887. [Population not of interest].
4. A Comparison Study Between the Fixed Dose Triple Combination of Fluticasone Furoate/ Umeclidinium/ Vilanterol Trifenatate (FF/UMEC/VI) With Budesonide/Formoterol in Subjects With Chronic Obstructive Pulmonary Disease (COPD). 2015 January. PMID: NCT02345161. [Population not of interest].
5. A Dose-Finding Study Evaluating Safety and Efficacy in Patients With Chronic Obstructive Pulmonary Disease. 2006 November. PMID: NCT00403286. [Population not of interest].
6. A Multicenter, Randomized, Double-Blind, Double-Dummy Trial of Azithromycin SR Compared With Levofloxacin for the Treatment of Acute Symptoms of Chronic Bronchitis. 2003 January. PMID: NCT00644449. [Population not of interest].
7. A Multicentre, Randomised, Open-Label Study To Compare The Efficacy And Safety Of Azithromycin For 5 Days With Those Of Amoxicillin-Clavulanic Acid In Patients With Chronic Bronchitis. 2002 October. PMID: NCT00649831. [Clinical Trial].
8. A Pilot Safety Study of Inhaled Dry Powder Mannitol in Acute Exacerbations of COPD. 2006 October. PMID: NCT00446667. [Study design not of interest].
9. A Pivotal Study of the Safety and Effectiveness of Arformoterol in Subjects With Chronic Obstructive Pulmonary Disease (COPD). 2002 February. PMID: NCT00685841. [Population not of interest].
10. A Randomised Effectiveness Study Comparing Fluticasone Furoate (FF, GW685698)/Vilanterol (VI, GW642444) With Standard Treatment in Chronic Obstructive Pulmonary Disease (COPD). 2012 March 13. PMID: NCT01551758. [Population not of interest].
11. A Study Comparing the Efficacy, Safety and Tolerability of Fixed Dose Combination (FDC) of FF/UMEC/VI With the FDC of FF/VI and UMEC/VI; Administered Once-daily Via a Dry Powder Inhaler (DPI) in Subjects With Chronic Obstructive Pulmonary Disease (COPD). 2014 June 30. PMID: NCT02164513. [Population not of interest].
12. A Study of Andrographolide Sulfonate in Patients With Acute Exacerbation of Chronic Bronchitis. Https://clinicaltrials.gov/show/nct03132610. 2017. PMID: CN-01493692. [Duplicate Study].
13. A Study of Arformoterol Tartrate Inhalation Solution and Tiotropium Bromide on Re-hospitalization in Chronic Obstructive Pulmonary Disease (COPD) Subjects. 2014 November. PMID: NCT02275481. [Population not of interest].
14. A Study to Evaluate the Efficacy and Safety of Fluticasone Furoate (FF)/GW642444 Inhalation Powder in Subjects With Chronic Obstructive Pulmonary Disease (COPD). 2009 September 25. PMID: NCT01009463. [Population not of interest].

15. A Study to Evaluate the Safety, Efficacy and Changes in Induced Sputum and Blood Biomarkers Following Daily Repeat Doses of Inhaled GSK2269557 in Chronic Obstructive Pulmonary Disease (COPD) Subjects With Acute Exacerbation. 2015 November 4. PMID: NCT02522299. [Clinical Trial].

16. A Study To Investigate The Effects Of GW856553 On Patients With COPD (Chronic Obstructive Pulmonary Disease). 2006 August. PMID: NCT00392587. [Population not of interest].

17. A Trial To Evaluate Two Antibiotics For The Treatment Of Acute Exacerbation Of Chronic Bronchitis (AECB). 2006 February. PMID: NCT00254566. [Population not of interest].

18. Aaron SD, Vandemheen K, Maltais F, et al. Randomized, double-blind, placebo-controlled trial of TNF-alpha antagonists for acute exacerbations of copd. American Journal of Respiratory and Critical Care Medicine. Conference: American Thoracic Society International Conference, ATS. 2012;185(MeetingAbstracts). PMID: 71987621. [Duplicate Study].

19. Aaron SD, Vandemheen KL, Maltais F, et al. TNFalpha antagonists for acute exacerbations of COPD: a randomised double-blind controlled trial. Thorax. 2013 Feb;68(2):142-8. PMID: 23161645. [Duplicate Study].

20. Aaron SD, Vandemheen KL, Maltais F, et al. TNFα antagonists for acute exacerbations of COPD: A randomised double-blind controlled trial. Thorax. 2013;68(2):142-8. [Intervention/Comparison not of interest].

21. Aaron SD. Controlled trial of oral glucocorticoids in outpatients with acute COPD exacerbations who present to the emergency department: a randomized, double-blind, placebo-controlled pilot study [Dissertation]. University of Ottawa. 1999. PMID: CN-00462253 UPDATE. [Study design not of interest].

22. Abdullah Al Mamun SM, Rahman S. Role of 7-day and 14-day courses of oral prednisolone treatment in acute exacerbation of COPD. Thorax. 2011 December;4):A172-A3. PMID: 70627568. [Abstract].

23. Active for Life: chronic Obstructive Pulmonary Disease. Https://clinicaltrials.gov/show/nct03201198. 2017. PMID: CN-01495280. [Population not of interest].

24. ADVAIR® DISKUS® Inhaler (Fluticasone Propionate/Salmeterol) Versus SEREVENT® DISKUS® Inhaler (Salmeterol) For The Treatment Of Chronic Obstructive Pulmonary Disease Exacerbations. ADVAIR® DISKUS® Inhaler and SEREVENT® DISKUS® Inhaler Are Trademarks of the GSK Group of Companies. 2004 October. PMID: NCT00144911. [Population not of interest].

25. Advair® DISKUS® Versus Serevent® DISKUS® For Chronic Obstructive Pulmonary Disease Exacerbations. 2004 December. PMID: NCT00115492. [Population not of interest].

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30. Air Liquide Santé I, Services I, Lincoln M, et al. The COPD Patient Management European Trial (COMET). 2010 September. PMID: NCT01241526. [Population not of interest].

31. Air Liquide Santé I. Efficacy of Helium/Oxygen Compared to Air/Oxygen in Severe Exacerbation of Chronic Obstructive Pulmonary Disease (COPD). 2010 May. PMID: NCT01155310. [Population not of interest].

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Appendix D. Characteristics of Included Studies

Table D.1. KQ1: Characteristics of included studies

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
Aaron, 2003[1]	Canada	Low risk	Diagnosis by a physician or had at least a one-year history of chronic dyspnea or cough with sputum production	The presence of at least two of the following three clinical criteria: a recent increase in breathlessness, sputum volume, or sputum purulence	Mild/Moderate	Prednisone	NR	74 patients aged 68.9± 11.2 years, 43% female
						Placebo	NR	73 patients aged 69.9± 10.4 years, 42% female
Albert, 1980[2]	United States of America 10/25/1976 to 03/27/1978	Low risk	Chronic bronchitis (FEV1≤60% predicted or FEV1≤60% than FVC)	Acute bronchitis (increase in cough, sputum production, and sputum color within prior 5 days) + acute respiratory failure (PaO2 <65 mmHg on room air, or PaCO2≥50 or pH<7.35)	Severe	Methylprednisolone	FEV1 (L): Mean 0.673±0.239	22 patients aged 61±9 years
						Placebo	FEV1 (L): Mean 0.719±0.313	22 patients aged 62±10 years

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
Anthonisen, 1987[3]	Canada 11/01/1981 to 09/1984	High risk	FEV1/FVC<0.7, FEV1<70% predicted, clinical diagnosis	Type I exacerbation: increased dyspnea, sputum volume, and sputum purulence Type II exacerbation: two of these three symptoms Type III: one of these three symptoms plus at least one of the following findings: upper respiratory infection (sore throat, nasal discharge) within the past 5 days, fever without other cause, increased wheezing, increased cough, or increase in respiratory rate or heart rate by 20% as compared with baseline.	Mild/Moderate	Placebo Antibiotics	FEV1: Mean 33.9±13.7	173 total patients aged 67.3±9.0 years, 20% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
Bathoorn, 2008[4]	Netherlands	High risk	Post bronchodilator FEV1 <85% predicted but >0.7 liters, and an Abnormal post bronchodilator FEV1/slow inspiratory vital capacity (VC) (<88% predicted in men and <89% predicted in women)	History of increased breathlessness and at least two of the following symptoms for ≥24 hours: increased cough frequency or severity, sputum volume or purulence, and wheeze.	Mild	Budesonide + Formoterol	NR	15 patients aged 61.4±8 years, 33% female
						Prednisolone	NR	15 patients aged 64.8±7 years, 15% female
						Placebo	NR	15 patients aged 64.6±9.1, 7% female
Brusse-Keizer, 2014[5]	Netherlands 05/2005 to 01/2007	Low risk	GOLD criteria	An acute negative change in dyspnea and/or sputum volume and/or color of sputum (yellowish or greenish) and/or cough, which warrants additional treatment with prednisolone with or without antibiotics by a physician, outpatient evaluation	Mild/Moderate	Antibiotics	FEV1: Mean 44.7±15.4	18 patients aged 68 years, 50% female
						Placebo	FEV1: Mean 52.2±15.1	17 patients aged 65 years, 29% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
Daniels, 2010[6]	Netherlands	High risk	GOLD criteria, stages I-IV	An acute (onset < 14 d) exacerbation Anthonisen type 1 [increased dyspnea, sputum volume, and sputum purulence] or type 2 [two of three symptoms]) that required hospitalization	Moderate to Severe	Doxycycline	FEV1: Mean 43.9±17.2 FVC: 71.1±17.7	128 patients aged 71±10.2 years, 43% female
						Placebo	FEV1: 46.9±18.5 FVC: 72.7±18.6	137 patients aged 72.8±9.2 years, 38% female
Davies, 1999[7]	United Kingdom	Intermediate risk	History of at least 20 pack-years of cigarette smoking, and had physiological evidence of airflow limitation with initial FEV1 less than 70% predicted and FEV1/forced vital capacity ratio less than 75%	Two of the following symptoms for 24 h or more: increased cough frequency or severity, increased sputum volume or purulence, and increased wheeze	Moderate to Severe	Prednisolone	FEV1: Mean 27.4±2.4	29 patients aged 66±1.3 years, 39% female
						Placebo	FEV1: Mean 21.4±2.5	27 patients aged 69±2.1 years, 23% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
Emerman, 1989[8]	United States of America 10/1986 to 11/1987	Intermediate risk	Patients, with a clinical history of emphysema or chronic bronchitis with an FEV1 less than 70% of predicted or a FEV /FVC% less than 60%.	Patients, with a clinical history of emphysema or chronic bronchitis presenting to the Emergency Department with acute respiratory distress and had initial spirometry in the Emergency Department with an FEV1 less than 70% of predicted or a FEV /FVC% less than 60%.	Mild to Moderate to Severe	Methylprednisolone	FEV1: Mean 29±14.4	52 patients aged 63.7±8.7 years, 47.91% female
						Placebo	FEV1: Mean 26±14.4	52 patients aged 64.3±8.6 years, 47.91% female
Gunen, 2007[9]	Turkey	High risk	American Thoracic Society criteria	Worsening in at least two of the following symptoms: cough, purulent sputum and dyspnea	Moderate to Severe	Management without Systemic corticosteroids	FEV1: Mean 36.7±11.9	53 patients aged 63.5±10.1, 10% female
						Prednisolone, 40mg total dose	FEV1: Mean 35.3± 11.7	53 patients aged 64.9±7.1, 18% female
						Nebulized Budesonide	FEV1: Mean 39.6±12.9	53 patients aged 63.9±9.7, 16.7% female
Hassan, 2015[10]	Egypt 04/2013-10/2014	High risk	NR	Increase in dyspnea, sputum purulence and increased sputum volume, outpatient evaluation	Mild	Placebo	NR	50 patients aged 63±6.1, 16% female
						Antibiotic	NR	50 patients aged 60.6±6.8, 18% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
Llor, 2012[11]	Spain 10/2007-07/2010	Low risk	FEV1/FVC <70%, post bronchodilator FEV1>50%, smoking history ≥10 pack years	Increase of dyspnea, sputum volume or sputum purulence	Mild to Moderate	Amoxicillin + Clavulanate, 1500mg + 375mg	Mild: 9.5% Moderate: 90.5% FEV1: Mean 64.2±11.8	162 patients aged 68.4±9.9, 16.5% female
						Placebo	Mild:13.2% Moderate: 86.8% FEV1: Mean 65.9±12.1	156 patients aged 67.8±11, 21.7% female
Maltais, 2002[12]	Belgium, Canada, and France	High risk	American Thoracic Society criteria, chronic bronchitis or emphysema	Increased breathlessness in the past 14 days, causing hospital admission	Moderate to Severe	Budesonide	NR	71 patients aged 69.1±8.7, 20% female
						Prednisolone	NR	62 patients aged 70.4±7.7, 16% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
			14 day history of acute COPD exacerbation defined as increased breathlessness. Patients were included in the study if they were more than 50 years old, had a smoking history of at least 20 pack years, and according to the attending physician had to be treated in hospital.			Placebo	NR	66 patients aged 70.4±8.9, 20% female
Niewoehner, 1999[13]	United States of America	High risk	Clinical diagnosis of COPD plus a history of 30 pack years or more of cigarette smoking, and either an FEV1 of 1.50 liters or less or an inability to undergo spirometry because of dyspnea.	Clinical diagnosis	Moderate to Severe	Glucocorticoid for 8 weeks	FEV1 (L): Mean 0.785±0.288	80 patients aged 68.1±6.8, 3.75% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
						Glucocorticoid for 2 weeks	FEV1 (L): Mean 0.772±0.286	80 patients aged 67.1±10.6, 0% female
						Placebo	FEV1 (L): Mean 0.750±0.271	111Patients, aged 67.8±10, 0% female
Thompson, 1996[14]	USA	High risk	Airflow obstruction, and a clinical diagnosis of chronic bronchitis or emphysema as defined by the American Thoracic Society	Subjective worsening of chronic baseline dyspnea or cough for more than 24 h duration and necessitating a hospital visit, required to have least a 250% increase in inhaled B-adrenoceptor agonist use for more than 24 h, or an increase in sputum production.	Mild	Prednisone	NR	13 Patients aged 65 (9), female 7%
						Placebo	NR	13 Patients aged 70(7), female 0%
Van Velzen, 2017 [15]	The Netherlands	Low Risk	Post-bronchodilator FEV1/ FVC	Increased dyspnea, cough, or	Mild	Doxycycline	FEV1 (L) Mean: 61.2 (18.0)	152 Patients aged 65.8 (9.3), female 35%

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
	12/2010-8/2013		<0.7, post-bronchodilator FEV1 ≥ 30% (GOLD stage 1-3), ≥10 pack year smoking history, ≥ 1 exacerbation in prior 3 years, no exacerbations in prior 4 weeks	sputum sufficient to warrant a change in management other than optimization of bronchodilator therapy. Hospital admission and fever excluded.		Placebo	FEV1 (L) Mean: : 60.5 (17.7)	153 Patients aged 66.4 (9.5), female 46%
Wang, 2016[16]	China 6/2014 9/2015	Low risk	GOLD 2014 criteria	Acute change in symptoms that were beyond normal day-to-day variation and that required a change in daily therapeutic drug regimen, hospital admission	Moderate to Severe	Antibiotic	NR	97 patients aged 73.4±10.1, 29.5% female
						Management without Antibiotic	NR	97 patients aged 72.5±9.2, 27.1% female

Note: ± denotes standard deviationd = day; FEV1 = forced expiration volume in 1 second; FVC = forced vital capacity; GOLD = global initiative for chronic obstructive lung disease; h = hour; L = liter; NR = not reported; PaCO2 = partial pressure of carbon dioxide in arterial blood; PaO2 = partial pressure of oxygen in arterial blood; pH = potential of hydrogen; VC = vital capacity

Table D.2. KQ2: Characteristics of included studies

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
Abreu Gonzalez, 2006[17]	Spain 10/2003 to 09/2004	High risk	NR	NR	Moderate to Severe	Magnesium Sulfate	FEV1: Mean 32.5±3.2	24 total patients aged 64 years, 0% female
						Placebo		
Austin, 2010[18]	Australia	High risk	Patient reported history of COPD or emphysema or greater than 10 pack year history of smoking.	Paramedics at the site of the emergency Determined the diagnosis on the basis of appropriate acute symptoms, a history of chronic obstructive pulmonary disease (or emphysema) from the patient, or a greater than 10 pack year history of smoking.	Moderate to Severe	High Flow/Free Flow Oxygen	FEV1: Mean 42.1±16.4	117 patients aged 68±10.2 years, 51% female
						Titrated Oxygen	FEV1: Mean 43.3±16.5	97 patients aged 67.9±10.3 years, 54% female
Ayfer Aytemur, 2015[19]	Turkey	High risk	Based on spirometry not otherwise specified, at least 20 pack year smoking history	Clinical diagnosis, sputum volume of 50 ml or greater, hospital admission	Moderate to Severe	N-Acetylcysteine	NR	20 patients aged 68.6±7.5 years, 11% female
						Placebo	NR	22 patients aged 69.4±9.9 years, 5% female
Basri, 2017[20]	Pakistan	Intermediate risk	Clinical diagnosis	Clinical diagnosis, hospital admission	Moderate to Severe	Management without Chest Physiotherapy	NR	30 patients aged 53±3.7 years, 40% female
						Chest Physiotherapy	NR	30 patients aged 55±3.8 years, 56% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
Bathoorn, 2008[4]	Netherlands	High risk	Post bronchodilator FEV1 <85% predicted but >0.7 liters, and an Abnormal post bronchodilator FEV1/slow inspiratory vital capacity (VC) (<88% predicted in men and <89% predicted in women)	History of increased breathlessness and at least two of the following symptoms for ≥24 hours: increased cough frequency or severity, sputum volume or purulence, and wheeze.	Mild	Budesonide + Formoterol	NR	15 patients aged 61.4±8 years, 33% female
						Prednisolone	NR	15 patients aged 64.8±7 years, 15% female
						Placebo	NR	15 patients aged 64.6±9.1, 7% female
Behnke, 2000[21]	Germany	High risk	Severe COPD according to international guidelines	Hospital admission	Moderate to Severe	Aerobic Exercise	FEV1: Mean 34.1± 7.4	23 patients aged 64.0±1.9 years, 20% female
						Management without Aerobic Exercise	FEV1: Mean 37.5±6.6	23 patients aged 68.0±2.2 years, 27% female
Black, 2004[22]	New Zealand 01/2001-10/2001	Intermediate risk	FEV1 ≤ 60% predicted FEV1/VC ≤ 70%.	An increased volume of sputum as well as breathlessness.	Moderate to Severe	N-acetylcysteine	FEV1: Mean 22±10	25 patients aged 73.6±7.8 years, 56% female
						Placebo	FEV1: Mean 24±12	25 patients aged 73±8.2 years, 24% female
Borges, 2014[23]	Brazil	Intermediate risk	FEV1/FVC ≤ 0.7	Increase in sputum or cough or worsening of	Moderate to Severe	Resistance Training	FEV1: Mean 41.7±13.6	21 patients aged 64.1±12.5 years, 29% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
				dyspnea, hospital admission		Management without Resistance Training	FEV1: Mean 39.1±15.5	25 patients aged 67.8±9 years, 47% female
Brown, 1987[24]	Canada	High risk	Chronic productive cough with at least 30 ml of sputum production daily	Acute episode of pneumonia or increase in sputum production to at least 30 ml of sputum production daily	Mild to Moderate to Severe	Chest Wall Vibration	FEV1: Mean 33.4±17.5	12 total patients aged 66.5±11.5 years, 29% female
						Positioning		
Centanni, 2002[25]	Italy	High risk	European Respiratory Society (ERS) guidelines,	A sustained worsening of the patient's condition, from the stable	Mild	Oxitropium	FEV1: Mean 58.6±17.7	50 patients aged 68±0.8 years, 34% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
			clinical history, physical findings and spirometry, current or previous smokers (>10 pack-years) reporting chronic cough with sputum production on most days during at least 3 consecutive months in 2 consecutive years, had a FEV1 < 65% and a forced vital capacity (FVC) < 70% of predicted normal after bronchodilators had been withheld for 24 h and a best post-bronchodilator FEV1/FVC of less than 0.7.	state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD.		Placebo		
Cox, 2018[26]	United Kingdom 09/2015 to 04/2016	Intermed iate risk	Admission to hospital with primary diagnosis of ECOPD	Clinical diagnosis, hospital admission	Moderate to Severe	Management without Aerobic Exercise	NR	15 patients aged 67.8±11.12 years, 67% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
			(clinically determined by treating physician, pH >7.35, unstable hypoxemia excluded			Aerobic Exercise	NR	15 patients aged 67.8±11.12 years, 60% female
Cross, 2012[27]	United Kingdom 11/2005 to 4/2008	Intermediate risk	Clinical diagnosis	Clinical diagnosis, hospital admission	Moderate to Severe	Manual Chest Physiotherapy	NR	258 patients aged 69.08±9.85 years, 44.57% female
						Management without Manual Chest Physiotherapy	NR	264 patients aged 69.58±9.51 years, 41.29% female
Du, 2018[28]	China	High risk	COPD according to the criteria established by the Global initiative for Chronic Obstructive Lung Disease	NR	Mild to Moderate	Simvastatin	NR	30 patients aged 62.44±8.27 years, 13% female
						Placebo	NR	30 patients aged 64.2±9.35 years, 10% female
Duffy, 2005[29]	United Kingdom	Low risk	FEV1 of 70% predicted, FEV1/FVC of 70% predicted, at least 20 pack year smoking history	Breathlessness and two or more of the following symptoms for at least 24 hours: increased cough frequency or severity, increased sputum volume or purulence, increased wheeze.	Moderate to Severe	Placebo	NR	41 patients aged 67.4±7.5 years, 46% female
						Aminophylline	NR	39 patients aged 69.6±8.0 years, 67% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
Eaton, 2009[30]	New Zealand 06/2005 to 10/2006	High risk	ATS/ERS criteria	Exertional dyspnea interfering with daily activity, hospital admission	Moderate to Severe	Early Pulmonary Rehabilitation	FEV1: Mean 36±16 0.8±0.4 L	47 patients aged 70.1±10.3 years, 55% female
						Management without Early Rehabilitation	FEV1: Mean 35±16 0.8±0.4 L	50 patients aged 69.7±9.4 years, 58% female
Edwards, 2013[31]	New Zealand 06/2008 to 11/2011	Low risk	FEV1/FVC < 0.7, post-bronchodilator FEV1 ≤ 50%, clinical diagnosis	Clinical diagnosis, ED evaluation	Moderate to Severe	Placebo	NR	64 patients aged 69.5±11.9 years, 49.2% female
						Magnesium Sulfate	NR	52 patients aged 73.2±9.8 years, 43.8% female
Goktalay, 2013[32]	Turkey 04/2009 to 07/2011	High risk	GOLD stage 3-4	Increased dyspnea, increased cough and sputum production, altered sputum color and/or viscosity, fever and radiologic consolidation, hospital admission	Moderate to Severe	Management without High-frequency Chest Wall Oscillation Therapy	FEV1: Mean 30±8.93	25 patients aged 66.52 ±6.59, 2% female
						High-frequency Chest Wall Oscillation Therapy	FEV1: Mean 28±8.95	25 patients aged 63.6±7.99, 2% female
Greening, 2014[33]	United Kingdom,	High risk	COPD diagnosis, MRC dyspnea 3 or greater	NR	Moderate to Severe	Early Pulmonary Rehabilitation	N/A	169 patients
						Management without Early Rehabilitation	N/A	151 patients
Greulich, 2014[34]	Germany 10/2010 to 07/2012	Intermed iate risk	NR	NR, hospital admission	Moderate to Severe	Management without Whole Body Vibration	FEV1: Mean 38.4±17.82	26 patients aged 70.4±10.1 years, 40% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
						Whole Body Vibration	FEV1: Mean 32.71±13.18	23 patients aged 66.4±9.93 years, 30% female
Gunen, 2007[9]	Turkey	High risk	American Thoracic Society criteria	Worsening in at least two of the following symptoms: cough, purulent sputum and dyspnea	Moderate to Severe	Management without Systemic Corticosteroids	FEV1: Mean 36.7±11.9	53 patients aged 63.5±10.1, 10% female
						Prednisolone, 40mg total dose	FEV1: Mean 35.3± 11.7	53 patients aged 64.9±7.1, 18% female
						Nebulized Budesonide	FEV1: Mean 39.6±12.9	53 patients aged 63.9±9.7, 16.7% female
He, 2015[35]	China 12/2011-11/2013	High risk	GOLD criteria	The worsening of respiratory symptoms beyond normal day-to-day variation and leading to a change in medication, MMRC > 0, and hospital admission	Moderate to Severe	Early Pulmonary Rehabilitation	FEV1: Mean: 38±16.7	66 patients aged 69.2±12.4 9.1% female
						Management without Early Rehabilitation	FEV1: Mean: 39±27.8	28 patients aged 73.9±9.7, 17.6% female
Kirsten, 1998[37]	Germany	High risk	International guidelines	Hospitalization	Moderate to Severe	Aerobic Exercise	NR	15 patients aged 65.5±11.8
						Management without Aerobic Exercise	NR	14 patients aged 62.3±9.1
Kodric, 2009[36]	Italy 03/2002-09/2002	High risk	GOLD criteria	Clinical history, physical examination, chest x-ray, severity score according to the Anthonisen Criteria	Moderate to Severe	Management without Chest physiotherapy technique	FEV1: Mean 52.3±18.7	29 patients aged 69.1±8.3, 33% female
						Chest physiotherapy technique ELTGOL (expiration with the glottis open in the lateral posture)	FEV1: Mean 55.6±27.6	30 patients aged 71.3±8.4, 28% female
Kurzaj, 2013[38]	Poland	High risk	NR	Worsening COPD symptoms, hospital admission	Moderate to Severe	Specialized Physiotherapy	NR	20 patients aged 57±5.7, 45% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
						Management without Specialized Physiotherapy	NR	10 patients aged 55±4.2, 30% female
Lellouche, 2016[39]	Canada 08/2011-02/2015	Intermediate risk	Clinical diagnosis, at least 10 pack year smoking history	Clinical diagnosis, hospital admission	Moderate to Severe	Free02 device oxygen titration,0-20 L/min	FEV1 in a stable state: Mean 40±11	25 patients aged 71±8, 46% female
						Manual Oxygen Titration	FEV1 in a stable state: Mean 51±20	25 patients aged 73±8, 46% female
Liao, 2015[40]	Taiwan	High risk	NR	An increased need for medication and feel the need to seek additional medical assistance, hospital admission	Moderate to Severe	Early Pulmonary Rehabilitation	NR	31 patients aged 68 (44-89), 46.7% female
						Management without Early Rehabilitation	NR	31 patients aged ±, 32.3% female
Mahmoud Abd El Hafiz, 2013[41]	Egypt	High risk	FEV1/FVC <70%, post bronchodilator reversibility FEV1 <12%, clinical diagnosis, history of 2 or more exacerbations in 2 years prior	Clinical diagnosis, hospital admission	Moderate to Severe	Management without N-acetylcysteine	NR	15 patients aged 55.5±9.2, 0% female
						Low Dose N-acetylcysteine, 600mg total dose	NR	15 patients aged 59.6±6.6, 0% female
						High Dose N-acetylcysteine	NR	15 patients aged 62±4.1, 0% female
Maltais, 2002[12]	Belgium, Canada, and France	High risk	American Thoracic Society criteria, chronic bronchitis or emphysema	Increased breathlessness in the past 14 days, causing hospital admission	Moderate to Severe	Budesonide	NR	71 patients aged 69.1±8.7, 20% female
						Prednisolone	NR	62 patients aged 70.4±7.7, 16% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
			14 day history of acute COPD exacerbation defined as increased breathlessness. Patients were included in the study if they were more than 50 year old, had a smoking history of at least 20 pack years, and according to the attending physician had to be treated in hospital.			Placebo	NR	66 patients aged 70.4±8.9, 20% female
Moretti, 2015[42]	Italy 10/2012-05/2013	High risk	Clinical diagnosis	Clinical diagnosis, fever, cough, and purulent sputum in the previous 24 hours, hospital admission	Moderate to Severe	Erdosteine, 900mg total dose	FEV1: Mean 47.5±12.6	20 patients aged 71.4±5.4, 20% female
						Management without Erdosteine	FEV1: Mean 46.4±14.1	20 patients aged 69.7±6, 15% female
Mukerji, 2015[43]	New Zealand 07/2013-10/2013	Intermediate risk	Documented COPD diagnosis	Clinical diagnosis, ED evaluation	Moderate to Severe	Magnesium Sulfate	100% had FEV1 < 50%, Mean (L): 0.637±0.293	14 patients aged 76.1±12.47, 15% female
						Placebo	100% had FEV1 < 50%, Mean (L): 0.691±0.288	19 patients aged 72.9±9.39, 41% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
Ogasawara, 2018[44]	Japan	Low risk	According to the GOLD criteria, not otherwise specified	The acute worsening of respiratory symptoms, which leads to the requirement of additional therapy	Moderate to Severe	Omega-3 fatty acid enriched diet (Eicosapentaenoic acid)	FEV1: mean: 64.2± 24.7	25 patients aged 77.4±9.7 years, 12% female
						Usual Diet	FEV1: mean: 68.2±34.8	25 patients aged 79.1±7 years, 5% female
Oncu, 2017[45]	Turkey 8/2013-5/2014	High risk	Clinical diagnosis	Worsening pulmonary function testing, hospital admission	Moderate to Severe	Transcutaneous Electrical Nerve Stimulation, 45 min/day	NR	41 patients, 20% female
						Management without Transcutaneous Electrical Nerve Stimulation	NR	41 patients, 25.7% female
Osadnik, 2014[46]	Australia 08/2010-01/2013	Low risk	NR	NR, hospital admission	Moderate to Severe	Management without Positive Expiratory Pressure	FEV1: Mean 44.4±20.2	46 patients aged 69.5±9.8, 37.8% female
						Positive Expiratory Pressure	FEV1: Mean 37.3±19.7	46 patients aged 67.8±11.6, 33.3% female
Pourrashid, 2018[47]	Iran 12/2015-10/2016.	High risk	Post-bronchodilator FEV1/FVC <0.7, post-bronchodilator FEV1 <80% predicted	Clinical diagnosis, hospital admission	Moderate to Severe	Placebo	Moderate: 31.3% Severe: 68.8%	35 patients aged 64.06±8.77, 15.6% female
						Vitamin D, 300000 IU	Moderate: 33.3% Severe: 66.7%	35 patients aged 62.73±8.26, 16.67% female
Rice, 1987[48]	United States of America	Low risk	FEV1/FVC ratio < 60%, FEV1 < 2	Worsening of dyspnea within previous several	Moderate to Severe	Aminophylline	FEV1 (L): Mean 0.597±0.2	16 patients aged 66±27.9, 0% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
			SD below predicted value	days, associated with increased cough and sputum, sufficiently severe to require hospital admission		Placebo	FEV1 (L): Mean 0.561±0.36	14 patients aged 64±22, 6.6% female
Sanjari, 2015[49]	Iran	Intermediate risk	ERS criteria (FEV1 <88 % for men, <89 % for women)	A dramatic degradation of COPD symptoms (for example, the quantity and the color of phlegm or shortness of breath) that last for a couple of days, ED evaluation	Moderate to Severe	Placebo	NR	45 patients aged 58.4±9.5, 30.8% female
						Vitamin D	NR	45 patients aged 55.8±9.5, 28.6% female
						Calcitriol	NR	45 patients aged 55.6±8.9, 12.8% female
Saudny-Unterberger, 1997[50]	Canada 11/1993 05/1996	High risk	Clinical diagnosis of, and a FEV1 that was equal or less than 60% predicted	NR	Moderate to Severe	Nutritional Support	FEV1: Mean 33.21±3.57	17 patients aged 69.21±8.30, 43% female
						Usual Diet	FEV1: Mean 34.70±4.42	14 patients aged 69.40±12.4, 30% female
Seidenfeld, 1984[51]	United States of America	Intermediate risk	American Thoracic Society criteria for chronic bronchitis	NR	Unclear	Aminophylline	FEV1 (L): Mean 0.7±0.3	22 patients aged 62±8, 0% female
						Placebo	FEV1 (L): Mean 0.9±0.5	30 patients aged 63±7, 0% female
Skorodin, 1995[52]	United States of America	High risk	American Thoracic Society criteria	NR	Moderate to Severe	Magnesium Sulfate	NR	36 patients aged 62.8±9, 3% female
						Placebo	NR	36 patients aged 66.5±7.3, 3% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
Solooki, 2014[53]	Iran	High risk	NR	NR, ED evaluation	Moderate to Severe	Magnesium Sulfate	FEV1: Mean 26±12	15 patients aged 67±10, 27% female
						Placebo	FEV1: Mean 35±18	15 patients aged 70±8, 33% female
Soltaninejad, 2016[54]	Iran	High risk	Clinical diagnosis	Clinical diagnosis, hospital admission	Moderate to Severe	Gentamicin	NR	43 patients aged 65.5±9.7, 62.8% female
						Placebo	NR	43 patients aged 66±12, 55.8% female
Tang, 2012[55]	Australia 7/2009 8/2010	Low risk	Admitted to hospital with primary diagnosis of ECOPD	NR	Moderate to Severe	Low-intensity Exercise Group	FEV1: Mean 45.1±18.6	11 patients aged 68±10.1, 55% female
						Moderate to high-intensity exercise group	FEV1: Mean 46.1±18.3	10 patients aged 73.6±10, 80% female
						Management without Exercise Training	FEV1: Mean 46.8±20.4	11 patients aged 78±8.8, 45% female
Torres-Sanchez, 2017[56]	Spain 12 /2013 07/2014	Low risk	Clinical diagnosis	American Thoracic Society criteria, hospital admission	Moderate to Severe	Resistance Training	FEV1: Mean 42.35±10.62	29 patients aged 75.65±6.25 24.13% female
						Management without Resistance Training	FEV1: Mean 39.12±12.06	29 patients aged 72.12±8.19, 31% female
Torres-Sanchez, 2017[57]	Spain 9/2015 6/2016	Intermediate risk	GOLD criteria not otherwise specified	Clinical diagnosis, hospital admission	Moderate to Severe	Management without Exercise Training	FEV1: Mean 30.39±10.76	30 patients aged 71.13±9.39, 20% female
						Controlled breathing + Range of motion exercises	FEV1: Mean 31.26±5.33	30 patients aged 75.07±8.71, 6.7% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
						Resistance Training	FEV1: Mean 30.13±8.26	30 patients aged 70.12±10.6, 13.3% female
Troosters, 2010[58]	Belgium 01/2004 03/2005	High risk	FEV1/FVC <70%	Clinical diagnosis, hospital admission	Severe	Management without Resistance Training	FEV1: Mean 50±18	20 patients aged 69±7, 26% female
						Resistance Training	FEV1: Mean 40±12	20 patients aged 67±8, 24% female
Tumer, 2009[59]	Turkey	High risk	American Thoracic Society criteria	Increase, in at least two of the three following symptoms: dyspnea, cough and sputum production, hospital evaluation	Moderate to Severe	Usual Diet	NR	15 patients aged 63.6±4.3, 0% female
						High-fat Low-carbohydrate Diet	NR	15 patients aged 60.9±7, 0% female
Vermeeren, 2004[60]	Netherlands	High risk	GOLD criteria	Recent increase in breathlessness, cough and sputum production of sufficient severity to warrant hospital admission	Moderate to Severe	Nutritional Intervention	NR	23 patients aged 66±8, 39% female
						Placebo(non-caloric fluid, vanilla flavored water)	NR	24 patients aged 65±10, 25% female
Woodruff, 2011[61]	United States of America	High risk	Clinical diagnosis of AECOPD, ≥10 pack-years smoking history, FEV1 < 60% predicted at time of inclusion or an inability to perform spirometry due to dyspnea.	Acute increase in dyspnea, sputum volume, and/or sputum purulence without other attributable cause), hospital admission	Moderate to Severe	Zileuton	FEV1: Mean 32 ±13	60 patients aged 62±8, 37% female
						Placebo	FEV1: Mean 32±11	59 patients aged 64±10, 30% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
Xiong, 2008[62]	China	High risk	GOLD criteria	NR	Moderate to Severe	Atomization Inhalation	NR	20 patients aged 65.1±5.83, 45% female
						Management without Atomization Inhalation	NR	20 patients aged 66.4±6.48, 55% female
Yohannes, 2003[63]	United Kingdom	High risk	FEV1 <70% predicted together with a <20% improvement in FEV1 following standard doses of beta agonist by inhalation or nebulization.	Clinical diagnosis	Moderate to Severe	Gutter Frame + Supplemental Oxygen	FEV1: Mean 38±11	30 patients aged 75±7, 54% female
						Gutter Frame + Supplemental Air	FEV1: Mean 38±15	30 patients aged 75±7, 42% female
						Rollator + Oxygen	FEV1: Mean 35±11	30 patients aged 74±8, 57% female
						Rollator + Supplemental Air	FEV1: Mean 39±10	30 patients aged 74±7, 32% female
Zuin, 2005[64]	Italy	Intermediate risk	Clinical diagnosis of COPD, FEV1 40-70% predicted	1 or more of following: dyspnea, wheezing, chest tightness, mucus production and fever	Mild	N-acetylcysteine 1200mg	FEV1 (L): Mean 1.44±0.45	39 patients aged 67±12, 35.9% female
						N-acetylcysteine 600mg	FEV1 (L): Mean 1.46±0.46	41 patients aged 68±13, 41.5% female
						Placebo	FEV1 (L): Mean 1.44±0.51	42 patients aged 65±12, 50% female

Note: ± denotes standard deviation ECOPD = exacerbation of chronic obstructive pulmonary disease; ATS = American Thoracic Society; COPD = chronic obstructive pulmonary disease; ED = emergency department; EPA = eicosapentaenoic acid; ERS = European Respiratory Society; FEV1 = forced expiration volume in 1 second; FVC = forced vital capacity; GOLD = global initiative for chronic obstructive lung disease; h = hour; IU = international unit; L = liter; mg = milligram; min = minute; ml = milliliter; MMRC = modified medical research council; NR = not reported; ONS = oral nutrition supplementation; pH = potential of hydrogen; SD = standard deviation; VC = vital capacity

Table D.3. KQ3: Characteristics of included studies

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
Koutsogiannis, 2000[65]	Australia	Intermediate risk	Clinical diagnosis based on spirometry or physician opinion	NR	Unclear	Salbutamol, 15mg Salbutamol, 500 µg Ipratropium Bromide	NR	16 patients
						Ipratropium Bromide, 5mg Salbutamol, 1500 µg Ipratropium Bromide	NR	15 patients
						Combined	NR	18 Patients
Moayyedi, 1995[66]	United Kingdom	High risk	Clinical diagnosis, at least 10 pack year smoking history, FEV1<65%	NR	Moderate to Severe	Salbutamol, 20mg total dose	FEV1 (L): Mean 0.77±0.34	37 patients aged 70.4±9.1
						Salbutamol + Ipratropium Bromide, 20mg + 2000µg	FEV1 (L): Mean 0.78±0.41	33 patients aged 67.8±6.7
Perri, 1985[67]	Italy	High risk		NR	Unclear	Salbutamol + Beclomethasone Dipropionate, 450µg + 300µg	NR	15 patients
						Fenoterol, 1200 µg overall	NR	15 patients

Note: ± denotes standard deviation

FEV1 = forced expiration volume in 1 second; IB= ipratropium; L=liter; mg= milligram; NR= not reported; µg= microgram

Table D.4. KQ4: Characteristics of included studies

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
Aggarwal, 2011[68]	India	Intermediate risk	GOLD criteria	An acute change in a patient's baseline dyspnea, cough and/or sputum beyond day-to-day variability, sufficient to warrant a change in treatment, hospital evaluation	Mild to Moderate	Hydrocortisone Followed by Prednisolone	FEV1 (L): Mean 0.6±0.23	50 patients aged 65±9.96 years, 34% female
						Methylprednisolone	FEV1 (L): Mean 0.5±0.18	47 patients aged 64±8.19 years, 25.5% female
Andre-Alves, 2007[69]	Brazil	High risk	NR	Increased cough, increased expectoration or worsening of dyspnea.	Mild	Azithromycin	FEV1: Mean 66.1±0.3	49 patients aged 60.4 years, 34.7% female
						Amoxicillin	FEV1: Mean 66.9±0.4	53 patients aged 59.8 years, 49.1% female
Aubier, 2002[70]	Argentina, Australia, Belgium, France, Germany, Republic of Ireland, South Africa, and United Kingdom 03/1998 - 05/1999	High risk	FEV1/FVC <70%, history of chronic bronchitis, clinical diagnosis, bronchodilator response <12%	Presumed bacterial infection (increased cough and/or dyspnea, increased production of sputum, and increased purulence of sputum), outpatient evaluation	Mild	Telithromycin	FEV/FVC <60%: 43.1% FEV/FVC 60-75: 44.4% FEV/FVC >75: 6.3%	163 patients aged 61.5 years, 41.9% female
						Amoxicillin + Clavulanate	FEV/FVC <60%: 43.8% FEV/FVC 60-75: 40.6% FEV/FVC >75 10.6%	161 patients aged 66 years, 35% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
Blasi, 2013[71]	Austria, Germany, Italy, Poland, Portugal, and Ukraine 04/22/2008-11/12/2010	Intermediate risk	FEV1/FVC < 0.7, post-bronchodilator FEV1 < 50%, at least 10 pack year smoking history, chronic bronchitis, based on American Thoracic Society criteria	The presence of the following three symptoms (or at least two including sputum purulence): increased dyspnea, increased of sputum volume and sputum purulence that had to be macroscopically confirmed by the investigator. Patients, requiring concomitant systemic corticosteroids administration (20-40 mg/day for 7 days), or Patients, in whom an increase of the daily dosage of their chronically corticosteroid-treatment was required.	Unclear	Prulifloxacin	FEV1: Mean 40.2±9.0	179 patients aged 60.1±10.01 years, 36.3%
						Levofloxacin	FEV1: Mean 40.7±7.7	178 patients aged 60.6±9.72 years, 39.3% female
Dark, 1993[72]	United States of America	High risk	NR	NR	Unclear	Azithromycin	NR	136 patients aged 56.3±12.75 years, 39% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
						Cefaclor	NR	65 patients aged 55.4±14 years, 52% female
de Jong, 2007[9]	Netherlands 05/2001 to 05/2003	High risk	History of at least 10 pack-years of cigarette smoking, and evidence of airflow limitation. Airflow limitation was defined as an FEV1/FVC ratio of < 70% and an FEV1 of <80% predicted (at least Global Initiative for Chronic obstructive Lung Disease [GOLD] severity stage II)	An exacerbation of COPD was defined as a history of increased breathlessness and the presence of at least two of the following symptoms for at least 24 h: increased cough frequency or severity; increased sputum volume or purulence; and increased wheeze.	Moderate to Severe	Intravenous Prednisolone	FEV1: Mean 36±14	107 patients aged 69.8±8.8 years, 23.4% female
						Oral Prednisolone	FEV1: Mean 39±17	103 patients aged 71.6±8.1 years, 27.2% female
Ding, 2016[73]	China	Intermed iate risk	Symptoms of chronic cough, expectoration, and/or dyspnea,	Unusual continuous exacerbation that required a	Moderate to Severe	Budesonide	NR	233 patients aged 73.49± 8.61 years, 19.1% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
			incomplete reversible airflow (FEV1/FVC is <70% after application of a bronchodilator)	change in the routine medication, cough, expectoration, dyspnea, and/or wheeze exacerbated, and to have an increased amount of expectoration, or to have a short-term change in the sputum, which can be accompanied with evident aggravation of inflammatory (infection) symptoms (such as fever)		Methylprednisolone	NR	238 patients aged 73.18±8.5 years, 18.9% female
Emami Ardestani, 2017[74]	Iran 2013 to 2014	High risk	Post-bronchodilator FEV1/FVC <0.7, GOLD not otherwise specified	Increased cough, sputum, wheezing, or acute respiratory distress for 24 hours or more, ED evaluation	Moderate to Severe	Dexamethasone	NR	34 patients aged 74.67±1.79 years, 17.7% female
						Methylprednisolone	NR	34 patients aged 73.35±2.25 years, 17.6% female
Giusti, 2016[75]	Italy	High risk	FEV1/FVC ≤ 0.7, FEV1 ≤ 80% and ≥ 30%	Purulent sputum, plus at least two of the following signs/symptoms of at least 3-day	Moderate to Severe	Levofloxacin	NR	128 patients aged 76.5±7.6 years, 28.9% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
				duration: increased cough, dyspnea, sputum volume, hospital admission		Prulifloxacin	NR	130 patients aged 75.1±7.5 years, 30% female
Gunen, 2007[9]	Turkey	High risk	American Thoracic Society criteria	Worsening in at least two of the following symptoms: cough, purulent sputum and dyspnea	Moderate to Severe	Management without Systemic Corticosteroids	FEV1: Mean 36.7±11.9	53 patients aged 63.5±10.1, 10% female
						Prednisolone, 40mg total dose	FEV1: Mean 35.3± 11.7	53 patients aged 64.9±7.1, 18% female
						Nebulized Budesonide	FEV1: Mean 39.6±12.9	53 patients aged 63.9±9.7, 16.7% female
Hamacher, 1995[76]	Germany 10/1992-12/1993	High risk	American Thoracic Society criteria	Rapid onset of signs and symptoms of	Moderate to Severe	Meropenem, 3g overall	NR	86 patients aged 64.0±11.5, 31% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
				infective exacerbation with aggravation or development of dyspnea or cough with increased amount and purulent quality of sputum. The confirmation of pathogenic organism in sputum was not required directly at study entry, but at least one adequate bacteriological sample had to be taken before the patient was treated and Reduced peak flow (< 350 L/min)		Imipenem + Cilastatin, 3g imipenem overall, 3g of cilastatin overall	NR	87 patients aged 64.4±12.7, 35% female
Hasani, 1998[77]	United Kingdom	High risk	NR	NR	Mild to Moderate	Amoxicillin, 1500mg total dose	NR	6 patients aged 63±7.3, 33% female
						Ciprofloxacin, 1000mg total dose	NR	6 patients aged 63±7.3, 17% female
Leophonte, 1998[78]	France, United	High risk	Chronic bronchitis,	Dyspnea or increased sputum	Mild	Trovafloxacin 200 mg	NR	144 patients aged 65.1±7.3

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
	States of America, Italy, Spain, South Africa, United Kingdom, Australia 07/1995-08/1996		FEV1/FVC <70% predicted	volume/purulence [gram stain sputum with >25 PMN])		Trovafloxacin 100 mg	NR	144 patients aged 65.3±9.3
Leuppi, 2013[79]	Switzerland 03/2006-02/2011	Low risk	At least 20 pack year smoking history, FEV1/FVC <70%	At least 2 of the following: change in baseline dyspnea, cough, or sputum quantity or purulence	Moderate to Severe	Methylprednisolone (day 1), Prednisone (days 2-5), Placebo (days 6-14)	FEV1: Mean 31.3±13.2	157 patients aged 69.8±10.6, 46.5% female
						Methylprednisolone (day 1), Prednisone (days 2-14)	FEV1: Mean 31.7±15.4	156 patients aged 69.8±11.3, 32.7% female
Llor, 2009[80]	Spain 10/2000-03/2005	High risk	FEV1/FVC < 0.7, FEV1 <80%	Anthonisen criteria (increased dyspnea, increased sputum volume and purulent sputum), outpatient evaluation	Mild	Amoxycillin, 1500mg total dose	Moderate: 72.5% Severe: 27.5% FEV1: Mean 62.9±11.0	68 patients aged 71.9±8.6, 22.1% female
						Amoxycillin + clavulanate, 1500mg + 375mg	Moderate: 76.3% Severe: 23.7% FEV1: Mean 60.4±11.9	69 patients aged 70.8±8.5, 18.8% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
Maltais, 2002[12]	Belgium, Canada, and France	High risk	American Thoracic Society criteria, chronic bronchitis or emphysema 14 day history of acute COPD exacerbation defined as increased breathlessness. Patients were included in the study if they were more than 50 years old, had a smoking history of at least 20 pack years, and according to the attending physician had to	Increased breathlessness in the past 14 days, causing hospital admission	Moderate to Severe	Budesonide	NR	71 patients aged 69.1±8.7, 20% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
			be treated in hospital.			Prednisolone	NR	62 patients aged 70.4±7.7, 16% female
						Placebo	NR	66 patients aged 70.4±8.9, 20% female
Mirici, 2003[81]	Turkey	Low risk	American Thoracic Society criteria	Increased symptoms requiring hospitalization	Moderate to Severe	Parenteral Corticosteroid (prednisolone), 40mg total dose	NR	22 patients aged 64.8±, 24% female
						Nebulized Corticosteroid (budesonide), 8mg total dose	NR	22 patients aged 63.06±, 32% female
Niewoehner, 1999[13]	United States of America	High risk	Clinical diagnosis of COPD plus a history of 30	Clinical diagnosis	Moderate to Severe	Glucocorticoid for 8 weeks	FEV1 (L): Mean 0.785±0.288	80 patients aged 68.1±6.8, 3.75% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
			pack years or more of cigarette smoking, and either an FEV1 of 1.50 liters or less or an inability to undergo spirometry because of dyspnea.			Glucocorticoid for 2 week	FEV1 (L): Mean 0.772±0.286	80 patients aged 67.1±10.6, 0% female
						Placebo	FEV1 (L): Mean 0.750±0.271	111Patients, aged 67.8±10, 0% female
Petitpretz, 2007[82]	France, Germany, Tunisia, Belgium, Austria and Turkey. 03/2003-11/2004	High risk	A history of chronic bronchitis characterized by cough and sputum production on most days for 3 consecutive months and for >2 consecutive years; chronic obstructive bronchitis confirmed by lung function test performed in a	The presence of the three Anthonisen's criteria of recent increase in sputum volume, sputum purulence and dyspnea.	Mild	Levofloxacin, 500mg total dose	FEV1: Mean 51.2±13.1	340 patients aged 64.3±10.1, 19% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
			stable condition in the previous 12 months showing a forced expiratory volume in 1 s (FEV1)/forced vital capacity ratio of <70% and an FEV1 in the range of 35–80% of the predicted value, and no significant reversibility following 2-agonist therapy (<200 ml and <15% increase in FEV1).			Cefuroxime, 500mg	FEV1: Mean 52.6±13.3	349 patients aged 64.2±9.9, 18.2% female
Phillips, 1993[83]	United States of America	High risk	NR	Cough, fever, or increased sputum production/purulence), absence of infiltrate on chest radiograph)	Mild to Moderate to Severe	Cefpodoxime, 400mg total dose	NR	194 patients aged 54.2±17.3, 54% female
						Cefaclor, 750mg total dose	NR	107 patients aged 51.9±16.5, 35% female
Rhee, 2015[84]	Korea	High risk	Post-bronchodilator FEV1/FVC <0.7	Worsening of the respiratory symptoms that is beyond normal	Moderate	Zabofloxacin, 367mg total dose	FEV1: Mean 50.5±18.1	175 patients aged 67.8±7.8, 12.6% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
				day-to-day variations and leads to a change in medication, purulent sputum or increased volume of sputum, outpatient evaluation		Moxifloxacin, 400mg total dose	FEV1: Mean: 49.1±17.2	167 patients aged 68.4±8, 4.8% female
Rizzato, 1998[85]	Italy	High risk	NR	Admitted to hospital for ECOPD, FEV1<70%, marked respiratory distress	Moderate to Severe	Deflazacort Hemisuccinate, 60mg total dose	FEV1 (L): Mean 0.84	30 patients aged 74.5±15.75, 27% female
						Methylprednisolone, 40mg total dose	FEV1 (L): Mean 0.76	30 patients aged 69.0±11, 33% female
Roede, 2007[86]	The Netherlands 11/2000-12/2003	Intermediate risk	A disorder characterized by abnormal tests of expiratory flow that did not change markedly during an observation period of several months.	An increase in dyspnea and the volume and purulence of sputum.	Moderate to Severe	Amoxycillin + Clavulanic for 3 days, 2500mg overall	NR	23 patients aged 69±4.25, 52% female
						Amoxycillin + Clavulanic for 10 days, 2500mg overall	NR	25 patients aged 66±2.5, 36% female
Ruiz-Gonzalez, 2007[87]	Spain	High risk	FEV1/FVC ratio ≤70%, and FEV1 ≤ 80% predicted.	Worsening of dyspnea, increase in sputum volume and increase in sputum purulence.	Mild to Moderate to Severe	Levofloxacin	Moderate: 16.7% Severe: 57.8% Very Severe: 24.4% FEV1: Mean 33.91±21.3	50 patients aged 64.3 years, 16% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
						Standard care (clarithromycin, cefuroxime, or amoxicillin/clavulanate)	Moderate: 16.7% Severe: 58.3% Very Severe: 25.0% FEV1: Mean 31.48±17.1	52 patients aged 61.8, 17% female
Sayiner, 2001[88]	Turkey	Intermediate risk	Smoking history at least 20 pack-years and severe airway obstruction (FEV1 <35% predicted)	Severe dyspnea preventing the patient from performing even minor activities (getting dressed or eating) and resulting in sleep disturbances, and the presence of respiratory failure, i.e. Pao2 less than or equal to 55 mmhg and/or Paco2 level greater than or equal to 45 mmhg.	Severe	Methylprednisolone for 3 days	FEV1: Mean 25.4±5.4	17 patients aged 67.4±1.4, 6% female
						Methylprednisolone for 10 days	FEV1: Mean 27.1±5.7	17 patients aged 64.1±2.2, 6% female
Stallberg, 2009[89]	Sweden 09/2005 07/2007	Intermediate risk	≥10 pack year smoking history, moderate COPD GOLD stage IIA or IIB	Increased dyspnea, sputum volume, or sputum purulence; the exacerbation had to be severe enough that the primary care	Mild	Budesonide + Formoterol	GOLD 1: 1.8% GOLD2: 98.2% FEV1: Mean 45.1±8.9	55 patients aged 67.2±9.7, 55% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
				physician thought that oral steroids were clinically indicated, but not severe enough to require hospitalization.		Prednisolone + formoterol	GOLD1: 1.9% GOLD2: 94.4% GOLD3: 3.7% FEV1: Mean 45.0±9.5	54 patients aged 66.7±9.3, 43% female
Sun, 2015[90]	China 1/2013 7/2013	High risk	GOLD criteria, at least 20 pack year smoking history	Clinical diagnosis, ECOPD due to bacterial infection only	Unclear	Inhaled Budesonide	FEV1: Mean 49.6±8.3	15 patients aged 62.8±7.3, 40% female
						Systemic Methylprednisolone	FEV1: Mean 48.0±8.8	15 patients aged 62±8.1, 47% female
Ucar, 2014[91]	Turkey	High risk	Gold NOS	"Moderate or severe" exacerbation requiring hospitalization (respiratory failure with mild to moderate hypoxemia (pao2 40-80 mmHg) but no carbon dioxide retention or acidosis	Moderate to Severe	Methylprednisolone	FEV1: Mean 39.4±11.3	33 patients aged 66.6±9.6, 27% female
						Budesonide 4 mg	FEV1: Mean 41.0±13.4	27 patients aged 66.7±9.7, 7% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
						Budesonide 8mg	FEV1: Mean 49.0±14.7	26 patients aged 69.9±8.5, 15% female
Umut, 1999[92]	Turkey	High risk	American Thoracic Society criteria	Increased amounts of purulent secretions, dyspnea, chest tightness	Unclear	Azithromycin	NR	24 patients aged 64±9
						Ampicillin + Sulbactam	NR	28 patients aged 64±9
						Ciprofloxacin	NR	25 patients aged 64±9
						Cefaclor	NR	29 patients aged 64±9
van Zanten, 2007[93]	Netherlands	High risk	GOLD classes 2-4.	NR, hospital admission	Moderate to Severe	Continuous Cefotaxime	NR	47 patients aged 65.3±8.4, 34.04% female
						Intermittent Cefotaxime	NR	46 patients aged 68.6±5.3, 28.3% female
Whitlock, 1995[94]	United States of America	High risk	History of COPD with persistent cough and sputum production for at least 3 months in at least 2 consecutive years	Least two of the following: fever (~37.8 °C) within the previous 24 hours, increased dyspnea, increased frequency of cough, and increased volume of sputum	Mild to Moderate	Azithromycin	NR	39 patients aged 61±9.5, 33% female
						Amoxicillin + Clavulanate	NR	31 patients aged 58.5±9.5, 39% female
Willaert, 2002[95]	Belgium 07/1999 03/2000	High risk	NR	1) increased dyspnea, 2) increased cough frequency or	Moderate to Severe	Intravenous Steroids + Aerosol Bronchodilators	FEV1 (L): Mean 1.14±0.43	23 patients aged 72±6, 8.7% female

Author, Year	Country, Study Period	Risk of Bias	COPD Definition	COPD Exacerbation	Severity of ECOPD	Intervention(s) and comparison	COPD Severity (% predicted unless specified)	Patient Characteristics
				severity, 3) increased production or purulence of sputum, 4) increased wheeze, lasting for at least 3 days and for which the patient sought medical attention		Oral steroids + Multiple Dose Inhaler Bronchodilators	FEV1 (L): Mean 1.1±0.51	25 patients aged 71±8, 16% female
Wilson, 2012[96]	30 countries	High risk	FEV1/FVC < 0.7, post-bronchodilator FEV1 < 60%, at least 20 pack year smoking history, chronic bronchitis, 2 or more exacerbations in the past year	Investigator-evaluated Anthonisen type I exacerbation and who were considered by the investigator to require antibiotic therapy, outpatient evaluation	Mild	Moxifloxacin	FEV1: Mean 39.28±11.62	686 patients aged 69.6±6.8, 21% female
						Amoxicillin + Clavulanic Acid	FEV1: Mean 39.19±11.36	686 patients aged 69.3±6.3, 21% female
Yoon, 2013[97]	Korea 11/2006-06/2009	Intermediate risk	Post-bronchodilator FEV1/FVC <0.7	A recently increased cough or dyspnea, recent change in color or amount of sputum, hospital admission	Unclear	Levofloxacin	NR	65 patients aged 70.95±8.81, 9.23% female
						Cefuroxime	NR	72 patients aged 69.63±8.3, 6.94% female

Note: ± denotes standard deviation

ECOPD = exacerbation of chronic obstructive pulmonary disease; COPD = chronic obstructive pulmonary disease; ED = emergency department; FEV1 = forced expiration volume in 1 second; FVC = forced vital capacity; g= gram; GOLD = global initiative for chronic obstructive lung disease; h= hour; L=liter; mg= milligram; min= minute;

ml=milliliter; mmHg= millimeters of mercury; NOS= not otherwise specified; NR= not reported; PaCO2 = partial pressure of carbon dioxide in arterial blood; Pao2 = partial pressure of oxygen in arterial blood; PMN= polymorphonuclear leukocytes

Appendix E. Risk of Bias

Table E.1. Risk of Bias (Cochrane ROB tool) for included studies

Author, Year	Sequence Generation	Allocation Concealment	Blinding of Participants, Personnel	Blinding of Outcome Assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias	Overall RoB
Aaron, 2003[1]	Low risk	Low risk	Low risk	Unknown	Low risk	Unknown	High risk	Low risk
Abreu Gonzalez, 2006[17]	Unknown	Unknown	Low risk	Unknown	Unknown	Unknown	Unknown	High risk
Aggarwal, 2011[68]	Low risk	Unknown	High risk	Unknown	Low risk	Unknown	High risk	Intermediate risk
Albert, 1980[2]	Low risk	Low risk	Low risk	Unknown	Low risk	Unknown	Unknown	Low risk
Andre-Alves, 2007[69]	Unknown	Unknown	Unknown	Unknown	Low risk	Low risk	Unknown	High risk
Anthonisen, 1987[3]	Unknown	Unknown	Low risk	Unknown	High risk	Unknown	High risk	High risk
Aubier, 2002[70]	Unknown	Unknown	Low risk	Unknown	Low risk	Unknown	High risk	High risk
Austin, 2010[18]	High risk	Unknown	High risk	High risk	High risk	Unknown	High risk	High risk
Ayfer Aytemur, 2015[19]	Unknown	Unknown	Low risk	Unknown	Low risk	Unknown	Low risk	High risk
Basri, 2017[20]	Low risk	Unknown	Low risk	Unknown	Unknown	Unknown	Low risk	Intermediate risk
Bathoorn, 2008[4]	Unknown	Unknown	Low risk	Unknown	Low risk	Unknown	Unknown	High risk
Behnke, 2000[21]	Unknown	Unknown	High risk	High risk	High risk	Unknown	Unknown	High risk
Black, 2004[22]	Low risk	Unknown	Low risk	Unknown	Low risk	Unknown	High risk	Intermediate risk
Blasi, 2013[71]	Low risk	Low risk	Low risk	Unknown	High risk	Unknown	Unknown	Intermediate risk
Borges, 2014[23]	Low risk	Low risk	Unknown	Low risk	High risk	Unknown	Low risk	Intermediate risk
Brown, 1987[24]	Unknown	Unknown	High risk	Unknown	Unknown	Unknown	Unknown	High risk
Brusse-Keizer, 2014[5]	Low risk	Low risk	Low risk	High risk	Low risk	Unknown	Low risk	Low risk
Centanni, 2002[25]	Unknown	Unknown	Low risk	Unknown	Low risk	Low risk	Unknown	High risk
Cox, 2018[26]	Low risk	Low risk	High risk	Low risk	High risk	Unknown	Low risk	Intermediate risk

Author, Year	Sequence Generation	Allocation Concealment	Blinding of Participants, Personnel	Blinding of Outcome Assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias	Overall RoB
Cross, 2012[27]	Low risk	Low risk	Unknown	Unknown	High risk	Unknown	Low risk	Intermediate risk
Daniels, 2010[6]	Low risk	Unknown	Low risk	Unknown	High risk	Unknown	High risk	High risk
Dark, 1993[72]	Unknown	Unknown	High risk	Unknown	Low risk	Unknown	High risk	High risk
Davies, 1999[7]	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	High risk	Intermediate risk
de Jong, 2007[98]	Low risk	Unknown	Low risk	Unknown	High risk	Unknown	Low risk	High risk
Ding, 2016	Low risk	High risk	High risk	Unknown	Low risk	Unknown	Low risk	Intermediate risk
Du, 2018[28]	Unknown	Unknown	High risk	High risk	Low risk	Low risk	Low risk	High risk
Duffy, 2005[29]	Low risk	Low risk	Low risk	Low risk	Low risk	Unknown	Unknown	Low risk
Eaton, 2009[30]	Low risk	Unknown	High risk	Low risk	High risk	Unknown	Low risk	High risk
Edwards, 2013[31]	Low risk	Low risk	Low risk	Unknown	Low risk	Unknown	Low risk	Low risk
Emami Ardestani, 2017[74]	Unknown	Unknown	High risk	Unknown	Unknown	Unknown	Low risk	High risk
Emerman, 1989[8]	Low risk	Unknown	Low risk	Low risk	Low risk	Unknown	High risk	Intermediate risk
Giusti, 2016[75]	Low risk	Unknown	High risk	Low risk	High risk	Unknown	High risk	High risk
Goktalay, 2013[32]	High risk	Unknown	Low risk	Low risk	High risk	Unknown	High risk	High risk
Greening, 2014[33]	Unknown	Unknown	High risk	High risk	Low risk	Unknown	Low risk	High risk
Greulich, 2014[34]	Low risk	Low risk	High risk	Low risk	High risk	Unknown	Low risk	Intermediate risk
Gunen, 2007[9]	Unknown	Unknown	Unknown	Unknown	High risk	Unknown	Low risk	High risk
Hamacher, 1995[76]	High risk	High risk	Unknown	Unknown	Low risk	High risk	Unknown	High risk
Hasani, 1998[77]	Unknown	Unknown	Low risk	Unknown	Unknown	Unknown	High risk	High risk
Hassan, 2015[10]	Unknown	Unknown	Low risk	Unknown	Unknown	Unknown	High risk	High risk
He, 2015[35]	Unknown	High risk	High risk	High risk	Low risk	Unknown	Low risk	High risk
Kirsten, 1998[37]	Unknown	Unknown	High risk	High risk	Low risk	Unknown	Unknown	High risk
Kodric, 2009[36]	Unknown	Unknown	Unknown	Unknown	High risk	Unknown	Unknown	High risk

Author, Year	Sequence Generation	Allocation Concealment	Blinding of Participants, Personnel	Blinding of Outcome Assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias	Overall RoB
Koutsogiannis, 2000[65]	Low risk	Unknown	Low risk	Unknown	Unknown	Unknown	Unknown	Intermediate risk
Kurzaj, 2013[38]	Unknown	Unknown	High risk	Unknown	Unknown	Unknown	Unknown	High risk
Lellouche, 2016[39]	Low risk	Low risk	High risk	Unknown	Low risk	Unknown	Unknown	Intermediate risk
Leophonte, 1998[78]	Unknown	Unknown	High risk	Unknown	Low risk	Low risk	High risk	High risk
Leuppi, 2013[79]	Low risk	Low risk	Low risk	Low risk	Low risk	Unknown	Unknown	Low risk
Liao, 2015[40]	Unknown	Unknown	Unknown	Low risk	Low risk	Unknown	Low risk	High risk
LIor, 2009[80]	Unknown	Unknown	Low risk	Unknown	Low risk	Unknown	Low risk	High risk
Llor, 2012[11]	Low risk	Low risk	Low risk	Unknown	Low risk	Low risk	Unknown	Low risk
Mahmoud Abd El Hafiz, 2013[41]	Unknown	Unknown	Low risk	Unknown	Unknown	Unknown	Unknown	High risk
Maltais, 2002[12]	Unknown	Unknown	Low risk	Unknown	High risk	Unknown	High risk	High risk
Mirici, 2003[81]	Low risk	Low risk	Low risk	Unknown	Low risk	Unknown	Unknown	Low risk
Moayyedi, 1995[66]	Unknown	Unknown	Low risk	Unknown	High risk	Unknown	Low risk	High risk
Moretti, 2015[42]	Unknown	Unknown	High risk	Unknown	Low risk	Low risk	High risk	High risk
Mukerji, 2015[43]	Low risk	Low risk	Low risk	Unknown	Low risk	Unknown	Low risk	Low risk
Niewoehner, 1999[13]	Unknown	Unknown	Low risk	Unknown	Low risk	Low risk	High risk	High risk
Ogasawara, 2018[44]	Low risk	Low risk	Unknown	Unknown	Low risk	Unknown	Low risk	Low risk
Oncu, 2017[45]	Low risk	Unknown	High risk	Unknown	High risk	Unknown	Low risk	High risk
Osadnik, 2014[46]	Low risk	Low risk	High risk	Low risk	Low risk	Unknown	Low risk	Low risk
Perri, 1985[67]	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	High risk
Petitpretz, 2007[82]	Low risk	Unknown	High risk	High risk	High risk	Unknown	High risk	High risk
Phillips, 1993[83]	Unknown	Unknown	High risk	Low risk	High risk	Unknown	Unknown	High risk
Pourrashid, 2018[47]	Low risk	Unknown	Low risk	Unknown	High risk	Unknown	Low risk	High risk
Rhee, 2015[84]	Low risk	Unknown	Low risk	Low risk	High risk	Unknown	High risk	High risk
Rice, 1987[48]	Low risk	Low risk	Low risk	Low risk	Low risk	Unknown	Unknown	Low risk

Author, Year	Sequence Generation	Allocation Concealment	Blinding of Participants, Personnel	Blinding of Outcome Assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias	Overall RoB
Rizzato, 1998[85]	Unknown	Unknown	Low risk	Unknown	Unknown	Unknown	High risk	High risk
Roede, 2007[86]	Low risk	Unknown	Low risk	Unknown	Low risk	Unknown	Unknown	Intermediate risk
Ruiz-Gonzalez, 2007[87]	Low risk	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	High risk
Sanjari, 2015[49]	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	High risk	Intermediate risk
Saudny-Unterberger, 1997[50]	Unknown	Unknown	High risk	Low risk	High risk	Unknown	Unknown	High risk
Sayiner, 2001[88]	Low risk	Low risk	High risk	Unknown	Low risk	Unknown	Unknown	Intermediate risk
Seidenfeld, 1984[51]	Low risk	Low risk	Low risk	Unknown	Unknown	Unknown	Unknown	Intermediate risk
Skorodin, 1995[52]	Unknown	Unknown	Low risk	Unknown	Unknown	Unknown	Unknown	High risk
Solooki, 2014[53]	Unknown	Unknown	Low risk	Unknown	Unknown	Unknown	Low risk	High risk
Soltaninejad, 2016[54]	Unknown	Unknown	Low risk	Unknown	Unknown	Unknown	Low risk	High risk
Stallberg, 2009[89]	Low risk	Low risk	Low risk	High risk	Low risk	Unknown	High risk	Intermediate risk
Sun, 2015[90]	Unknown	Unknown	Unknown	Unknown	Low risk	Unknown	Low risk	High risk
Tang, 2012[55]	Low risk	Low risk	High risk	Low risk	Low risk	Unknown	Unknown	Low risk
Thompson, 1996[14]	Unknown	Unknown	Low risk	Unknown	Unknown	Unknown	Unknown	High risk
Torres-Sanchez, 2017[56]	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk	Intermediate risk
Torres-Sanchez, 2017[57]	Low risk	Low risk	High risk	Unknown	Low risk	High risk	Low risk	Low risk
Troosters, 2010[58]	Low risk	Unknown	High risk	High risk	High risk	Unknown	High risk	High risk
Tumer, 2009[59]	High risk	Unknown	High risk	High risk	Low risk	Unknown	Unknown	High risk
Ucar, 2014[91]	Low risk	Unknown	Unknown	Unknown	High risk	Low risk	Unknown	High risk
Umut, 1999[92]	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	High risk
van Velzen, 2017[15]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Author, Year	Sequence Generation	Allocation Concealment	Blinding of Participants, Personnel	Blinding of Outcome Assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias	Overall RoB
van Zanten, 2007[93]	Unknown	Unknown	High risk	High risk	Low risk	Unknown	High risk	High risk
Vermeeren, 2004[60]	Unknown	Unknown	Low risk	Unknown	High risk	Unknown	Low risk	High risk
Wang, 2016[16]	Low risk	Low risk	Unknown	Low risk	Low risk	Unknown	Low risk	Low risk
Whitlock, 1995[94]	Unknown	Unknown	High risk	Unknown	High risk	Unknown	Unknown	High risk
Willaert, 2002[95]	Unknown	Unknown	Unknown	Unknown	High risk	Unknown	Unknown	High risk
Wilson, 2012[96]	Low risk	Unknown	Low risk	Unknown	High risk	Unknown	Low risk	High risk
Woodruff, 2011[61]	Unknown	Unknown	High risk	Unknown	High risk	Unknown	Low risk	High risk
Xiong, 2008[62]	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	High risk
Yohannes, 2003[63]	Unknown	Unknown	High risk	High risk	Low risk	Unknown	Unknown	High risk
Yoon, 2013[97]	Low risk	Unknown	Unknown	Unknown	Low risk	Unknown	Low risk	Intermediate risk
Zuin, 2005[64]	Low risk	Unknown	Low risk	Unknown	Unknown	Unknown	Unknown	Intermediate risk

ROB = risk of bias

Appendix F. Results From Included Studies

Table F.1. KQ1: Intervention description and conclusions

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Followup (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
Aaron, 2003[1]	Emergency department	1	1) Prednisone	Oral	40mg, 1x/24 hours (total of 40 mg/24 hours) for 10 days	Patients in the Prednisone group were found to have statistically significantly more improvements in FEV1 absolute values, and dyspnea (Chronic Respiratory Disease Index Questionnaire) than patients in the placebo group. There was no statistically significant difference in 30-day relapse, quality of life (Chronic Respiratory Disease Index Questionnaire.), hospitalizations, and mortality. Patients in the prednisone group were statistically significantly more likely to report increase in appetite, weight gain than patients in the placebo group. Serious adverse events requiring hospitalization were reported two cases in the prednisone group (1 for epistaxis, 1 for seizure) and 1 case in the placebo group (1 for schizophrenia).
			2) Placebo	Oral	Placebo, 1x/24 hours for 10 days	

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Followup (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
Albert, 1980[2]	Inpatient hospital floor	N/A	1) Methylprednisolone	IV	0.5mg/kg, 4x/24hours (total of 2mg/kg/24hours) for 3 days	The methylprednisolone group had a significantly larger increase in pre- and post-bronchodilator FEV1 than the placebo group. There was no statistically significant difference in mortality.
			2) Placebo	IV	Placebo 4x/24hours for 3 days	
Anthonisen, 1987[3]	Outpatient	N/A	1) Placebo	Oral	placebo matching prescribed antibiotic 10 days	The antibiotic group was found to have significantly more treatment success and less treatment failures than the placebo group. There was no statistically significant difference in the incidence of adverse events.
			2) Antibiotics	Oral	Trimethoprim-sulfamethoxazole: 160mg,800mg, 2x/24hours (total of 320mg/24hours, 1600mg/24hours) for 10 days. or Amoxicillin: 0.25g, 4x/24hours (total of 1g/24hours) for 10 days or Doxycycline: 200mg initially, followed by 0.1g, 1x/24hours (total of 0.1g/24hours) for 10 days	
Bathoorn, 2008[4] Non-inferiority trial	Outpatient Inpatient hospital floor	3	1) Budesonide + Formoterol	Inhalation and Oral	160µg, 4.5 µg, 4x/24hours (total of 640µg,189µg/24hours) for 14 days.	Patients in the budesonide + formoterol group and patients in the prednisolone group had significantly better symptom scores (Total Symptom Score) than
			2) Prednisolone	Inhalation and Oral	30mg, 1x/24hours (total of	

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Followup (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
					30mg/24hours) for 14 days	those in the placebo group. Patients in the Budesonide + Formoterol group had significantly better quality of life (Chronic Respiratory Disease Questionnaire) than those in the prednisolone group (p=0.02); however the difference between the budesonide + formoterol group and the placebo group was not significant. There was no statistically significant difference in FEV1, treatment failures between the groups. No hospital admission was reported in any of the three groups.
			3) Placebo	Inhalation and Oral	14 days	
Brusse-Keizer, 2014[5]	Outpatient	4	1) Antibiotics	Oral	Amoxicillin/Clavulanic Acid: 500mg,125mg, 3x/24hours (total of 1500mg,375mg/24hours) for 7 days	There was no statistically significant difference between the two groups in dyspnea (Chronic Respiratory Disease Questionnaire), repeat exacerbation, quality of life (Chronic Respiratory Disease Questionnaire), FEV1, total symptom scores (Clinical COPD Questionnaire), and relapse of ECOPD.
			2) Placebo	Oral	3x/24hours for 7 days	

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Followup (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
Daniels, 2010[6]	Inpatient hospital floor	1	1) Doxycycline	Oral	200mg, 1x/24hours (total of 200mg/24hours) for 7 days	At the end of treatment, patients in the doxycycline group were more likely to have clinical cure, better cough score (VAS), better total symptom score (Total Symptom Score), and better dyspnea (VAS) than those in the placebo group. At the end of the followup, there was no statistically significant difference between doxycycline and placebo in clinical cure, FEV1, total symptom scores, dyspnea, cough, and death.
			2) Placebo	Oral	200mg, 1x/24hours (total of 200mg/24hours) for 7 days	
Davies, 1999[7]	Emergency department, Inpatient hospital floor	1.5	1) Prednisolone	Oral	30mg, 1x/24hours (total of 30mg/24hours) for 14 days	Upon hospital discharge, the patients in the prednisolone group had significantly more increase in % predicted FEV1 than the placebo group. There was no statistically significant difference in repeat exacerbation and hospital readmissions.
			2) Placebo	Oral		
Emerman, 1989[8]	Emergency department	N/A	1) Methylprednisolone	IV	100mg for one time treatment for 1 day.	There was no statistically significant difference in % predicted FEV1 values and repeat exacerbation.
			2) Placebo	IV	100mg for one time treatment for 1 day.	
Gunen, 2007[9]	Inpatient hospital floor	1	1) Management without Systemic Corticosteroids	Inhalation		Patients in the nebulized budesonide group had statistically significant higher FEV1 % predicted

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Followup (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
			2) Prednisolone	IV	40mg, 1x/24hours (total of 40mg/24hours) for more than 10 days	than those in the prednisolone group or the management without systemic corticosteroids group. There was no statistically significant difference in hospital readmissions, repeat exacerbations, % predicted FEV1, and death.
			3) Nebulized Budesonide	Nebulized	1500µg, 4x/24hours (total of 0.5mg/24hours)	
Hassan, 2015[10]	Outpatient	21 days	1)Placebo	N/A	Matching placebo	Patients in the antibiotics group were found to have significantly higher clinical cures and lower clinical failures than patients in the placebo group. There was no statistically significant difference in FEV1 values.
			2) Antibiotic	N/A	Quinolone: 500mg, 2x/24hours (total of 1000mg/24hours) or Amoxicillin: 500mg, 3x/24hours (total of 1500mg/24hours) for 10 days	
Llor, 2012[11]	Outpatient	12	1Amoxicillin + Clavulanate	Oral	500mg, 125mg, 3x/24hours (total of 1500mg/24hours, 375mg/24hours) for 8 days	The amoxicillin + clavulanate group had statistically significant more clinical cure rates and less clinical failures than the placebo group.
			1)Placebo	Oral		
Maltais, 2002[12]	Inpatient hospital floor	0.25	1) Budesonide	Nebulized	2mg, 4x/24hours (total of 8mg/24hours for 3 days	The budesonide group and the prednisolone group had a significantly larger increase in absolute FEV1 than the placebo group. Increases in FEV1 were not significantly different in the budesonide group and the prednisolone group. There was no statistically
				Inhaled	Then: 2000µg, 1x/24hours (total of 2000µg/24hours) for 7 days	

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Followup (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
			2) Prednisolone	Oral	30mg, 2x/24hours (total of 60mg/24hours) for 3 days, then 40mg/24hours for 7 days	significant difference in dyspnea (Modified Borg Scale), need for intubation, and death between the three groups.
			3) Placebo	Nebulized	For 72 hours	
				Inhaled	For 7 days	
				Oral	For 72 hours, then for 7 days	
Niewoehner, 1999[13]	Emergency department	6	1) Glucocorticoid for 8 weeks	IV	Methylprednisolone: 125mg, 4x/24hours (total of 500mg/24hours) for 3 days	Patients in the 8-week glucocorticoid group and 2-week glucocorticoid group had significantly less clinical failures than the placebo group. There was no statistically significant difference in death, FEV1, need for intubations, and hospital readmissions.
				Oral	Prednisone: 60mg on days 4 through 7, 40mg on days 8 through 11, 20mg on days 12 through 43, 10mg on days 44 through 50, and 5mg on days 51 through 57	
			2) Glucocorticoid for 2 week	IV	Methylprednisolone: 125mg, 4x/24hours (total of 500mg/24hrs) for 3 days	
				Oral	Prednisone: 60mg on days 4 through 7, 40mg on days 8 through 11, and 20mg on days 12 through 15 Placebo capsules on days 16 through 57	
			3) Placebo	IV	5% dextrose solution: 125mg, 4x/24hrs (total of 500mg/24hrs) for 3 days	

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Followup (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
				Oral	Placebo capsules on days 4 through 57	
Thompson, 1996[14]	Outpatient	N/A	Prednisone	Oral	60mg, 1x/24hrs (total of 60mg/24hrs) for 3 days 40mg, 1x/24hrs (total of 40mg/24hrs) for 3 days 20mg 1x/24hrs (total of 20mg/24hrs) for 3 days	Patients in the prednisone group had statistically significant more increase in absolute FEV1 values and lower clinical failures than patients in the placebo group. There was no statistically significant difference in dyspnea scale (VAS).
			Placebo	Oral	Vitamin B6 for 9 days.	
van Velzen, 2017[15]	Outpatient	24	Doxycycline	Oral	100mg, 2x/24hrs (total of 200mg/24hrs) for 1 day. Then, 100mg, 1x/24hrs (total of 100mg/24hrs) 6 days.	There was no statistically significant difference in death, clinical failures, incidence of adverse events, or serious adverse events.
			Placebo	Oral		
Wang, 2016[16]	Inpatient hospital floor	1	Antibiotics		Variable and determined by physicians	There was no statistically significant difference in clinical cure, 30-day mortality, FEV1 % predicted, need for intubations, 30-day repeat exacerbation, 30-day hospital readmissions, and symptom scores (VAS).
			Management without Antibiotics			

* Study provided different numbers and conclusions. We used the numbers.

ECOPD = acute exacerbation of chronic obstructive pulmonary disease; COPD = chronic obstructive pulmonary disease; FEV1 = forced expiration volume in 1 second; g = gram; IV = intravenous; Kg = kilogram; mg = milligram; µg = microgram; N/A = not applicable; VAS = Visual Analog Scale

Table F.2. KQ2: Intervention description and conclusions

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
Abreu Gonzalez, 2006[17]	Inpatient hospital floor	N/A	1) Magnesium Sulfate	IV	1.5g dissolved in 100mL of 0.9%saline solution over 20min infusion, 1x/24hrs (total of 1.5g/24hrs) for 1 day	There was no statistically significant difference between magnesium sulfate and placebo in FEV1 values after 45 mins of application.
			2) Placebo	IV	100mL of 0.9%saline solution over 20min infusion, 1x/24hrs (total of 100mL/24hrs) for 1 day	
Austin, 2010[18]	Ambulance to hospital	N/A	1) High Flow /Free Flow Oxygen	N/A	8-10liters/min during ambulance ride and up to 30 mins in the ER (until blood gas analysis was taken)	Patients in the titrated oxygen group had significantly lower mortality than those in the high flow oxygen group (RR=0.22, 95% CI: 0.05 to 0.91). There was no statistically significant difference in need for intubation.
			2) Titrated Oxygen	N/A	During ambulance ride and up to 30 mins in the ER (until blood gas analysis was taken)	
Ayfer Aytemur, 2015[19]	Inpatient hospital floor	6	1) N-Acetylcysteine	Oral	200mg, 3x/24hrs (total of 600mg/24hrs) for 30 days	There was no statistically significant difference in FEV1, dyspnea (1-7 Scale), hospital admission, and recurrent exacerbations.
			2) Placebo	Oral	Identical-looking placebo for 30 days	
Basri, 2017[20]	Inpatient hospital floor	N/A	1) No Chest Physiotherapy	N/A	N/A	Patients in the chest physiotherapy group had significantly better dyspnea scores (VAS) than those without chest physiotherapy.
			2) Chest Physiotherapy	N/A	For 14 days.	
Bathoorn, 2008[4] Non-inferiority trial	Outpatient Inpatient hospital floor	3	1) Budesonide + Formoterol	Inhalation and Oral	160µg,4.5µg, 4x/24hrs (total of 640µg,189µg/24hrs) for 14 days.	Patients in the budesonide + formoterol group and patients in the prednisolone group had significantly better symptom scores (Total
			2) Prednisolone	Inhalation and Oral	30mg, 1x/24hrs (total of 30mg/24hrs) for 14 days	

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
			3) Placebo	Inhalation and Oral	For 14 days.	Symptom Score) than those in the placebo group. Patients in the Budesonide + Formoterol group had significantly better quality of life (Clinical COPD Questionnaire) than those in the prednisolone group (p=0.02); however the difference between the budesonide + formoterol group and the placebo group was not significant. There was no statistically significant difference in FEV1, treatment failures between the groups. No hospital admission was reported in any of the three groups.
Behnke, 2000[21]	Inpatient hospital floor	6	1) Aerobic Exercise	N/A	10 day walking training program in hospital followed by 60 day at home	The aerobic exercise group was found to have statistically significant

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
			2) Management without Aerobic Exercise	N/A	N/A	more improvement in 6-minute walking distance test, and dyspnea (measured by the modified categorical Borg Scale and the Transitional Dyspnea Index), and quality of life (measured by the Chronic Respiratory Disease Questionnaire). There was no significant difference in mortality (one death in each group), FEV1 absolute, repeat exacerbation, and number of withdrawals.
Black, 2004[22]	Inpatient hospital floor	N/A	1) N-acetylcysteine	Oral	600mg, 2x/24hrs (total of 1200mg/24hrs) for 7 days or until discharge whichever occurred first	There was no statistically significant difference in FEV1 values and dyspnea (Breathlessness Likert Scale) between the two groups.
			2) Placebo	Oral	600mg, 2x/24hrs (total of 1200mg/24hrs) for 7 days or until discharge whichever occurred first	
Borges, 2014[23]	Inpatient hospital floor	1	1) Resistance Training	N/A	A minimum of 3 sessions of whole-body resistance training program over 3 days.	The exercise training group was found to have significantly more improvements in 6-min walking distance test than the management without resistance training group. There was no statistically significant difference in FEV1, quality of life (Health-related Quality of Life), hospital readmission, and death.
			2) Management without Resistance Training	N/A	N/A	

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
Brown, 1987[24]	Outpatient Inpatient hospital floor	N/A	1) Chest Wall Vibration	N/A	Mechanical vibration for 15 mins on day 1. Positioning on day 2 over 2 days.	No statistically significant difference in FEV1 values were observed between the two groups.
			2) Positioning	N/A	Positioning on day 1. Mechanical vibration for 15 mins on day 2 over 2 days.	
Centanni, 2002 [25],Crossover RCT	Outpatient	N/A	1) Oxitropium	Inhaled	100µg puff, 2puffs (total of 200µg) for 2 days	There was a statistically significant improvement in FEV1 values 30 mins after inhalation of oxitropium. No significant improvements were found after inhalation of placebo.
			2) Placebo	Inhaled	100µg puff, 2puffs (total of 200µg) for 2 days	
Cox, 2018[26]	Outpatient Inpatient hospital floor	3	1) Aerobic Exercise	N/A	Four exercise sessions over 14 days in the patient's home	There was no significant difference between hospital pulmonary rehabilitation and usual care in 6-mins walking distance test, quality of life (COPD Assessment Test), repeat exacerbations, and hospital readmissions. No death was reported.
			2) Management without Aerobic Exercise	N/A	16 revolutions of the bike on both set of limbs, three times a day for 5 consecutive days	
Cross, 2012[27]	Inpatient hospital floor	6	1) Manual Chest Physiotherapy	N/A	Active Cycle of Breathing Technique: Mean: 2.53 sessions/ 11.9 mins per session	There was no significant difference in the SGRQ total score, the SGRQ symptom score, Breathlessness Cough and Sputum Scale (BCSS), and death.
			2) Management without Manual Chest Physiotherapy	N/A	N/A	
Du, 2018[28] 10254	Inpatient hospital floor	N/A	1) Simvastatin	Oral	20mg, 1x/24 hours (total of 20mg/24 hours) for 14 days	Patients in the simvastatin group

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
			2) Placebo	NR	NR	reported significantly higher FEV1% values after the intervention than those in the placebo group.
Duffy, 2005[29]	Emergency department	1.5	1)Placebo	IV		There was no statistically significant difference in FEV1, dyspnea, (BORG Scale) death, and symptom scores (VAS).
			2)Aminophylline	IV	5mg/kg over 30 mins for 5 days.	
Eaton, 2009[30]	Outpatient, Inpatient hospital floor	3	1) Early Pulmonary Rehabilitation	N/A	1-h sessions of supervised exercise training, twice weekly for 56 days.	There was no statistically significant difference in hospital readmission, dyspnea score (Modified Medical Research Council Questionnaire), and 6-min walking distance test. No adverse events were reported in any group.
			2) Management without Early Rehabilitation	N/A		
Edwards, 2013[31]	N/A	N/A	1)Placebo	Nebulized	Isotonic saline: 2.5 ml 3 times at 30 min intervals for 1 day.	There was no statistically significant difference in FEV1. No clinically significant adverse events were reported.
			2)Magnesium Sulfate	Nebulized	2.5 mg salbutamol mixed with 2.5 ml isotonic magnesium sulphate (151mg) 3 times at 30 min intervals for 1 day.	
Goktalay, 2013[32]	Inpatient hospital floor	N/A	1) Management without High-frequency Chest Wall Oscillation Therapy	N/A	N/A	There was no statistically significant difference in FEV1, Modified Medical Research Council dyspnea scale, and 6-min walking distance test.
			2)High-frequency Chest Wall Oscillation Therapy	N/A	20 mins, 3x/24hrs (total of 60 mins) for 5 days Application and oscillation frequency were standardized at 20 Hz and 10 Hz	

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
Greening, 2014[33]	Inpatient hospital floor	12	1) Early Pulmonary Rehabilitation	N/A	Daily timed walks and Daily strength training, comprising three sets of eight repetitions resistance training exercises with weights for 10 days.	There was no significant difference between the two groups in hospital readmissions.
			2) Management without Pulmonary Rehabilitation	N/A		
Greulich, 2014[34]	Inpatient hospital floor	N/A	1) Management without Whole Body Vibration	N/AN/A	Standard program: 5 min mobilization, 5 min passive movement, and 10 min respiratory exercises	Patients in the Whole Body Vibration group had statistically significant better outcomes in 6-minute walking distance test, and quality of life (SGRQ). There was no statistically significant difference in % predicted FEV1 values.
			2)Whole Body Vibration	N/A	Standard program: 5 min mobilization, 5 min passive movement, and 10 min respiratory exercises complemented with sessions on the WBV device	
Gunen, 2007[9]	Inpatient hospital floor	1	1) Management without Systemic Corticosteroids	Inhalation	For 10 days.	Patients in the nebulized budesonide group had statistically significant higher FEV1 % predicted than those in the prednisolone group or the management without systemic corticosteroids group. There was no statistically significant difference in hospital readmissions, repeat exacerbations, % predicted FEV1, and death.
			2)Prednisolone	IV	40mg, 1x/24hrs (total of 40mg/24hrs) for 10 days	
			3)Nebulized Budesonide	Nebulized	1500µg, 4x/24hrs (total of 0.5mg/24hrs) for 10 days.	

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
He, 2015[35]	Inpatient hospital floor	N/A	1) Early Pulmonary Rehabilitation	N/A	Each PR session included exercise training, relaxation, breathing retraining and education (from the second day of admission until discharge) for a mean of 10 days	Patients in the pulmonary rehabilitation group were found to have significantly more improvements in 6-minute walking distance test (P<0.001), dyspnea (Modified Medical Research Council Dyspnea Scale) than patients in the routine care group.
			2) Management without Early Rehabilitation	N/A	Mean of 10 days	
Kirsten, 1998[37]	Inpatient hospital floor	N/A	1) Aerobic Exercise	N/A	6-min treadmill walking test and five walking sessions per day for 10 days	There was no statistical difference between the two groups in 6-minute walking distance test, FEV1 % predicted,
			2) Management without Aerobic Exercise	N/A		
Kodric, 2009[36]	Inpatient hospital floor	6	1) Management without Chest Physiotherapy	N/A	N/A	The chest physiotherapy group had significantly more improvements in the Borg scale (p<0.01) than the management without chest physiotherapy group. There was no statistically significant difference in repeat exacerbations, hospital readmissions, % predicted FEV1 value, quality of life, or the Medical Research Council Dyspnea scale.
			2) Chest Physiotherapy ELTGOL (expiration with the glottis open in the lateral posture)	N/A	For 7 days	
Kurzaj, 2013[38]	Inpatient hospital floor	N/A	1)Specialized Physiotherapy	N/A	Series of 6 massages, each lasting for 30 mins for 7 days.	Patients in the specialized physiotherapy group had significantly more

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
			2) Management without Specialized Physiotherapy	N/A	N/A	improvements in % predicted FEV1 values. There was no statistically significant difference in 6 –minute walking distance tests, and dyspnea (Modified Medical Research Council Dyspnea Scale).
Lellouche, 2016[39]	Inpatient hospital floor	6	1)Free02 device oxygen titration	Inhalation	Oxygen flow 0-20 liters /min	There was no statistically significant difference in need for intubation, ICU admission, and hospital readmissions.
			2)Manual Oxygen Titration	Inhalation	N/A	
Liao, 2015[40]	Inpatient hospital floor	N/A	1) Early Pulmonary Rehabilitation	N/A	RP sessions were conducted a minimum of twice per day for 10 mins per session for 4 days.	The respiratory rehabilitation group had statistically significant better outcomes in dyspnea (Modified Borg Scale), 6-minute walking distance test, and frequency of coughing.
			2) Management without Early Rehabilitation	N/A	Usual care and health education for 4 days.	
Mahmoud Abd El Hafiz, 2013[41]	Inpatient hospital floor	N/A	1) Management without N-acetylcysteine	N/A	Standard COPD exacerbation treatment : according to GOLD 2011 (systemic glucocorticoids oral prednisolone 30-40 mg / day, short acting B2 agonist (SABA) salbutamol and antibiotics)for 10 days	Patients in the high dose N-acetyl Cysteine group had significantly higher % predicted FEV1 than those in the low dose group and the management without N-acetylcysteine group. % predicted FEV1 was not statistically significant difference between the low dose group and the
			2) Low Dose N-acetylcysteine	N/A	Standard treatment + N-acetyl Cysteine: 200mg, 3x/24hrs (total of 600mg/24hrs) for 10 days	

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
			3) High Dose N-acetylcysteine	N/A	Standard treatment + N-acetyl Cysteine: 400mg, 3x/24hrs (total of 1200mg/24hrs) for 10 days	Management without N-acetylcysteine group.
Maltais, 2002[12]	Inpatient hospital floor	0.25	1) Budesonide	Nebulized	2mg, 4x/24hrs (total of 8mg/24hrs for 3 days	The budesonide group and the prednisolone group had a significantly larger increase in absolute FEV1 than the placebo group. Increases in FEV1 were not significantly different in the budesonide group and the prednisolone group. There was no statistically significant difference in dyspnea (Modified Borg Scale), need for intubation, and death between the three groups.
				Inhaled	Then: 2000µg, 1x/24hrs (total of 2000µg/24hrs) for 7 days	
			2) Prednisolone	Oral	30mg, 2x/24hrs (total of 60mg/24hrs) for 3 days, then 40mg/24hrs for 7 days	
			3) Placebo	Nebulized	For 72 hours	
				Inhaled	For 7 days	
				Oral	For 72 hours, then for 7 days	
Moretti, 2015[42]	Inpatient hospital floor	2	1) Erdosteine	Oral	300mg, 3x/24hrs (total of 900mg/24hrs) for 10 days	After intervention, the erdosteine group had

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
			2) Management without Erdosteine	N/A	N/A	significantly more improvements in % predicted FEV1 and Breathlessness-Sputum-Cough Scale than the management without erdosteine group. However, the difference was not significantly in the followup. After the 2-month followup, the erdosteine group had significantly less repeat exacerbations than those in the placebo group.
Mukerji, 2015[43]	Emergency department	N/A	1) Magnesium Sulfate	IV	2g magnesium sulphate made up to 20 mins in 0.9% sodium chloride solution (saline) over 15 mins for 1 day.	Patients in the magnesium sulphate group had significantly more increase in absolute FEV1 values than those in the placebo group. There was no statistically significant difference in need for intubation.
			2) Placebo	IV	20 ml of saline over 15 mins for 1 day.	
Ogasawar, 2018[44] 10048	Inpatient hospital floor	N/A	1) Omega-3 fatty acid anriched diet (Eicosapentaenoic acid) acid).	Oral	1g, 1x/24 hours (total of 1g/24 hours)	There was no statistically difference between the two groups in physical activities (steps per day), dyspnea (Modified Medical Research Council Dyspnea Scale), and quality of life (COPD Assessment Test).
			2) Usual Diet	Oral	1g, 1x/24 hours (total of 1g/24 hours)	
Oncu, 2017[45]	Outpatient, Inpatient hospital floor	N/A	1) Transcutaneous Electrical Nerve Stimulation	Transcutaneous	20 sessions (TENS device) each for 45 minute application once a day for 20 days.	Patients in the stimulation group had significantly more improvements in 6-

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
			2) Management without Transcutaneous Electrical Nerve Stimulation	Transcutaneous	20 sessions (TENS device without electrical output) each for 45- minute application once a day for 20 days.	minute walking distance test than patients in the placebo group. There was no statistically significant difference in absolute FEV1 values, quality of life (St George's Respiratory Questionnaire), and dyspnea (Medical Research Council Dyspnea Scale).
Osadnik, 2014[46]	Inpatient hospital floor	6	1) Management without Positive Expiratory Pressure	N/A	N/A	There was no statistically significant difference in modified Medical Research Council dyspnea scale, FEV1 % predicted, the Breathlessness, Cough and Sputum Scale, quality of life (St George's Respiratory Questionnaire), repeat exacerbations, 6-minute walking distance test, and hospital admissions.
			2) Positive Expiratory Pressure	Mask	3session/ day, (five repetitions for each session, as tolerated for approximately 20 mins duration, one session was supervised), daily therapy continued until hospital discharge or 24 h without sputum expectoration, whichever came first	
	Inpatient hospital floor	4	1) Placebo	IM	Single injection	

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
Pourrashid, 2018[47]			2) Vitamin D3	IM	Single injection of 300,000 IU	At the end of followup, the Vitamin D3 group had significantly more improvements in quality of life (St George's Respiratory Questionnaire, p<0.001). There was no statistically significant difference in mortality, hospital readmissions, and dyspnea (Modified Medical Research Council Dyspnea Scale).
Rice, 1987[48]	Emergency department, outpatient	N/A	1) Aminophylline	IV	Loading dose: 6mg/kg or 3mg/kg based on time of last administered dose of standard or sustained release Theophylline. Maintenance dose: 0.5 mg/kg, or 0.3mg/kg to achieve the desired serum theophylline levels of 72 to 94µmol/ L An additional loading dose of 1 mg/kg body weight was given for each desired increase of 11µmol/ L in the Theophylline level for 3 days.	There was no statistically significant difference in absolute FEV1 values, dyspnea (Verbal dyspnea index), need for intubations, and number of adverse events.
			2) Placebo	IV	Frequent adjustments were made to maintain the double-blinded nature of the study for 3 days.	
Sanjari, 2015[49]	Inpatient hospital floor	N/A	1) Placebo	Oral	Daily for 7 days	Patients in the calcitriol had significantly improvements in dyspnea
			2) Vitamin D	Oral	50000 IU, 1x/24hrs (total of 50000IU/24hrs) for 7 days	

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
			3) Calcitriol	Oral	0.25µg, 1x/24hrs (total of 0.25µg/24hrs) for 7 days	(Modified Medical Research Council Dyspnea Scale) than those in the placebo group or the Vitamin D group. No statistically significant difference was observed between the Vitamin D group and the placebo group in dyspnea. There was no statistically significant difference in % predicted FEV1.
Saudny-Unterberger, 1997[50]	Inpatient hospital floor	N/A	1) Nutritional Support	Oral	An additional 10 kcal/kg/day for 14 days.	There was no statistically significant difference in death, % predicted FEV1, dyspnea (Oxygen-cost diagram), 6-minute walking distance test, and quality of life (Genreal Well-being).
			2) Usual Diet	Oral	Usual feeding for 14 days.	
Seidenfeld, 1984[51]	Emergency department	6	1) Aminophylline	IV	5.6mg/kg over one hour by constant infusion pump, or reduced the dosage to 2.8mg/kg if the patient had received a theophylline-containing preparation within the previous six hours for 1 day.	There was no statistically significant difference in death, % predicted FEV1, dyspnea (1-5 scale), and cough (1-5 scale).
			2) Placebo	IV	For 1 day.	
Skorodin, 1995[52]	Emergency department	0.5	1) Magnesium Sulfate	IV	1.2g in 150ml of saline over 20 mins for 1 day.	There was no statistically significant difference in hospital admission and dyspnea score (Ordinal Scale) between the two groups.
			2)Placebo	IV	2.4ml over 20 mins for 1 day.	

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
Solooki, 2014[53]	Emergency department, Inpatient hospital floor	N/A	1)Magnesium Sulfate	IV	2g diluted in 100ml saline over 20 mins for 4 days.	There was no statistically significant difference in % predicted FEV1.
			2)Placebo	IV	100cc over 20 min for 4 days.	
Soltaninejad, 2016[54]	Inpatient Hospital	N/A	1)Gentamicin	Nebulized	80mg, 2x/24hrs (total of 160mg/24hrs) for 5 days	The gentamicin group had significantly more increase in absolute FEV1 values than the placebo group.
			2)Placebo	Nebulized	2cc distilled water, 2x/24hrs for 5 days	
Tang, 2012[55]	Inpatient hospital floor	N/A	1)Low-intensity Exercise Group	N/A	15-minute exercise sessions 2 times a day: walking at 40% of 3-min walk test for 7.5 min and completing 2 sets of an upper and lower limb resistance exercise with elasticized bands at each session	There was no statistically significant difference between the 3 groups in the 3-muntue walking distance test, upper limb muscle strength, FEV1 % predicted, and the incidence of adverse events.
			2)Moderate to high-intensity Exercise group	N/A	15-minute exercise sessions 2 times a day: walking at 70% of their 3-minute walk test for 7.5 mins and completing 2 sets of an upper and lower limb resistance exercise with elasticized bands at each session	
			3) Management without Exercise Training	N/A	Once-daily physical therapy, including sputum clearance techniques, mobility assessments, and functional training required for safe discharge	
	Inpatient hospital floor	N/A	1) Resistance Training	N/A	Cycling exercise intervention using a pedal exerciser	The exercise group had statistically significant

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
Torres-Sanchez, 2017[56]			2) Management without Resistance Training	N/A	Standard Care	more improvements in lower-limb strength, balance, and number of steps than the management without exercise training group.
Torres-Sanchez, 2017[57]	Inpatient hospital floor	N/A	1) Management without Exercise Training	N/A	Standard medical treatment for 9 days.	The resistance exercise group had significantly more improvement in dyspnea (Modified Borg scale) than the management without exercise Training group. The resistance exercise group and the controlled breathing + range of motion exercises group had significantly more improvements in quality of life (EQ-5D VAS) than the placebo. No significant difference was found in quality of life between the resistance exercise group and the controlled breathing + range of motion exercises group. There was no statistically significant difference in FEV1 % predicted between the 3 groups.
			2)Controlled breathing + Range of motion exercises	N/A	Daily 30-40min sessions of physical therapy (relaxation, pursed lips breathing, active expiration) plus active range of motion exercises for 9 days.	
			3)Resistance training	N/A	A 5-min warm-up starting at a low and progressively increased the resistance of the elastic bands and the repetitions performed. Global movements of upper and lower limbs were performed against resistance during 30–40 min in individual supervised sessions. The number of repetitions was adapted to the subject's response taken into account the perceived dyspnea and fatigue during the exercise performance for 9 days,	
Troosters, 2010[58]	Inpatient hospital floor	1	1) Management without Resistance Training	N/A	Standard doses of oral corticosteroids to treat the exacerbation for 7 days.	There was no statistically significant difference in 6-minute walking distance test and hospital readmission between the groups.

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
			2)Resistance training	N/A	3 sets of 8 repetitions quadriceps resistance training once a day for 7 days	
Tumer, 2009[59]	Inpatient hospital floor	N/A	1)Usual Diet	N/A	Standard hospital diet, 1800 kcal/day for 10 days.	There was no statistically significant difference in FEV1 values.
			2)High-fat, Low-carbohydrate Diet	N/A	50% hospital diet and 50% a specific enteral product (pulmocare and hospital diet composed of 50% fat and 28% CHO) for 10 days.	
Vermeeren, 2004[60]	Inpatient hospital floor	3	1)Nutritional Intervention	N/A	Respifor: 125mL, 3x/24hours (total of 375mL/24hours) 2.38 MJ/day, 20 energy% protein, 20 energy% fat and 60 energy% carbohydrate for 9 days.	There was no statistically significant difference in hospital admissions, FEV1 % predicted and dyspnea scores (VAS) between the two groups.
			2) Placebo(non-caloric fluid, vanilla flavored water)	N/A	vanilla flavored water: 125mL, 3x/24hours (total of 375mL/24hours) with 0 MJ/day for 9 days.	
Woodruff, 2011[61]	Inpatient hospital floor	1	1) Zileuton	N/A	600mg, 4x/24hours (total of 2400mg/24hours) for 14 days	Based on the intention-to-treat principle, patients in

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
			2)Placebo	N/A	For 14 days	the zileuton group had significantly higher FEV1 absolute values than those in the placebo group. However, the difference was not significant based on per-protocol analysis. There was no statistically significant difference in clinical failures, death, need for intubations, hospital 30-day hospital readmission, FEV1 % predicted, and adverse events.
Xiong, 2008[62]	Inpatient hospital floor	N/A	1) Atomization Inhalation	N/A	For 14 Days	Patients in the budesonide+ terbutaline, atomization inhalation group had statistically significant more improvements in FEV1 absolute and % predicted than those in the conventional group ($p<0.05$).
			2) Management without Atomization Inhalation	N/A	For 14 days.	
Yohannes, 2003[63]	Inpatient hospital floor	1	1)Gutter Frame + Supplemental Oxygen	N/A	Exercise: 15 min sessions, 3 times a day for 10 days. Oxygen: 2 L/min	There was no statistically significant difference in dyspnea (Borg Score), hospital readmission, and death.
			2)Gutter Frame + Supplemental Air	N/A	Exercise: 15 min sessions, 3 times a day for 10 days. Supplemental Air: 2 L/min	
			3)Rollator + Oxygen	N/A	Exercise: 15 min sessions, 3 times a day for 10 days. Oxygen: 2 L/min	

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up (months)	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
			4) Rollator + Air	N/A	Exercise: 15 min sessions, 3 times a day for 10 days. Supplemental Air: 2 L/min	
Zuin, 2005[64]	Outpatient	N/A	1)N-acetylcysteine 1200 mg	Oral	1200mg, 1x/24hours (total of 1200mg/24hours) for 10 days	No significant difference was found in cough frequency and intensity between the N-acetylcysteine 1200 mg and N-acetylcysteine 600 mg group. However, compared with the placebo group, patients in the two groups had significantly more improvements in cough intensity and cough frequency. There was no statistically significant difference in absolute FEV1 values.
			2)N-acetylcysteine 600mg	Oral	600mg, 1x/24hours (total of 600mg/24hours) for 10 days.	
			3)Placebo	Oral		

* Study provided different numbers and conclusions. We used the numbers.

CI = confidence interval; COPD = chronic obstructive pulmonary disease; ER = emergency room; EPA = eicosapentaenoic acid; FEV1 = forced expiration volume in 1 second; g = gram; GOLD = global initiative for chronic obstructive lung disease; Hz = hertz; ICU = intensive care unit; IM = intramuscular; IU = international unit; IV = intravenous; kcal = kilocalorie; kg = kilogram; L = liter; mg = milligram; min = minute; mJ = millijoule; ml = milliliter; N/A = not applicable; ONS = oral nutrition supplementation; PR = pulmonary rehabilitation; RR = relative risk; TENS = transcutaneous electrical nerve stimulation; VAS = visual analog scale; µg = microgram; µmol = micromole

Table F.3. KQ3: Intervention description and conclusions

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Followup	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
Koutsogiannis, 2000[65]	Emergency department	N/A	1) Salbutamol	Oral salbutamol, IB nebulizer	Salbutamol: 5mg at 0, 15 min, & 30 min Once IB 500µg at time 0 for 1 day.	There was no statistically significant difference in % predicted FEV1 and absolute FEV1 values.
			2)Ipratropium Bromide	Nebulizer, oral salbutamol.	Salbutamol: 5mg at time 0 & Ipratropium Bromide 500µg at 0, 15, 30min for 1 day.	
			3)Combined	Oral/nebulizer	Salbutamol 5mg & IB 500µg at time 0, 15, 30min	
Moayyedi, 1995[66]	Inpatient hospital floor	N/A	1) Salbutamol	Nebulized	5mg, 4x/24hours (total of 20mg/24hours)	There was no statistically significant difference in FEV1 values.
			2) Salbutamol + Ipratropium Bromide	Nebulized	Salbutamol: 5mg, 4x/24hours (total of 20mg/24hours) IB: 500µg, 4x/24hours (total of 2000µg/24hours)	
Perri, 1985[67]	Inpatient hospital floor	N/A	1) Salbutamol + Beclomethasone Dipropionate	Inhaled	Salbutamol: 75µg/puff, 2puffs, 3x/24hours (total of 450µg/24hours) for 28 days Beclomethasone Dipropionate: 50µg/puff, 2 puffs, 3x/24hours (total of 300µg/24hours) for 28 days	There was no statistically significant difference in % predicted FEV1 values, clinical cures, and clinical failures.
			2) Fenoterol	Inhaled	200µg/puff, 2 puffs, 3x/24hours (total of 1200µg/24hours) for 28 days	

FEV1 = forced expiration volume in 1 second; IB = ipratropium bromide; mg = milligram; µg = microgram; min/s = minutes; N/A = not applicable

Table F.4. KQ4: Intervention description and conclusions

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
Aggarwal, 2011[68]	Emergency department	0.5	1) Hydrocortisone i.v. Followed by Prednisolone oral	IV hydrocortisone then oral prednisolone	Hydrocortisone: 200mg, 4x/24hours (total of 800mg/24hours) for 14 day Prednisolone: 0.75mg/kg, 1x/24hours (total of 0.75mg/kg/24hours) for 14 days	After 2-week followup, the patients who received IV methylprednisolone and oral methylprednisolone were found to have significantly more improvements in FEV1 than the patients who received IV hydrocortisone and oral prednisolone. There was no statistically significant difference in mortality, need for intubation, treatment failure, and dyspnea (Medical Research Council Dyspnea Scale).
			2) Methylprednisolone iv, Followed by Methylprednisolone oral	IV then oral	IV Methylprednisolone: 125mg bolus then 40mg, 4x/24hours (total of 160mg/24hours) for 14 days Oral Methylprednisolone: 0.6mg/kg, 1x/24hours (total of 0.6mg/kg/24hours) for 14 days	
Andre-Alves, 2007[69]	Outpatient	1	1) Azithromycin	Oral	500mg, 1x/24hours (total of 500mg/24hours) for 3 days	Patients in the amoxicillin group had significantly higher FEV1 % predicted than those in the azithromycin group*. There was no statistically significant difference between azithromycin and amoxicillin in clinical cure, clinical failure, and absolute FEV1 values.*
			2) Amoxicillin	Oral	500mg, 3x/24hours (total of 1500mg/24hours) for 10 days	
Aubier, 2002[70]	Outpatient	1	1) Telithromycin	Oral	Telithromycin: 800mg, 1x/24hours (total of 800mg/24hours) for 5 days. Then Placebo for 5 days.	There was no statistically significant difference in clinical cure rate between the two groups. However, significantly fewer patients in the telithromycin group

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
			2) Amoxicillin + Clavulanate	Oral	500mg,125mg, 3x/24hours (total of 1500mg,375mg/24hours) for 10 days.	reported adverse events. No death was reported in either group.
Blasi, 2013[71]	Outpatient Inpatient hospital floor	6	1) Prulifloxacin	Oral	600mg, 1x/24hours (total of 600mg/24hours) for 7 days	The prulifloxacin group had statistically significant more repeat exacerbations than the levofloxacin group after 6 weeks of treatment. There was no statistically significant difference between the two groups in FEV1, symptoms scores (Total Symptom Score), dyspnea (Dyspnea Score 0-3), rate of clinical cure, rate of clinical failure, and repeat exacerbations at 6 months of treatment. No death was reported in any of the two groups.
			2) Levofloxacin	Oral	500mg, 1x/24hours (total of 500mg/24hours) for 7 days	
Dark, 1993[72]	Outpatient	1	1) Azithromycin	NR	500mg on day 1, 1x/24hours (total of 500mg/24hours), then 250mg, 1x/24hours (total of 250mg/24hours) on days 2 to 5.	There was no statistically significant difference between cefaclor and azithromycin in clinical cure, clinical failure, and number of adverse events.
			2) Cefaclor	NR	500mg, 3x/24hours (total of 1500mg/24hours) for 10 days	
de Jong, 2007[98]	Inpatient hospital floor	3	1)Intravenous Prednisolone	IV	60mg, 1x/24hours (total of 60mg/24hours) for 5 days	There was no statistically significant difference in treatment failure, quality of

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
			2)Oral Prednisolone	Oral	60mg, 1x/24hours (total of 60mg/24hours) for 5 days	life (SGRQ), absolute FEV1 values, hospital readmission for COPD, and death.
Ding, 2016[73] 20000	Inpatient hospital floor	12	1) Budesonide	Inhaled	2mg,1x3/24 hours (total of 6 mg/24 hours	There was no statistically significantly difference in quality of life (COPD Assessment Test), FEV1 absolute values, and repeat exacerbation between the groups
			2) Methylprednisolone	IV	40mg, 1x/24 hours (total of 40mg/24 hours	
Emami Ardestani, 2017[74]	Emergency department	N/A	1) Dexamethasone	IV	Methylprednisolone: 2mg/kg, 1x/24hours (total of 2mg/kg) for 3 days. Then, 40mg, 1x/24hours (total of 40mg/24hours) for 3 days. Then switched to oral Prednisone: 30mg, 1x/24hours (total of 30mg/24hours) tapered every 3 days with 5 mg decrease in dosage (for 15 days). Then inhaled budesonide: 400µg, 2x/24hours (total of 800µg/24hours) for at least 3 months.	Patients in the methylprednisolone group were significantly more likely to have improvement of cough than patients in the dexamethasone group. There was no statistically significant difference between groups for shortness of breath and general wellbeing.

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
			2) Methylprednisolone	IV	Dexamethasone: 0.375mg/kg, 1x/24hours (total of 0.375mg/kg/24hours), then gradually tapered for 7 to 14 days. Then Methylprednisolone: 30mg, 1x/24hours (total of 30mg/24hours), and continued by the same protocol as MP group for 6 days.	
Giusti, 2016[75]Non-inferiority trial	Inpatient hospital floor	12	1)Levofloxacin	Oral	500mg, 1x/24hours (total of 500mg/24hours) for 10 days (early interruption at 7 days if all symptoms resolved)	There was no statistically significant difference in repeat exacerbation, mortality, clinical cure, and Total Symptom Scores.
			2)Prulifloxacin	Oral	600mg, 1x/24hours (total of 600mg/24hours) for 10 days (early interruption at 7 days if all symptoms resolved)	
Gunen, 2007[9]	Inpatient hospital floor	1	1) Systemic Corticosteroids	Inhalation		Patients in the nebulized budesonide group had statistically significant higher FEV1 % predicted than those in the prednisolone group or the control group. There was no statistically significant difference in hospital readmissions, repeat exacerbations, FEV1 % predicted, and death.
			2)Prednisolone	IV	40mg, 1x/24hours (total of 40mg/24hours) for more than 10 days	
			3)Nebulized Budesonide	Nebulized	1500µg, 4x/24hours (total of 0.5mg/24hours)	

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
Hamacher, 1995[76]	Inpatient hospital floor	1	1) Meropenem	IV	1g infused over 20-30 mins, 3x/24hours (total of 3g/24hours) for a mean of 8.9 days	There was no statistically significant difference in clinical cure, clinical failure, and repeated exacerbation.
			2)Imipenem + Cilastatin	IV	1g of each infused over 30 mins, 3x/24hours (total of 3g/24hours) for a mean of 9 days	
Hasani, 1998[77]	Outpatient	1	1)Amoxicillin	Oral	500mg, 3x/24hours (total of 1500mg/24hours) for 7 days	There was no statistically significant difference in FEV1 values.
			2)Ciprofloxacin	Oral	500mg, 2x/24hours (total of 1000mg/24hours) for 7 days	
Leophonte, 1998[78]	N/A	0.75	1)Trovafloxacin 200 mg	N/A	200mg, 1x/24hours (total of 200mg/24hours) for 5 days	There was no statistically significant difference in clinical cure and death between the groups.
			2)Trovafloxacin 100 mg	N/A	100mg, 1x/24hours (total of 100mg/24hours) for 5 days	
Leuppi, 2013[79]	Emergency department, Inpatient hospital floor	6	1) Methylprednisolone (day 1), Prednisone (days 2-5), Placebo (days 6-14)	Methylprednisolone IV Prednisone PO Placebo PO	Methylprednisolone: 40mg, 1x/24hours (total of 40mg/24hours) for 1 day Prednisone: 40mg, 1x/24hours (total of 40mg/24hours) during days 2-5 Placebo days 6-14	There was no statistically significant difference in repeat exacerbations, death, need for intubations, and % predicted FEV1 values, dyspnea score (Medical Research Council Dyspnea Scale), quality of

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
			2) Methylprednisolone (day 1), Prednisone (days 2-14)	Methylprednisolone IV Prednisone PO	Methylprednisolone: 40mg, 1x/24hours (total of 40mg/24hours) for 1 day Prednisone: 40mg, 1x/24hours (total of 40mg/24hours) during days 2-14	life (Bronchitis-Associated Quality of Life).
LIor, 2009[80]Non-inferiority trial	Outpatient	1	1)Amoxicillin	Oral	500mg, 3x/24hours (total of 1500mg/24hours) for 10 days	There was no statistically significant difference between the two groups in clinical cure rates.
			2)Amoxicillin + Clavulanate	Oral	500mg, 125mg, 3x/24hours (total of 1500mg/24hours, 375mg/24hours) for 10 days	
Maltais, 2002[12]	Inpatient hospital floor	10 days	1) Budesonide	Nebulized	2mg, 4x/24hours (total of 8mg/24hours for 3 days	The budesonide group and the prednisolone group had a significantly larger increase in absolute FEV1 than the placebo group. Increases in FEV1 were not significantly different in the budesonide group and the prednisolone group. There was no statistically significant difference in dyspnea (Modified Borg Scale), need for intubation, and death between the three groups.
				Inhaled	Then: 2000µg, 1x/24hours (total of 2000µg/24hours) for 7 days	
			2) Prednisolone	Oral	30mg, 2x/24hours (total of 60mg/24hours) for 3 days, then 40mg/24hours for 7 days	
			3) Placebo	Nebulized	For 72 hours	
				Inhaled	For 7 days	
				Oral	For 72 hours, then for 7 days	
Mirici, 2003[81]	Emergency department, Inpatient hospital floor	N/A	1) Parenteral Corticosteroid (prednisolone)	IV	40mg, 1x/24hours (total of 40mg/24hours) for 10 days	No adverse events were reported in any of the two groups.

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
			2) Nebulized Corticosteroid (budesonide)	Nebulized	4mg, 2x/24hours (total of 8mg/24hours) for 10 days	
Niewoehner, 1999[13]	Emergency department	6	1) Glucocorticoid for 8 weeks	IV	Methylprednisolone: 125mg, 4x/24hours (total of 500mg/24hours) for 3 days	Patients in the 8-week glucocorticoid group and 2-week glucocorticoid group had significantly less clinical failures than the placebo group. There was no statistically significant difference in death, FEV1, need for intubations, and hospital readmissions.
				Oral	Prednisone: 60mg on days 4 through 7, 40mg on days 8 through 11, 20mg on days 12 through 43, 10mg on days 44 through 50, and 5mg on days 51 through 57	
			2) Glucocorticoid for 2 week	IV	Methylprednisolone: 125mg, 4x/24hours (total of 500mg/24hours) for 3 days	
				Oral	Prednisone: 60mg on days 4 through 7, 40mg on days 8 through 11, and 20mg on days 12 through 15 Placebo capsules on days 16 through 57	
			3) Placebo	IV	5% dextrose solution: 125mg, 4x/24hours (total of 500mg/24hours) for 3 days	
				Oral	Placebo capsules on days 4 through 57	

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
Petitpretz, 2007[82]Non-inferiority trial	Outpatient	6	1) Levofloxacin	Oral	500mg, 1x/24hours (total of 500mg/24hours) for 10 days	There was no statistically significant difference in clinical cure rates, repeat exacerbation, and number of adverse events between the two groups.
			2) Cefuroxime/axetil	Oral	cefuroxime/axetil: 300.72mg (250mg cefuroxime), 2x/24hours (total of 601.44mg/24hours (500mg/24hours)) for 10 days	
Phillips, 1993[83]	Outpatient, Inpatient hospital floor	1	1) Cefpodoxime	Oral	200mg, 2x/24hours (total of 400mg/24hours) for 10 days	There was no statistically significant difference in clinical cures, clinical failures, repeat exacerbations, and incidence of adverse events.
			2) Cefaclor	Oral	250mg, 3x/24hours (total of 750mg/24hours) for 10 days	
Rhee, 2015[84]Non-inferiority trial	Outpatient	1	1) Zabofloxacin	Oral	367mg, 1x/24hours (total of 367mg/24hours) for 5 days	Patients in the zabofloxacin group had significantly better outcomes in symptoms (Exacerbations of Chronic Pulmonary Disease Tool, $p<0.01$) and quality of life (COPD Assessment Test, $p<0.01$). There was no statistically significant difference in clinical cures, and clinical failures, suggesting Zabofloxacin is not inferior to Moxifloxacin.
			2) Moxifloxacin	Oral	400mg, 1x/24hours (total of 400mg/24hours) for 7 days	
Rizzato, 1998[85]	Inpatient hospital floor	N/a	1) Deflazacort Hemisuccinate	IV	60mg, 1x/24hours (total of 60mg/24hours) for 7 days	There was no statistically significant difference in

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
			2) Methylprednisolone-ne	IV	40mg, 1x/24hours (total of 40mg/24hours) for 7 days	absolute FEV1 values and death.
Roede, 2007[86]Non-inferiority trial	Inpatient hospital floor	3	1) Amoxycillin + Clavulanic acid for 3 days	Oral/ IV	625mg, 4x/24hours (total of 2500mg/24hours) for 3 days. Then Placebo: 625mg, 4x/24hours (total of 2500mg/24hours) for 7 days.	There was no statistically significant difference in clinical cure, clinical failure, symptom scores (combined with shortness of breath, sputum volume, and sputum color), hospital readmissions, death, repeat exacerbations, and adverse events.
			2) Amoxycillin + Clavulanic acid for 10 days	Oral/ IV	Oral/ IV: 625mg, 4x/24hours (total of 2500mg/24hours) for 3 days. Then oral: 625mg, 4x/24hours (total of 2500mg/24hours) for 7 days.	
Ruiz-Gonzalez, 2007[87]	Emergency department, Inpatient hospital floor	6	1) Levofloxacin	Unclear	500mg, 1x/24hours (total of 500mg/24hours) for 10 days	Patients in the levofloxacin group had significantly less hospital admissions than patients

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
			2) Standard care (Clarithromycin, Cefuroxime, or Amoxicillin +Clavulanate)	Unclear	One of the following: Clarithromycin: 500mg, 2x/24hours (total of 1000mg/24hours). Cefuroxime axetil: 500mg, 2x/24hours (total of 1000mg/24hours). Amoxicillin/ Clavulanate: 875mg, 125mg, 3x/24hours (total of 2625mg, 375mg/24hours).	in the standard care group. There was no statistically significant difference in mortality, % predicted FEV1 and quality of life (Airways Questionnaire 20), and repeat exacerbations.
Sayiner, 2001[88]	Inpatient hospital floor	6	1) Methylprednisolone for 3 days	IV	0.5mg/kg, 4x/24hours (total of 2mg/kg/24jrs) for 3 days	Patients in the 10-day methylprednisolone group had significantly more increase in absolute FEV1 values than those in the 3-day group immediately after treatment. There was no statistically significant difference in repeat exacerbations, dyspnea (1-7 scale), and cough (1-7 scale).
			2) Methylprednisolone for 10 days	IV	0.5mg/kg, 4x/24hours (total of 2mg/kg/24jrs) for 3 days Then 0.5mg/kg, 2x/24hours (total of 1mg/kg/24hours) for 3 days and 0.5mg/kg, 1x/24hours (total of 0.5mg/kg/24hours) for 4 more days.	
Stallberg, 2009[89]Non-inferiority trial	Outpatient	3	1)Budesonide + Formoterol	Inhalation	Budesonide: 320µg, 4x/24hours (total of 1280µg/24hours) for 14 days Formoterol: 9µg, 4x/24hours (total of 36µg/24hours) for 14 days	There was no statistically significant difference in % predicted and absolute FEV1 values, quality of life (Clinical COPD Questionnaire), treatment failures, repeat

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
			2)Prednisolone + Formoterol	Inhalation	Prednisone: 30mg, 1x/24hours (total of 30mg/24hours) Formoterol 9µg, 2x/24hours (total of 18µg) for 14 days.	exacerbations, hospitalization, dyspnea (Difficulty Breathing), cough (0-4 Scale), and incidence of adverse events.
Sun, 2015[90]	Inpatient hospital floor	0.25	1)Inhaled Budesonide	Inhalation	3mg, 2x/24hours (total of 6mg/24hours) for 10 days	Patients in the inhaled budesonide group had significantly lower incidence of adverse events than those in the systemic methylprednisolone group. There was no statistically significant difference in % predicted FEV1 values.
			2)Systemic Methylprednisolone	Injection and oral	Methylprednisolone acetate injectable suspension: 40mg, 4x/24hours (total of 160mg/24hours) for 3 days. Methylprednisolone tablets: 8mg, 2x/24hours (total of 16mg/24hours) for 7 days.	
Ucar, 2014[91]	Inpatient hospital floor	N/A	1)Methylprednisolone	IV	40mg, 1x/24hours (total of 40mg/24hours)	There was no statistically significant difference in FEV1 % predicted, and dyspnea (Borg Scale) between the groups.
			2)Budesonide 4mg	Nebulized	2mg, 2x/24hours (total of 4mg/24hours)	
			3)Budesonide 8mg	Nebulized	4mg, 2x/24hours(total 8/24hours)	
Umut, 1999[92]	Inpatient hospital floor	N/A	1)Azithromycin	N/A	500mg, 1x/24hours (total of 500mg/24hrs) for 3 days	There was no statistically significant difference in absolute FEV1 and clinical cure between the groups.
			2)Ampicillin + Sulbactam	N/A	1.5g, 1x/24hrs (total of 1.5g/24hrs) for 10 days	
			3)Ciprofloxacin	N/A	1g, 1x/24hrs (total of 1g/24hrs) for 10 days	
			4)Cefaclor	N/A	1.5g, 1x/24hours (total of 1.5g/24hours) for 10 days	

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
van Zanten, 2007[93]	Inpatient hospital floor	N/A	1)Continuous Cefotaxime	IV	An initial loading dose of 1g given over 30 min. Then, a continuous infusion of cefotaxime (2 g/ 24hours) for 7 days	There was no statistically significant difference in clinical cures and clinical failures.
			2)Intermittent Cefotaxime	IV	1g, 3x/24hours (total of 3g/24hours) for 7 days.	
Whitlock, 1995[94]	Outpatient	0.5	1)Azithromycin	Oral	250mg, 2x/24hours (total of 500mg/24hours) for 1 day Then, 250mg, 1x/24hours (total of 250mg/24hours) for 4 days.	There was no statistically significant difference in clinical cures, clinical failures, Incomplete cure and incidence of adverse events between the two groups.
			2)Amoxicillin + Clavulanate	Oral	500mg, 3x/24hours (total of 1500mg/24hours) for 10 days	

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
Willaert, 2002[95]	Inpatient hospital floor	1	1)Intravenous Steroids + Aerosol Bronchodilators	N/A	Methylprednisolone IV: 40mg, 1x/24hours (total of 40mg/24hours) for 10 days. Then, 20mg, 1x/24hours (total of 20mg/24hours). Then Methylprednisolone PO: 4mg, 1x/24hours (total of 4mg/24hours) for 4 days Aerosol Salbutamol: 10mg, 1x/24hours (total of 10mg/24hours) Ipratropium bromide: 1 mg, 1x/24hours (total of 1mg/24hours) administered in 4 aerosols.	There was no statistically significant difference in FEV1 absolute, quality of life (Chronic Respiratory Disease Index Questionnaire), clinical failures, death, hospital readmission, and ICU admissions.
			2)Oral steroids + Multiple Dose Inhaler Bronchodilators	N/A	Oral Methylprednisolone: 32mg, 1x/24hours (total of 32mg/24hours) for 1 week Then, 24mg, 1x/24hours (total of 24mg/24hours) for 4 days Then 20mg, 1x/24hours (total of 20mg/24hours) for 1 week Duovent: 4x4 puffs/day with a cumulative dose of 1.6mg/24hours Fenoterol and 640mg/24hours Ipratropium Bromide	

Author, Year, study design*	Study setting (outpatients, hospitalized patients)	Length of Follow up	Intervention(s) and comparator	Route of administration	Dose and Duration	Conclusion
Wilson, 2012[96]Non-inferiority trial	Outpatient	2	Moxifloxacin	Oral	400mg, 4x/24hours (total of 1600mg/24hours) for 5 days.	There was no statistically significant difference in clinical failures, death, hospital admissions, quality of life (SGRQ), FEV1 absolute and % predicted, and incidence of adverse events.
			Amoxicillin + Clavulanic Acid	Oral	875mg,125mg, 2x/24hours (total of 1750mg,250mg/24hours) for 7 days	
Yoon, 2013[97]	Outpatient	0.25	Levofloxacin	N/A	500mg, 1x/24hours (total of 500mg/24hours) for 7 days	There was no statistically significant difference in clinical cures, clinical failures, and adverse events between the two groups. No death was reported.
			Cefuroxime	N/A	Moderate exacerbations: 250mg, 2x/24hours (total of 500mg/24hours) for 7 days. Sever exacerbations: 500mg, 2x/24hours (total of 1000mg/24hours) for 7 days.	

* Study provided different numbers and conclusions. We used the numbers.

COPD = chronic obstructive pulmonary disease; FEV1 = forced expiration volume in 1 second; g = gram; ICU = intensive care unit; IV = intravenous; Kg = kilogram; mg = milligram; µg = microgram; Min/s = minutes; MP = Methylprednisolone; N/A = not applicable; N/A = not reported; SGRQ = St. George Respiratory Questionnaire; VAS = Visual Analog Scale

Appendix G. Results by Severity

Table G.1. KQ1 results: mild ECOPD severity- antibiotics vs. placebo

Outcome	Findings	Study Design and Sample Size
Mortality Longest Followup	OR: 1.28; 95% CI: 0.49 to 3.33, I^2=N/A	1 RCT[15] with 305 patients
Dyspnea (questionnaire: CRQ, dyspnea) Longest Followup	WMD: 0.00; 95% CI: -0.97 to 0.97, I^2=N/A	1 RCT[5] with 35 patients
Other Symptoms CCQ symptom score End of Intervention	WMD: 0.00; 95% CI: -0.66 to 0.66, I^2=N/A	1 RCT[5] with 35 patients
Quality of Life CRQ Longest Followup	WMD: 0.00; 95% CI: -1.79 to 1.79, I^2=N/A	1 RCT[5] with 35 patients
FEV1 % Predicted Longest Followup	WMD: -0.80; 95% CI: -6.67 to 5.07, I^2=N/A	1 RCT[5] with 35 patients
FEV1 Absolute End of Intervention	WMD: 1.30; 95% CI: -3.83 to 6.43, I^2=N/A	1 RCT[10] with 100 patients
FEV1 Absolute Longest Followup	WMD: -0.05; 95% CI: -0.21 to 0.11, I^2=N/A	1 RCT[5] with 35 patients
Repeat Exacerbation End of Intervention	OR: 2.24; 95% CI: 0.58 to 8.69, I^2=N/A	1 RCT[5] with 35 patients
Repeat Exacerbation 30 days	OR: 2.00; 95% CI: 0.16 to 24.33, I^2=N/A	1 RCT[5] with 35 patients
Repeat Exacerbation 6 Month	OR: 2.24; 95% CI: 0.58 to 8.69, I^2=N/A	1 RCT[5] with 35 patients
Repeat Exacerbation Longest Followup	OR: 2.24; 95% CI: 0.58 to 8.69, I^2=N/A	1 RCT[5] with 35 patients
Clinical Cure End of Intervention	OR: 2.04; 95% CI: 1.33 to 3.12, I^2=0.0	2 RCTs[10, 11] with 418 patients
Clinical Cure Longest Followup	OR: 1.92; 95% CI: 1.18 to 3.11, I^2=N/A	2 RCTs[5, 11] with 353 patients
Clinical Failure End of Intervention	OR: 0.54; 95% CI: 0.34 to 0.86, I^2=20.32	2 RCTs[10, 15] with 405 patients
Clinical Failure Longest Followup	OR: 0.96; 95% CI: 0.6 to 1.51, I^2=N/A	1 RCT[15] with 305 patients

CCQ = clinical COPD question are; CI = confidence interval; CRQ = clinical respiratory questionnaire; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; SMD = standardized mean difference; WMD = weighted mean difference

Table G.2. KQ1 results: moderate-severe ECOPD severity-antibiotics vs. control

Comparison	Outcome	Findings	Study Design and Sample Size
Antibiotics vs. Management without Antibiotics	Mortality End of Intervention	OR: 2.02; 95% CI: 0.18 to 22.66, I^2=N/A	1 RCT[16] with 194 patients
Antibiotics vs. Placebo or Management without Antibiotics	Mortality Longest Followup	OR: 2.58; 95% CI: 0.89 to 7.46, I^2=0.0	2 RCTs[6, 16] with 459 patients
Antibiotics vs. Placebo	Dyspnea (numeric scale: VAS) End of Intervention	WMD: -0.80; 95% CI: -1.49 to -0.11, I^2=N/A	1 RCT[6] with 265 patients
Antibiotics vs. Placebo	Dyspnea (numeric scale: VAS) Longest Followup	WMD: -0.60; 95% CI: -1.27 to 0.07, I^2=N/A	1 RCT [6]with 265 patients
Antibiotics vs. Placebo	Cough (VAS) End of Intervention	WMD: -1.10; 95% CI: -1.80 to -0.40, I^2=N/A	1 RCT[6] with 265 patients
Antibiotics vs. Placebo	Cough (VAS) Longest Followup	WMD: -0.40; 95% CI: -1.13 to 0.33, I^2=N/A	1 RCT[6] with 265 patients
Antibiotics vs. Placebo or Management without Antibiotics	Other Symptoms (Total Symptom Score) End of Intervention	WMD: -0.54; 95% CI: -1.60 to 0.53, I^2=61.53	2 RCTs[6, 16] with 459 patients
Antibiotics vs. Placebo	Other Symptoms (Total Symptom Score) Longest Followup	WMD: -1.10; 95% CI: -3.13 to 1.11, I^2=N/A	1 RCT [6] with 265 patients
Antibiotics vs. Management without Antibiotics	FEV1 % Predicted End of Intervention	WMD: -1.70; 95% CI: -7.31 to 3.91, I^2=N/A	1 RCT[16] with 194 patients
Antibiotics vs. Placebo	FEV1 Absolute End of Intervention	WMD: 0.05; 95% CI: -0.01 to 0.11, I^2=N/A	1 RCT[6] with 265 patients
Antibiotics vs. Placebo	FEV1 Absolute Longest Followup	WMD: 0.07; 95% CI: 0 to 0.14, I^2=N/A	1 RCT[6] with 265 patients
Antibiotics vs. Management without Antibiotics	Hospital Readmission 30 days	OR: 1.72; 95% CI: 0.68 to 4.36, I^2=N/A	1 RCT[16] with 194 patients
Antibiotics vs. Management without Antibiotics vs. Management without Antibiotics	Repeat Exacerbation End of Intervention	OR: 1.66; 95% CI: 0.73 to 3.76, I^2=N/A	1 RCT[16] with 194 patients
Antibiotics vs. Management without Antibiotics	Repeat Exacerbation 30 days	OR: 1.66; 95% CI: 0.73 to 3.76, I^2=N/A	1 RCT[16] with 194 patients
Antibiotics vs. Management without Antibiotics	Repeat Exacerbation Longest Followup	OR: 1.66; 95% CI: 0.73 to 3.76, I^2=N/A	1 RCT [16]with 194 patients
Antibiotics vs. Management without Antibiotics	Intubation End of Intervention	OR: 0.49; 95% CI: 0.04 to 5.55, I^2=N/A	1 RCT[16] with 194 patients
Antibiotics vs. Placebo	Clinical Cure End of Intervention	OR: 2.02; 95% CI: 1.23 to 3.32, I^2=N/A	1 RCT[6] with 265 patients
Antibiotics vs. Management without Antibiotics	Clinical Cure Longest Followup	OR: 1.30; 95% CI: 0.83 to 2.02, I^2=49.97	2 RCTs[6, 16] with 459 patients
Antibiotics vs. Placebo	Clinical Failure Longest Follow-up	OR: 0.68; 95% CI: 0.41 to 1.11, I^2=N/A	1 RCT[6] with 265 patients

CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; SMD = standardized mean difference; WMD = weighted mean difference; VAS = visual analog scale

Table G.3. KQ1 results: Mild Severity-systemic corticosteroids vs. placebo

Outcome	Findings	Study Design and Sample Size
Mortality End of Intervention	OR: 2.00; 95% CI: 0.18 to 22.55, I^2=N/A	1 RCT[1] with 147 patients
Dyspnea (numeric scale: VAS) End of Intervention	WMD: -13.10; 95% CI: -28.55 to 2.35, I^2=N/A	1 RCT[14] with 26 patients
FEV1 Absolute End of Intervention	WMD: 0.42; 95% CI: 0.3 to 0.54, I^2=92.95	2 RCTs[4, 14] with 56 patients
Clinical Failure End of Intervention	OR: 0.02; 95% CI: 0 to 0.49, I^2=N/A	1 RCT[14] with 26 patients
Clinical Failure Longest followup	OR: 0.50; 95% CI: 0.25 to 1, I^2=N/A	1 RCT[1] with 147 patients
Hospital admission Longest followup	OR: 0.47; 95% CI: 0.19 to 1.19, I^2=N/A	1 RCT[1] with 147 patients
QoL (CRQ) End of Intervention	WMD: 0.38; 95% CI: -0.09 to 0.85, I^2=N/A	1 RCT[1] with 147 patients

CI = confidence interval; CRQ = chronic respiratory questioner; N/A = not applicable; OR = odds ratio; QoL = quality of life; RCT = randomized controlled trial; SMD = standardized mean difference; WMD = weighted mean difference; VAS = visual analog scale

Table G.4. KQ1 results: Moderate-severe severity- systemic corticosteroids vs. control

Comparison	Outcome	Findings	Study Design and Sample Size
Systemic Corticosteroids vs. Placebo or Management without Systemic Corticosteroids	Mortality End of Intervention	OR: 1.55; 95% CI: 0.4 to 5.98, I^2=0.0	3 RCTs [9, 12, 13]with 363 patients
Systemic Corticosteroids vs. Placebo or Management without Systemic Corticosteroids	Mortality Longest Followup	OR: 0.89; 95% CI: 0.37 to 2.16, I^2=0.0	3 RCTs[7, 9, 13] with 353 patients
Systemic Corticosteroids vs. Placebo	Dyspnea (numeric scale: Modified Borg Scale) End of Intervention	WMD: -0.80; 95% CI: -1.65 to 0.05, I^2=N/A	1 RCT[12] with 128 patients
Systemic Corticosteroids vs. Placebo or Management without Systemic Corticosteroids	FEV1 % Predicted End of Intervention	WMD: 5.71; 95% CI: 1.40 to 10.03, I^2=0.0	3 RCTs[2, 7, 9] with 206 patients
Systemic Corticosteroids vs. Placebo	FEV1 % Predicted Longest Followup	WMD: 7.75; 95% CI: -0.30 to 15.80, I^2=0.62	2 RCTs[2, 7] with 100 patients
Systemic Corticosteroids vs. Placebo	FEV1 Absolute End of Intervention	WMD: 0.30; 95% CI: 0.18 to 0.42, I^2=N/A	1 RCT[7] with 56 patients
Systemic Corticosteroids vs. Placebo	Hospital Readmission 30 days	OR: 0.54; 95% CI: 0.10 to 2.88, I^2=N/A	1 RCT[13] with 191 patients

Comparison	Outcome	Findings	Study Design and Sample Size
Systemic Corticosteroids vs. Placebo	Hospital Readmission Longest Followup	OR: 1.07; 95% CI: 0.49 to 2.36, I^2=N/A	1 RCT [13]with 191 patients
Systemic Corticosteroids vs. Placebo or Management without Systemic Corticosteroids	Repeat Exacerbation End of Intervention	OR: 0.73; 95% CI: 0.35 to 1.52, I^2=34.27	2 RCTs[7, 9] with 162 patients
Systemic Corticosteroids vs. Placebo	Repeat Exacerbation 3 months	OR: 1.29; 95% CI: 0.40 to 4.13, I^2=N/A	1 RCT[13] with 56 patients
Systemic Corticosteroids vs. Placebo	Repeat Exacerbation Longest Followup	OR: 1.29; 95% CI: 0.40 to 4.13, I^2=N/A	1 RCT [13]with 56 patients
Systemic Corticosteroids vs. Placebo	Intubation End of Intervention	OR: 0.42; 95% CI: 0.06 to 2.68, I^2=0.0	2 RCTs[12, 13] with 319 patients
Systemic Corticosteroids vs. Placebo	Intubation Longest Followup	OR: 0.92; 95% CI: 0.15 to 5.66, I^2=N/A	1 RCT [13]with 191 patients
Systemic Corticosteroids vs. Placebo	Clinical Failure Longest Followup	OR: 1.52; 95% CI: 0.81 to 2.86, I^2=N/A	1 RCT[13] with 191 patients

CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; SMD = standardized mean difference; WMD = weighted mean difference

Table G.5. KQ2 results: Mild severity- mucolytics vs management without mucolytics.

Outcome	Findings	Study Design and Sample Size
FEV1 Absolute End of Intervention	WMD: 0.07; 95% CI: -0.14 to 0.28, I^2=N/A	1 RCT[64] with 83 patients

CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; SMD = standardized mean difference; WMD = weighted mean difference

Table G.6. KQ2 results: Moderate-severe severity - mucolytics vs placebo.

Outcome	Findings	Study Design and Sample Size
Dyspnea BCSS End of Intervention	WMD: -1.00; 95% CI: -0.56 to 0.44, I^2= N/A	1 RCT[58] with 40 patients
Dyspnea BCSS Longest Followup	WMD: -0.90; 95% CI: -1.80 to 0.02, I^2= N/A	1 RCT[58] with 40 patients
Dyspnea (numeric scale: Dyspnea, Breathlessness Likert Scale) End of intervention	WMD: -0.18; 95% CI: -0.43 to 0.06, I^2=0.00%	2 RCTs[19, 22] with 92 patients
FEV1 % Predicted End of Intervention	WMD: 1.98; 95% CI: 0.51 to 3.44, I^2=83.21%	2 RCTs[22, 42] patients 70 pts
FEV1 % Predicted Longest Followup	WMD: 8.30; 95% CI: -0.69 to 17.29, I^2= N/A	1 RCT[42] with 40 patients
FEV1 Absolute End of Intervention	WMD: 0.06; 95% CI: -0.27 to 0.39, I^2= N/A	1 RCT [19] with 42 patients
Repeat Exacerbation 1 month	OR: 0.05; 95% CI: 0 to 1.04, I^2= N/A	1 RCT[42] with 40 patients
Repeat Exacerbation 3 months	OR: 0.14; 95% CI: 0.03 to 0.65, I^2= N/A	1 RCT[42] with 40 patients
Repeat Exacerbation Longest Followup	OR: 0.14; 95% CI: 0.03 to 0.65, I^2= N/A	1 RCT[42] with 40 patients

BCSS = breathlessness, cough, and sputum scale; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; SMD = standardized mean difference; WMD = weighted mean difference

Table G.7. KQ2 results: Moderate-severe severity-inhaled corticosteroids vs control

Comparison	Outcome	Findings	Study Design and Sample Size
ICS (Budesonide)vs Placebo	Dyspnea (numeric scale: MRC) End of intervention	WMD: 0.04; 95% CI: -0.29 to 0.38, I^2= N/A	1 RCT[12] with 137 patients
ICS (Budesonide) vs Management without ICS	FEV1 % Predicted End of intervention	WMD: 10.10; 95% CI: 4.23 to 15.97, I^2=N/A	1 RCT[9] with 106 patients
ICS (Budesonide) vs Placebo	Intubation End of Intervention	OR: 0.31; 95% CI: 0.01 to 7.63, I^2=N/A	1 RCT[12] with 137 patients
ICS (Budesonide) vs Management without ICS	Mortality Longest Followup	OR: 0.33; 95% CI: 0.01 to 8.21, I^2=N/A	1 RCT[9] with 106 patients

CI = confidence interval; ICS = inhaled corticosteroids; MRC = medical research council scale; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; SMD = standardized mean difference; WMD = weighted mean difference

Table G.8. KQ2 results: Moderate-severe severity-inhaled corticosteroids with inhaled short-acting bronchodilators vs management without inhaled corticosteroids

Outcome	Findings	Study Design and Sample Size
FEV1 % Predicted End of Intervention	WMD: 8.30; 95% CI: 2.92 to 13.68, I^2=N/A	1 RCT[62] with 40 patients
FEV1 Absolute End of Intervention	WMD: 0.35; 95% CI: 0.05 to 0.65, I^2=N/A	1 RCT[62] with 40 patients

CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; SMD = standardized mean difference; WMD = weighted mean difference

Table G.9. KQ2 results: Mild severity-inhaled corticosteroids with inhaled long acting bronchodilators vs placebo

Outcome	Findings	Study Design and Sample Size
FEV1 Absolute End of intervention	WMD: 0.18; 95% CI: -0.17 to 0.53, I^2=N/A	1 RCT[4] with 30 patients
Clinical Failure End of Intervention	OR: 1.00; 95% CI: 0.06 to 17.62, I^2=N/A	1 RCT[4] with 30 patients

CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial; SMD = standardized mean difference; WMD = weighted mean difference

Appendix H. Adverse Events

Table H.1. KQ1: Adverse events. Antibiotics compared with control

Comparison	Outcome	Findings	Study Design
Antibiotics vs. Placebo	Cardiovascular AE	Rate Ratio: 1.92; 95% CI: 0.93 to 3.99, I^2=N/A	1 RCT[15]
Antibiotics vs. Placebo	Dermatological AE	Rate Ratio: 1.00; 95% CI: 0.14 to 7.10, I^2=N/A	1 RCT[10]
Antibiotics vs. Placebo	Gastrointestinal AE	Rate Ratio: 1.02; 95% CI: 0.58 to 1.80, I^2=0.00%	3 RCTS[6, 10, 15]
Antibiotics vs. Placebo	General Internal Medicine AE	Rate Ratio: 0.42; 95% CI: 0.15 to 1.19, I^2=N/A	1 RCT[15]
Antibiotics vs. Placebo	Musculoskeletal AE	Rate Ratio: 1.38; 95% CI: 0.56 to 3.44, I^2=N/A	1 RCT[15]
Antibiotics vs. Placebo	Oncological AE	Rate Ratio: 0.60; 95% CI: 0.22 to 1.66, I^2=N/A	1 RCT[15]
Antibiotics vs. Placebo	Serious AE	Rate Ratio: 1.095; 95% CI: 0.70 to 1.71, I^2=0.0%	2 RCTs[6, 15]
Antibiotics vs. Placebo	Total number of AEs	Rate Ratio: 1.09; 95% CI: 0.88 to 1.35, I^2=0.0%	4 RCTS[6, 10, 11, 15]
Antibiotics vs. Placebo or Management without Antibiotics	Withdrawal	OR: 0.89; 95% CI: 0.55 to 1.40, I^2=7.37%	4 RCTS[6, 10, 11, 15, 16]
Antibiotics vs. Placebo or Management without Antibiotics	Withdrawal due to AE	OR: 1.93; 95% CI: 0.94 to 3.96, I^2=0.00%	3 RCTS[6, 15, 16]

AE = adverse event; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.2. KQ1: Adverse events. Systemic corticosteroids compared with control

Comparison	Outcome	Findings	Study Design
Systemic Corticosteroids vs. Placebo	Endocrine AE	Rate Ratio: 4.86; 95% CI: 1.60 to 14.75, I^2=N/A	1 RCT[13]
Systemic Corticosteroids vs. Placebo	Infectious AE	Rate Ratio: 0.88; 95% CI: 0.43 to 1.81, I^2=N/A	1 RCT[13]
Systemic Corticosteroids vs. Placebo	Psychiatric AE	Rate Ratio:1.66; 95% CI:0.99 to 2.79, I^2=0.0%	2 RCTs[1, 13]
Systemic Corticosteroids vs. Placebo	Serious AE	Rate Ratio: 0.73; 95% CI: 0.27 to 1.97, I^2=0.0%	2 RCTs[1, 12]
Systemic Corticosteroids vs. Placebo	Total number of AEs	Rate Ratio: 1.55; 95% CI: 1.14 to 2.10, I^2=39.8%	4 RCTS[1, 2, 12, 13]
Systemic Corticosteroids vs. Placebo or Management without Systemic Corticosteroids	Withdrawal	OR: 0.67; 95% CI: 0.39 to 1.16, I^2=0.65%	4 RCTS[1, 2, 9, 12]
Systemic Corticosteroids vs. Placebo	Withdrawal due to AE	OR: 0.47; 95% CI: 0.20 to 1.10, I^2=14.53	3 RCTS[2, 7, 12]

AE = adverse event; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.3. KQ2: Adverse events. Intravenous aminophyllines compared with placebo

Outcome	Findings	Study Design
Cardiovascular AE	Rate Ratio: 1.65; 95% CI: 0.64 to 4.26, I^2=N/A	1 RCT[29]
Gastrointestinal AE	Rate Ratio: 2.10; 95% CI: 1.30 to 3.40, I^2=N/A	1 RCT[29]
Neurological AE	Rate Ratio: 1.11; 95% CI: 0.55 to 2.24, I^2=0.00%	2 RCT[29, 48]
Total number of AEs	Rate Ratio: 1.80; 95% CI: 1.26 to 2.59, I^2=25.80%	2 RCT[29, 48]
Withdrawal	OR: 0.94; 95% CI:0.35 to 2.55, I^2=N/A	1 RCT[29]
Withdrawal due to AE	OR: 0.56; 95% CI:0.15 to 2.07, I^2=N/A	1 RCT[29]

AE = adverse event; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.4. KQ2: Adverse events. Oral mucolytics compared with placebo

Outcome	Findings	Study Design
Gastrointestinal AE	Rate Ratio: 0.50; 95% CI: 0.05 to 5.51, I^2=N/A	1 RCT[22]
Total number of AEs	Rate Ratio: 1.00; 95% CI: 0.20 to 4.95, I^2=N/A	1 RCT[22]

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial

Table H.5. KQ2: Adverse events. Inhaled corticosteroids with or without inhaled short- and long acting bronchodilators compared with placebo

Outcome	Findings	Study Design
Severe AE	Rate Ratio: 0.83; 95% CI: 0.32 to 2.14, I^2=N/A	1 RCT[12]
Total number of AEs	Rate Ratio: 0.88; 95% CI: 0.57 to 1.38, I^2=N/A	1 RCT[12]
Withdrawal	OR: 0.76; 95% CI: 0.43 to 1.34, I^2=73.73%I^2	2 RCTs[9, 12]
Withdrawal due to AE	OR: 0.92; 95% CI: 0.38 to 2.21, I^2=N/A	1 RCT[12]

AE = adverse event; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.6. KQ2: Adverse events. 5-lipoxygenase inhibitor (zileuton) compared with placebo

Outcome	Findings	Study Design
Respiratory AE	Rate Ratio: 0.68; 95% CI: 0.29 to 1.59, I^2=N/A	1 RCT[61]
Severe AE	Rate Ratio: 0.93; 95% CI: 0.48 to 1.80, I^2=N/A	1 RCT[61]
Total number of AEs	Rate Ratio: 0.82; 95% CI: 0.49 to 1.39, I^2=N/A	1 RCT[61]
Withdrawal	OR: 0.89; 95% CI: 0.38 to 2.10, I^2=N/A	1 RCT[61]
Withdrawal due to AE	OR: 0.48; 95% CI: 0.04 to 5.48, I^2=N/A	1 RCT[61]

AE = adverse event; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.7. KQ2: Adverse events. Chest physiotherapy using breathing technique compared with management without chest physiotherapy

Outcome	Findings	Study Design
Withdrawal	OR: 0.94; 95% CI: 0.66 to1.34, I^2=0.00%	2 RCT [27, 36]
Withdrawal due to AE	OR: 0.90; 95% CI: 0.55 to1.48, I^2=0.00%	2 RCT[27, 36]

AE = adverse event; CI = confidence interval; OR = odds ratio; RCT = randomized controlled trial

Table H.8. KQ2: Adverse events. Chest physiotherapy using vibration/percussion/massage compared with management without chest physiotherapy

Outcome	Findings	Study Design
Withdrawal	0 events in each arm	1 RCT[24]

RCT = randomized controlled trial

Table H.9. KQ2: Adverse events. Chest physiotherapy using positive expiratory pressure compared with management without positive expiratory pressure

Outcome	Findings	Study Design
Severe AE	Rate Ratio: 1.50; 95% CI: 0.53 to 4.21, I^2=N/A	1 RCT[46]
Total number of AEs	Rate Ratio: 1.13; 95% CI: 0.43 to 2.92, I^2=N/A	1 RCT[46]
Withdrawal	OR: 0.68; 95% CI: 0.20 to 2.32, I^2=N/A	1 RCT[46]
Withdrawal due to AE	OR: 0.63; 95% CI: 0.17 to 2.42, I^2=N/A	1 RCT[46]

AE = adverse event; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.10. KQ2: Adverse events. Exercise using resistance training compared with management without resistance training

Outcome	Findings	Study Design
Withdrawal	OR: 0.72; 95% CI: 0.30 to 1.69, I^2=0.0%	2 RCTs [21, 23]

CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.11. KQ2: Adverse events. Exercise using combined aerobic + resistance training compared with management without exercise training.

Outcome	Findings	Study Design
Total number of AEs	Rate Ratio: 1.00; 95% CI: 0.14 to 7.10, I^2=N/A	1 RCT[55]

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial

Table H.12. KQ2: Adverse events. Early pulmonary rehabilitation compared with management without early pulmonary rehabilitation

Outcome	Findings	Study Design
Infectious AE	Rate Ratio: 1.07; 95% CI: 0.07 to 17.13, I^2=N/A	1 RCT[26]
General AE	Rate Ratio: 1.07; 95% CI: 0.07 to 17.13, I^2=N/A	1 RCT[26]
Musculoskeletal AE	Rate Ratio: 1.07; 95% CI: 0.07 to 17.13, I^2=N/A	1 RCT[26]
Respiratory AE	Rate Ratio: 1.16; 95% CI: 0.53 to 2.54, I^2=N/A	1 RCT[26]
Severe AE	Rate Ratio: 0.80; 95% CI: 0.28 to 2.32, I^2=N/A	1 RCT[26]
Total number of AEs	Rate Ratio: 1.03; 95% CI: 0.62 to 1.74, I^2=N/A	1 RCT[26]
Withdrawal	OR: 1.21; 95% CI: 0.48 to 3.06, I^2=20.79%	2 RCT[26 30]
Withdrawal due to AE	OR: 1.68; 95% CI: 0.44 to 6.38, I^2=N/A	1 RCT [30]

AE = adverse event; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.13. KQ2: Adverse events. Whole body vibration training during ECOPD compared with management without whole body vibration

Outcome	Findings	Study Design
Withdrawal	OR: 0.50; 95% CI: 0.11 to 2.28, I^2=N/A	1 RCT [34]

CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.14. KQ2: Adverse events. Transcutaneous electrical nerve stimulation (TENS) during ECOPD compared with vs management without Transcutaneous Electrical Nerve Stimulation

Outcome	Findings	Study Design
Withdrawal	OR: 0.81; 95% CI: 0.23 to 2.90, I^2=N/A	1 RCT[45]

CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.15. KQ2: Adverse events. Gutter frame with supplemental oxygen compared with gutter frame supplemental air

Outcome	Findings	Study Design
Respiratory AE	Rate Ratio: 0.33; 95% CI: 0.03 to 3.20, I^2=N/AI^2	1 RCT[63]
Withdrawal	OR: 0.46; 95% CI: 0.78 to 2.75, I^2=N/A	1 RCT[63]
Withdrawal due to AE	OR: 0.22; 95% CI: 0.02 to 2.14, I^2=N/A	1 RCT[63]
Total number of AEs	Rate Ratio: 0.33; 95% CI: 0.03 to 3.20, I^2=N/AI^2	1 RCT[63]

AE = adverse event; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.16. KQ2: Adverse events. Rollator with supplemental oxygen compared with gutter frame supplemental air

Outcome	Findings	Study Design
Respiratory AE	Rate Ratio: 1.00; 95% CI: 0.14 to 7.10, I^2=N/A	1 RCT[63]
Withdrawal	OR: 1.00; 95% CI: 0.13 to 7.61, I^2=N/A	1 RCT[63]
Withdrawal due to AE	OR: 1.00; 95% CI: 0.13 to 7.61, I^2=N/A	1 RCT[63]
Total number of AEs	Rate Ratio: 1.00; 95% CI: 0.14 to 7.10, I^2=N/A	1 RCT[63]

AE = adverse event; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.17. KQ2: Adverse events. Dietary intervention using a caloric supplement during ECOPD compared with usual diet

Outcome	Findings	Study Design
Withdrawal	OR: 0.39; 95% CI: 0.07 to 2.03, I^2=N/A	1 RCT[50]

CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.18. KQ2: Adverse events. Dietary intervention using a caloric and a protein supplement during ECOPD compared with Placebo (non-caloric fluid, vanilla flavored water)

Outcome	Findings	Study Design
Gastrointestinal AE	Rate Ratio: 3.13; 95% CI: 0.33 to 30.09, I^2=N/A	1 RCT[60]
Total number of AEs	Rate Ratio: 3.13; 95% CI: 0.33 to 30.09, I^2=N/A	1 RCT[60]
Withdrawal due to AE	OR: 2.47; 95% CI: 0.54 to 11.37, I^2=N/A	1 RCT[60]

AE = adverse event; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table. H.19. KQ. Adverse events. Dietary intervention using omega-3 fatty acid compared with usual diet

Outcome	Findings	Study Design
Withdrawal	OR: 0.22; 95% CI: 0.02 to 2.11, I^2=N/A	1 RCT[44]

AE = adverse event; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.20. KQ2: Adverse events. Dietary intervention using vitamin D during ECOPD compared with placebo

Outcome	Findings	Study Design
Withdrawal due to AE	OR: 2.13; 95% CI: 0.61 to 7.43, I^2=N/A	2 RCTs[47, 49]

AE = adverse event; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.21. KQ3: Adverse events. ICS+ SABA (beclomethasone+ salbutamol compared with SABA (Fenoterol)

Outcome	Finding	Study Design
General Internal Medicine AE	Rate Ratio: 0.50; 95% CI: 0.05 to 5.51, I^2=0.00%	1 RCT[67]
Neurological AE	Rate Ratio: 0.20; 95% CI: 0.02 to 1.71, I^2=0.00%	1 RCT[67]
Total number of AEs	Rate Ratio: 0.29; 95% CI: 0.06 to 1.38, I^2=0.00%	1 RCT [67]

AE = adverse event; CI = confidence interval; RCT = randomized controlled trial

Table H.22. KQ4: Adverse events. Aminopenicillin plus beta-lactamase compared with fluoroquinolone

Outcome	Finding	Study Design
Gastrointestinal AE	Rate Ratio: 1.31; 95% CI: 0.68 to 2.52, I^2=82.1%I^2	2 RCTs [78, 96]
Neurological AE	Rate Ratio: 0.60; 95% CI: 0.14 to 2.51, I^2=N/AI^2	1 RCT[96]
Total number of AEs	Rate Ratio: 1.01; 95% CI: 0.84 to 1.20, I^2=0.0%I^2	2 RCTs[78, 96]
Serious AE	Rate Ratio: 0.99; 95% CI: 0.69 to 1.43, I^2=45.8%I^2	2 RCTs[78, 96]

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial

Table H.23. KQ4: Adverse events. Ciprofloxacin compared with amoxicillin

Outcome	Finding	Study Design
Withdrawal	OR: 25; 95% CI: 1.20 to 520.739, I^2=N/A	1 RCT[77]

CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.24. KQ4: Adverse events. "Standard" antibiotic therapy (clarithromycin or cefuroxime or amoxicillin + clavulanic acid) compared with levofloxacin

Outcome	Finding	Study Design
Gastrointestinal AE	Rate Ratio: 0.35; 95% CI: 0.04 to 3.33, I^2=N/A	1 RCT[87]
Serious AE	Rate Ratio: 1.28; 95% CI: 0.44 to 3.70, I^2=N/A	1 RCT[87]
Total number of AEs	Rate Ratio: 1.28; 95% CI: 0.44 to 3.70, I^2=N/A	1 RCT[87]

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial

Table H.25. KQ4: Adverse events. Amoxicillin compared with azithromycin

Outcome	Finding	Study Design
Gastrointestinal AE	Rate Ratio: 1.66; 95% CI: 0.56 to 4.97, I^2=N/A	1 RCT[69]
Serious AE	Rate Ratio: 0.37; 95% CI: 0.07 to 1.91, I^2=N/A	1 RCT[69]
Total number of AEs	Rate Ratio: 0.76; 95% CI: 0.45 to 1.26, I^2=N/A	1 RCT[69]

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial

Table H.26. KQ4: Adverse events. Cephalosporin compared with fluoroquinolone

Outcome	Finding	Study Design
Dermatological AE	Rate Ratio: 0.97; 95% CI: 0.06 to 15.58, I^2=N/A	1 RCT[82]
Gastrointestinal AE	Rate Ratio: 1.30; 95% CI: 0.45 to 3.74, I^2=N/A	1 RCT[82]
General AE	Rate Ratio: 0.54; 95% CI: 0.17 to 1.68, I^2=0	2 RCTs[82, 97]
Infectious AE	Rate Ratio: 0.24; 95% CI: 0.03 to 2.18, I^2=N/A	1 RCT[82]
Musculoskeletal AE	Rate Ratio: 0.24; 95% CI: 0.03 to 2.18, I^2=N/A	1 RCT[82]
Respiratory AE	Rate Ratio: 0.97; 95% CI: 0.06 to 15.58, I^2=N/A	1 RCT[82]
Total number of AEs	Rate Ratio: 0.77; 95% CI: 0.45 to 1.32, I^2=0.0%I^2	2 RCTs[82, 97]
Serious AE	Rate Ratio: 0.97; 95% CI: 0.06 to 15.58, I^2=N/AI^2	1 RCT[82]

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial

Table H.27. KQ4: Adverse events. Azithromycin compared with cefaclor

Outcome	Finding	Study Design
Dermatological AE	Rate Ratio: 0.96; 95% CI: 0.09 to 10.54, I^2=N/A	1 RCT[72]
Gastrointestinal AE	Rate Ratio: 0.88; 95% CI: 0.43 to 1.77, I^2=N/A	1 RCT[72]
Neurological AE	Rate Ratio: 1.43; 95% CI: 0.29 to 7.1, I^2=N/A	1 RCT[72]
Psychiatric AE	Rate Ratio: 0.48; 95% CI: 0.07 to 3.39, I^2=N/A	1 RCT[72]
Total number of AEs	Rate Ratio: 1.10; 95% CI: 0.62 to 1.94, I^2=N/A	1 RCT[72]
Withdrawal	OR: 0.11; 95% CI: 0.01 to 1.03, I^2=N/A	1 RCT[72]
Withdrawal due to AE	OR: 0.11; 95% CI: 0.01 to 1.03, I^2=N/A	1 RCT[72]

AE = adverse event; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.28. KQ4: Adverse events. Amoxicillin compared with amoxicillin plus clavulanic acid

Outcome	Finding	Study Design
Gastrointestinal AE	Rate Ratio: 0.38; 95% CI: 0.10 to 1.43, I^2=N/A	1 RCT[80]
Total number of AEs	Rate Ratio: 0.63; 95% CI: 0.21 to 1.94, I^2=N/A	1 RCT[80]
Withdrawal	OR: 5.26; 95% CI: 0.25 to 100.00, I^2=N/A	1 RCT[80]

AE = adverse event; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.29. KQ4: Adverse events. Amoxicillin plus clavulanic acid compared with telithromycin

Outcome	Finding	Study Design
Gastrointestinal AE	Rate Ratio: 3.76; 95% CI: 1.63 to 8.66, I^2=N/A	1 RCT[70]
Respiratory AE	Rate Ratio: 6.07; 95% CI: 1.36 to 27.14, I^2=N/A	1 RCT[70]
Serious AE	Rate Ratio: 0.87; 95% CI: 0.29 to 2.58, I^2=N/A	1 RCT[70]
Total number of AEs	Rate Ratio: 1.57; 95% CI: 1.05 to 2.36, I^2=N/A	1 RCT[70]

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial

Table H.30. KQ4: Adverse events. Aminopenicillin plus beta-lactamases inhibitor plus clavulanic acid compared with macrolides

Outcome	Finding	Study Design
Gastrointestinal AE	Rate Ratio: 1.62; 95% CI: 0.6 to 4.34, I^2=N/A	1 RCT[94]
General Internal Medicine AE	Rate Ratio: 1.26; 95% CI: 0.08 to 20.11, I^2=N/A	1 RCT[94]
Hepatic AE	Rate Ratio: 1.26; 95% CI: 0.08 to 20.11, I^2=N/A	1 RCT[94]
Neurological AE	Rate Ratio: 0.25; 95% CI: 0.03 to 2.15, I^2=N/A	1 RCT[94]
Total number of AEs	Rate Ratio: 1.26; 95% CI: 0.60 to 2.64, I^2=N/A	1 RCT[94]

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial

Table H.31. KQ4: Adverse events. Amoxicillin + Clavulanic acid compared azithromycin

Outcome	Finding	Study Design
Gastrointestinal AE	Rate Ratio: 1.62; 95% CI: 0.60 to 4.34, I^2=N/A	1 RCT[94]
General Internal Medicine AE	Rate Ratio: 1.26; 95% CI: 0.08 to 20.11, I^2=N/A	1 RCT[94]
Hepatic AE	Rate Ratio: 1.26; 95% CI: 0.08 to 20.11, I^2=N/A	1 RCT[94]
Neurological AE	Rate Ratio: 0.25; 95% CI: 0.03 to 2.15, I^2=N/A	1 RCT[94]
Total number of AEs	Rate Ratio: 1.26; 95% CI: 0.6 to 2.64, I^2=N/A	1 RCT[94]

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial

Table H.32. KQ4: Adverse events. Levofloxacin compared with prulifloxacin

Outcome	Finding	Study Design
Gastrointestinal AE	Rate Ratio: 0.63; 95% CI: 0.21 to 1.92, I^2=N/A	1 RCT[71]
Neurological AE	Rate Ratio: 1.14; 95% CI: 0.45 to 4.44, I^2=N/A	1 RCT[71]
Serious AE	Rate Ratio: 1.2; 95% CI: 0.36 to 3.98, I^2=0.0%	2 RCTs[71, 75]
Total number of AEs	Rate Ratio: 0.93; 95% CI: 0.67 to 1.29, I^2=0.0%	2 RCTs[71, 75]
Withdrawal	OR: 1.07; 95% CI: 0.74 to 1.56, I^2=0.0%	2 RCTs[71, 75]
Withdrawal due to AE	OR: 1.39; 95% CI: 0.69 to 2.78, I^2=0.00%	2 RCTs[71, 75]

AE = adverse event; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.33. KQ4: Adverse events. Moxifloxacin compared with zabofloxacin

Outcome	Finding	Study Design
Dermatological AE	Rate Ratio: 0.70; 95% CI: 0.12 to 4.18, I^2=N/A	1 RCT[84]
Gastrointestinal AE	Rate Ratio: 0.84; 95% CI: 0.33 to 2.12, I^2=N/A	1 RCT[84]
Neurological AE	Rate Ratio: 0.84; 95% CI: 0.23 to 3.12, I^2=N/A	1 RCT[84]
Respiratory AE	Rate Ratio: 1.05; 95% CI: 0.07 to 16.75, I^2=N/A	1 RCT[84]
Serious AE	Rate Ratio: 1.20; 95% CI: 0.43 to 3.30, I^2=N/A	1 RCT[84]
Total number of AEs	Rate Ratio: 0.88; 95% CI: 0.53 to 1.48, I^2=N/A	1 RCT[84]
Withdrawal	OR: 1.05; 95% CI: 0.07 to 16.90, I^2=N/A	1 RCT[84]
Withdrawal due to AE	OR: 1.05; 95% CI: 0.21 to 5.27, I^2=N/A	1 RCT[84]

AE = adverse event; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.34. KQ4: Adverse events. Cefaclor compared with cefpodoxime

Outcome	Finding	Study Design
Gastrointestinal AE	Rate Ratio: 0.85; 95% CI: 0.37 to 1.98, I^2=N/A	1 RCT[83]
Total number of AEs	Rate Ratio: 1.07; 95% CI: 0.54 to 2.13, I^2=N/A	1 RCT[83]
Withdrawal due to AE	OR: 0.60; 95% CI: 0.06 to 5.85, I^2=N/A	1 RCT[83]

AE = adverse event; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.35. KQ4: Adverse events. Imipenem+cilastatin compared with meropenem

Outcome	Finding	Study Design
Dermatological	Rate Ratio: 0.99; 95% CI: 0.06 to 15.80, I^2=N/A	1 RCT[76]
Gastrointestinal AE	Rate Ratio: 2.72; 95% CI: 0.87 to 8.54, I^2=N/A	1 RCT[76]
General Internal Medicine AE	Rate Ratio: 0.99; 95% CI: 0.06 to 15.80, I^2=N/A	1 RCT[76]
Total number of AEs	Rate Ratio: 2.64; 95% CI: 1.03 to 6.74, I^2=N/A	1 RCT[76]
Withdrawal	OR: 0.87; 95% CI: 0.32 to 2.36, I^2=N/A	1 RCT[76]
Withdrawal due to AE	OR: 1.67; 95% CI: 0.39 to 7.29, I^2=N/A	1 RCT[76]

AE = adverse event; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.36. KQ4: Adverse events. Trovafloxacin 200 mg compared with trovafloxacin 100 mg

Outcome	Finding	Study Design
General Internal Medicine AE	Rate Ratio: 2.00; 95% CI: 0.37 to 10.92, I^2=N/A	1 RCT[78]
Gastrointestinal AE	Rate Ratio: 0.25; 95% CI: 0.03 to 2.24, I^2=N/A	1 RCT[78]
Serious AE	Rate Ratio: 1.63; 95% CI: 0.67 to 3.92, I^2=N/A	1 RCT[78]
Total number of AEs	Rate Ratio: 1.29; 95% CI: 0.64 to 2.59, I^2=N/A	1 RCT[78]

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial

Table H.37. KQ4: Adverse events. Intermittent intravenous cefotaxime compared with continuous intravenous cefotaxime

Outcome	Finding	Study Design
Withdrawal	OR: 0.40; 95% CI: 0.10 to 1.65, I^2=N/A	1 RCT[93]

CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.38. KQ4: Adverse events. Amoxicillin + clavulanic for 10 days compared with amoxicillin + Clavulanic for 3 days

Outcome	Finding	Study Design
Gastrointestinal AE	Rate Ratio: 4.60; 95% CI: 0.54 to 39.37, I^2=N/A	1 RCT[86]
Total number of AEs	Rate Ratio: 4.60; 95% CI: 0.54 to 39.37, I^2=N/A	1 RCT[86]
Withdrawal	OR: 0.44; 95% CI: 0.04 to 5.18, I^2=N/A	1 RCT[86]

AE = adverse event; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.39. KQ4: Adverse events. Deflazacort hemisuccinate compared with methylprednisolone

Outcome	Finding	Study Design
Endocrine AE	Rate Ratio: 0.50; 95% CI: 0.05 to 5.51, I^2=N/A	1 RCT[85]
Gastrointestinal AE	Rate Ratio: 0.40; 95% CI: 0.08 to 2.06, I^2=N/A	1 RCT[85]
Total number of AEs	Rate Ratio: 0.27; 95% CI: 0.08 to 0.98, I^2=N/A	1 RCT[85]
Withdrawal	OR: 0.19; 95% CI: 0.01 to 4.06, I^2=N/A	1 RCT[85]

AE = adverse event; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.40. KQ4: Adverse events. Hydrocortisone i.v. followed by prednisolone oral compared with methylprednisolone i.v. followed by methylprednisone oral

Outcome	Finding	Study Design
Gastrointestinal AE	Rate Ratio: 5.64; 95% CI: 0.68 to 46.85, I^2=N/A	1 RCT[68]
General Internal Medicine AE	Rate Ratio: 2.19; 95% CI: 0.57 to 8.48, I^2=N/A	1 RCT[68]
Total number of AEs	Rate Ratio: 3.05; 95% CI: 1.00 to 9.37, I^2=N/A	1 RCT[68]
Withdrawal	OR: 0.22; 95% CI: 0.02 to 2.04, I^2=N/A	1 RCT[68]

AE = adverse event; CI = confidence interval; i.v = intravenous; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.41. KQ4: Adverse events. Nebulized budesonide compared with oral prednisolone

Outcome	Finding	Study Design
Endocrine AE	Rate Ratio: 0.12; 95% CI: 0.02 to 1.01, I^2=N/A	1 RCT[12]
Total number of AEs	Rate Ratio: 0.77; 95% CI: 0.50 to 1.19, I^2=N/A	1 RCT[12]
Respiratory AE	Rate Ratio: 1.46; 95% CI: 0.35 to 6.09, I^2=N/A	1 RCT[12]
Serious AE	Rate Ratio: 1.40; 95% CI: 0.46 to 4.27, I^2=N/A	1 RCT[12]
Withdrawal	OR; 2.04; 95% CI: 0.87 to7.76, I^2=N/A	1 RCT[12]
Withdrawal due to AE	OR: 1.89; 96% CI: 0.66 to 5.26, I^2=N/A	1 RCT[12]

AE = adverse event; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.42. KQ4: Adverse events. Oral prednisolone + inhaled formoterol compared with inhaled budesonide + formoterol

Outcome	Finding	Study Design
Total number of AEs	Rate ratio: 0.85; 95% CI: 0.43 to 1.68, I^2=N/A	1 RCT[89]

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial

Table H.43. KQ4: Adverse events. Inhaled budesonide + formoterol compared with systemic methylprednisolone

Outcome	Finding	Study Design
Cardiovascular AE	Rate Ratio: 2.00; 95% CI: 0.18 to 22.06, I^2=N/A	1 RCT[90]
Gastrointestinal AE	Rate Ratio: 0.50; 95% CI: 0.09 to 2.73, I^2=N/A	1 RCT[90]
General Internal Medicine AE	Rate Ratio: 1; 95% CI: 0.06 to 15.99, I^2=N/A	1 RCT[90]
Total number of AEs	Rate Ratio: 0.56; 95% CI: 0.19 to 1.66, I^2=N/A	1 RCT[90]

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial

Table H.44. KQ4: Adverse events. Inhaled Budesonide 40mg compared with Intravenous Methylprednisolone (initially intravenous, then oral)

Outcome	Finding	Study Design
Endocrine AE	Rate Ratio: 0.28; 95% CI: 0.14 to 0.57, I^2=N/A	1 RCT[73]
Total number of AEs	Rate Ratio: 0.28; 95% CI: 0.14 to 0.57, I^2 = N/A	1 RCT [73]

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial

Table H.45. KQ4: Adverse events. Inhaled Budesonide 4mg compared with Intravenous Methylprednisolone

Outcome	Finding	Study Design
Respiratory AE	Rate Ratio: 5.78; 95% CI: 0.70 to 47.99, I^2 = N/A	1 RCT[91]
Total number of AEs	Rate Ratio: 5.78; 95% CI: 0.70 to 47.99, I^2 = N/A	1 RCT[91]

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial

Table H.46. KQ4: Adverse events. Inhaled Budesonide 8mg compared with intravenous methylprednisolone

Outcome	Finding	Study Design
Respiratory AE	Rate Ratio: 0.63; 95% CI: 0.06 to 7.00, I^2=N/A	1 RCT[91]
Total number of AEs	Rate Ratio: 0.63; 95% CI: 0.06 to 7.00, I^2=N/A	1 RCT[91]

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial

Table H.47. KQ4: Adverse events. Oral prednisolone compared with intravenous prednisolone

Outcome	Finding	Study Design and Sample Size
Withdrawal	OR: 1.33; 95% CI: 0.60 to 2.92, I^2=N/A	1 RCT[98]

CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.48. KQ4: Adverse events. Oral methyl-prednisolone compared with intravenous methyl-prednisolone

Outcome	Finding	Study Design
Withdrawal	OR: 1.29; 95% CI: 0.39 to 4.30, I^2=N/A	1 RCT [95]

CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.49. KQ4: Adverse events. Glucocorticoid for 2 weeks compared with glucocorticoid for 8 weeks

Outcome	Finding	Study Design
Endocrine AE	Rate Ratio: 1.40; 95% CI: 0.62 to 3.15, I^2=N/A	1 RCT[13]
General Internal Medicine AE	Rate Ratio: 1.50; 95% CI: 0.42 to 5.32, I^2=N/A	1 RCT[13]
Infectious AE	Rate Ratio: 0.67; 95% CI: 0.32 to 1.38, I^2=N/A	1 RCT[13]
Psychiatric AE	Rate Ratio: 2.5; 95% CI: 0.49 to 12.86, I^2=N/A	1 RCT[13]
Total number of AEs	Rate Ratio: 0.95; 95% CI: 0.66 to 1.37, I^2=N/A	1 RCT[13]

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial

Table H.50. KQ4: Adverse events. Methylprednisolone for 5 days compared with methylprednisolone for 14 days

Outcome		Finding	Study Design
Endocrine AE		Rate Ratio: 1.01; 95% CI: 0.73 to 1.39, I^2=N/A	1 RCT[79]
General Internal Medicine AE		Rate Ratio: 1.54; 95% CI: 0.81 to 2.96, I^2=N/A	1 RCT[79]
Total number of AEs		Rate Ratio: 1.08; 95% CI: 0.83 to 1.41, I^2=N/A	1 RCT[79]
Withdrawal		OR: 1.52; 95% CI: 0.53 to 4.38, I^2=N/A	1 RCT[79]

AE = adverse event; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Table H.51. KQ4: Adverse events. Methylprednisolone for 3 days compared with methylprednisolone for 10 days

Outcome	Finding	Study Design
Endocrine AE	RR: 1.00; 95% CI: 0.14 to 7.10, I^2=N/A	1 RCT[88]
Total number of AEs	Rate Ratio: 1.00; 95% CI: 0.20 to 4.95, I^2=N/A	1 RCT[88]
Withdrawal	OR: 1.00; 95%CI: 0.06 to 17.41, I^2=N/A	1 RCT[88]
Withdrawal due to AE	OR: 1.00; 95% CI: 0.06 to 17.41, I^2=N/A	1 RCT[88]

AE = adverse event; CI = confidence interval; N/A = not applicable; OR = odds ratio; RCT = randomized controlled trial

Appendix I. Inclusion and Exclusion Criteria of Included Studies

Table I.1. Inclusion and exclusion criteria of included studies

Author, Year	Inclusion Criteria	Exclusion Criteria
Aaron, 2003[1]	Age >35 years, who presented at the ED with an exacerbation of COPD (the presence of at least two of the following three clinical criteria: a recent increase in breathlessness, sputum volume, or sputum purulence), History of 15 pack-years or more of cigarette smoking and evidence of irreversible airflow obstruction defined as FEV1/FVC ratio of 0.70 or less, FEV1 not more than 70% of the predicted value, and an improvement in the FEV1 of <20% after the administration of a bronchodilator. All enrolled patients either had previously been given a diagnosis of COPD by a physician or had at least a one-year history of chronic dyspnea or cough with sputum production.	Admitted to the hospital, had been given a diagnosis of asthma or atopy, had used oral or intravenous corticosteroids within the preceding 30 days, had received oral or intravenous corticosteroids in the emergency department, had findings on chest radiography consistent with the presence of pneumonia or congestive heart failure, had had adverse reactions to oral corticosteroids, or had severe uncontrolled diabetes mellitus or renal, hepatic or cardiac failure.
Abreu Gonzalez, 2006[17]	Diagnosed with an exacerbation of COPD.	Diagnosed with pneumonia, HF, arrhythmias, or kidney failure and those who did not show a sufficient level of cooperation.
Aggarwal, 2011[68]	Aged >50 years known to have COPD as defined in The GOLD guidelines, who presented to the ED with moderate (FEV1 50–80% of predicted) or severe (FEV1 30–50% of predicted) exacerbation of COPD.	Significant co-morbid conditions such as pneumonia, CHF or interstitial lung disease, previous diagnosis of bronchial asthma, and use of systemic glucocorticoids within the last30 days, patients who required assisted ventilation on arrival at the ED or failed to use the PEF meter, Patients who required mechanical ventilation within 1 h of arrival at the ED.
Albert, 1980[2]	Acute RF (PaO2 <65 mmHg on room air, or PaCO2 ≥ 50 or pH<7.35), Chronic bronchitis (FEV1 ≤ 60% predicted or FVC ≤ 60%), acute bronchitis (increase in cough, sputum production, and sputum color within prior 5 days).	Personal or family history of asthma, bronchodilator response FEV1 >=30%, eczema, allergic rhinitis, consolidation on chest radiograph, corticosteroid therapy in the past 30 days.

Author, Year	Inclusion Criteria	Exclusion Criteria
Andre-Alves, 2007[69]	30 and 70 years with infectious exacerbation of COPD. Required to have been under outpatient treatment with simple chest X-ray that showed no evidence of pneumonia performed within the 48 hours.	Females who were breastfeeding, pregnant or planning to become pregnant (during the study or up to one month after the end of the study), women of childbearing age who were not using some efficacious method of contraception, history of hypersensitivity to azithromycin or amoxicillin; undergoing treatment with systemic antibiotics within the two weeks preceding the study outset; use of antibiotics foreseen for other clinical condition, as well as the use of allopurinol, probenecid, digoxin, warfarin or ergotamine during the study; having a history of human immunodeficiency virus infection, acute bronchitis or bronchiectasis; suspected of having lung abscess or empyema; suspected of having active tuberculosis, cystic fibrosis or lung cancer (primary or metastatic); having any clinical or psychological condition deemed by the examiner to potentially impair participation in the study; a history of alcohol or substance abuse; undergoing treatment with immunosuppressive drugs, including doses of corticosteroids higher than the equivalent to 10 mg/ day of prednisone; presenting any of the following laboratory test results: leukocyte count lower than 2500/mm^3 – neutrophil count lower than 1000/mm^3 – elevated transaminase levels of over twice the upper limit of normality – alkaline phosphatase or bilirubin levels greater than 1.5 times the upper limit of normality; donating blood during the study or within one month after the conclusion of the study.
Anthonisen, 1987[3]	At least 35 years old, clinical diagnosis of COPD, live close enough to the clinical center for home visits, reliable (keep two consecutive outpatient appointments), FEV1<70% predicted, FEV1/FVC<0.7, TLC >80% predicted.	Asthma, post-bronchodilator FEV1 increasing to >80% predicted, other disease serious enough to influence the quality of life or clinical course (e.g. cancer, left ventricular failure, stroke), other disease likely to require antibiotic therapy (e.g. recurrent sinusitis, urinary tract infection).
Emami Ardestani, 2017[74]	Adult COPD patients with acute respiratory distress, increased cough frequency and severity, increased sputum volume, and/or increased wheezing for 24 hours or more were eligible for entry to the study.	Patients with history of asthma or atopy, onset of respiratory distress before the age of 35 years, absence of spirometric data, or having received oral or intravenous steroids in the month prior to presentation.
Aubier, 2002[70]	History of chronic bronchitis and COPD (FEV1/FVC<70%), a bronchodilator response (with 0.4 mg salbutamol) defined as an increase of <12% from baseline in FEV1 from a lung function test performed within 1 year prior to inclusion, and a clinical diagnosis of AECB due to presumed bacterial infection (i.e. increased cough and/or dyspnea, increased production of sputum, and increased purulence of sputum).	Acute bronchitis, pneumonia, asthma, bronchiectasis, cystic fibrosis, lung cancer, active pulmonary tuberculosis, or acute RF.

Author, Year	Inclusion Criteria	Exclusion Criteria
Austin, 2010[18]	Aged 35 years or older with breathlessness and a history or risk of chronic obstructive pulmonary disease. Paramedics at the site of the emergency determined the diagnosis on the basis of appropriate acute symptoms, a history of COPD (or emphysema) from the patient, or a greater than 10 pack year history of smoking.	Patients with no lung function data or who did not fulfil spirometric criteria for COPD.
Ayfer Aytemur, 2015[19]	Had a spirometrically confirmed prior diagnosis of COPD, had a smoking history of at least 20 pack –years, hospitalized for their current exacerbation, and reported increased sputum production of more than 50 ml per day.	Presence of a prior diagnosis of asthma or bronchiectasis, radiographic evidence of pneumonia, and use of any mucolytic drug during the preceding week.
Basri, 2017[20]	45-60 years age, COPD with acute exacerbation as a primary diagnosis and chronic bronchitis as a secondary diagnosis, pronounced symptoms of sputum retention with coughing, ability to tolerate active techniques and well-oriented patients.	Sever attack with longer expected hospital stay up-to >2 weeks, Cardiac or any other condition that contraindicated chest physiotherapy, COPD with secondary diagnosis of emphysema, any other associated lung pathological condition, pain with more than 2 points on visual analogue scale while doing active techniques, history of lung surgery.
Bathoorn, 2008[4]	COPD, age >40 years, post bronchodilator FEV1 <85% predicted but >0.7 liters, and an abnormal post bronchodilator FEV1/slow inspiratory VC <88% predicted in men and <89% predicted in women).Patients were not allowed to use oral corticosteroids, oxygen therapy, beta-blockers, or long-acting anticholinergics. All other bronchodilators were allowed.	Asthma or a history suspicious for asthma. Patients had no significant other disease that could influence the results of the study.
Behnke, 2000[21]	We included patients with severe COPD according to international guidelines, who were admitted to the hospital due to an acute exacerbation of their disease. The study was started 4±7 days after admission, when the patients' condition had stabilized.	Exclusion criteria were: evidence of unstable cardiac disease, or pulmonale decompensation or other disabling diseases which prevented participation in the exercise program, such as orthopedic inabilities or peripheral vascular disease.
Black, 2004[22]	A physician diagnosis of COPD, age ≥ 50 years, have an FEV1 ≤ 60% predicted, FEV1/VC ≤ 70% and ≥ 10 pack year smoking history and had been admitted to hospital with an acute exacerbation of their COPD in the previous 24 hours.	Asthma (as the primary diagnosis), HF, bronchiectasis, bronchial carcinoma, interstitial lung disease, pneumonia. Also if patients were unable to comply with the study procedures because they did not speak English or were demented or if they had any other medical problems that in the opinion of the investigator would interfere with the conduct of the study.

Author, Year	Inclusion Criteria	Exclusion Criteria
Blasi, 2013[71]	Aged 40 years or older, smokers, or ex-smokers (>10 pack-years) with spirometrically confirmed severe COPD (FEV1≤ 50% predicted and FEV1/FVC ratio < 0.7) and diagnosed with an AECB, requiring concomitant systemic corticosteroids administration (20-40 mg/day for 7 days), or whom an increase of the daily dosage of their chronically corticosteroid treatment was required.	Antibiotic use in the previous week, bronchial asthma, pregnancy and breast feeding, recent or past history of psychiatric illness, epilepsy, cardiac disease, rhythm disorders or clinically significant EKG abnormalities, latent or known deficiencies for the glucose-6-phospste dehydrogenase activity, pneumonia, cystic fibrosis, bronchiectasis of origin other than COPD, active neoplasm, tracheotomy, concomitant treatment with hypoglycemic drugs, immunosuppression, hypersensitivity or allergy to fluoroquinolones, history of tendinopathy, and inability to provide informed consent.
Borges, 2014[23]	COPD exacerbation (increase in sputum or cough or worsening of dyspnea), no hospitalization in 30 days, 40-85 years , no musculoskeletal or neurologic conditions that might affect exercise performance; no participation in a rehabilitation program in the last 6 months and absence of any other pulmonary diseases.	Transferred to the ICU before the second day of hospitalization, exhibiting changes in mental status, worsening of hypoxemia or respiratory acidosis, hospitalization time <5 days; or inability to complete any of the evaluations.
Brown, 1987[24]	Chronic productive cough with sputum expectoration of 30ml or more in 24hrs and had acute episode of pneumonia determined by CXR or AECOPD with sputum expectoration of 30ml or more in 24hrs.	NR
Brusse-Keizer, 2014[5]	COPD according to the GOLD criteria, current or ex-smoker, age 40–80 years, presenting at the outpatient clinic with an AECOPD, ability to produce a spontaneous sputum sample, presenting with one or two of the clinical characteristics: a positive Gram's stain of sputum, a clinically relevant lung function decrease (decrease in FEV1 of >200 mL and >12% from baseline), or >2 AECOPDs in the previous year.	Requirement of hospitalization, pneumonia based on chest X-ray, AECOPD or use of antibiotics or prednisolone 4 weeks prior to enrolment, except for low-dose prednisolone (≤ 5 mg) as maintenance therapy, disease that influences bronchial symptoms or lung function, maintenance therapy with antibiotics, medical condition with low survival or serious psychiatric morbidity, known hypersensitivity to amoxicillin/ clavulanic acid, medical condition with low survival or serious psychiatric morbidity, uncontrolled DM, need for domiciliary oxygen therapy, participation in another clinical trial.

Author, Year	Inclusion Criteria	Exclusion Criteria
Centanni, 2002[25]	50 consecutive outpatients' patients suffering from AECOPD and with a history of IHD or arrhythmias supported by EKG and/or Holter EKG, or echocardiogram. >40 years of age, current or previous smokers (410 pack-years) reporting chronic cough with sputum production on most days during at least 3 consecutive months in consecutive years, had no change in symptom severity or treatment in the preceding 4 weeks, had shown no signs of a respiratory tract infection in the month preceding or during the trial, were not taking oral or inhaled corticosteroids for at least 3 months and had a FEV1 < 65% and FVC < 70% of predicted normal after bronchodilators had been withheld for 24 h and a best post-bronchodilator FEV1/FVC of less than 0.7.	History of asthma, allergic rhinitis, atopy, skin-test positivity or with a total blood eosinophil count over 400 mm-3, patients with co-morbidities (such as CHF or PE) or complications of COPD (e.g. pneumothorax) as the etiology of exacerbation of their symptoms.
Cox, 2018[26]	Aged ≥ 35 years who were admitted with AECOPD.	Acute myocardial infarction/HF within the last 6 weeks, Suspected/confirmed PE within the last 6 weeks, known abdominal aortic aneurysm of > 5.5 cm (or > 4.5 cm if the ultrasound scan is > 3 months old), Known cardiovascular instability: heart rate of > 120 beats per minute and/or systolic blood pressure of < 100 mmHg at the time of screening or the requirement for inotropic support or patients with an implantable cardioverter defibrillator, known extensive pulmonary fibrosis, Absolute contraindications to exercise or musculoskeletal conditions limiting exercise capacity as assessed by a trained physiotherapist, Unable to give full informed consent, Non-English speaker (to allow fully informed consent and the completion of questionnaires).
Cross, 2012[27]	Admitted to hospital with an exacerbation of COPD.	Any contraindication to the use of : Manual chest physiotherapy techniques or with no evidence of excess sputum production on auscultation., Osteoporosis, hemoptysis, bronchial hyper-reactivity, respiratory system malignancy, raised intracranial pressure, uncontrolled hypertension, PE, coagulopathy, bronchopleural fistula, subcutaneous emphysema and left ventricular failure as primary diagnosis.
Daniels, 2010[6]	45 years of age or older; GOLD stage I-IV COPD, an acute (onset < 14 d) exacerbation (type 1 [increased dyspnea, sputum volume, and sputum purulence] or type 2 [two of three symptoms]) that required hospitalization).	Fever (>38.5°C) with pneumonia, antibiotic treatment for at least 24 hours, and radiographic signs of pneumonia, CHF (NYHA III-IV), apparent immunodeficiency, impaired renal function.

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Dark, 1993[72]	16 or older, diagnosis of acute bacterial exacerbation of COPD, including acute exacerbations of concurrent COPD, chronic bronchitis, emphysema, asthma, bronchiectasis, or asthmatic bronchitis.	Treated with another investigational drug within 4 weeks of study entry, taken other antibiotics <72 hours before study entry, or if the use of additional antibiotics was anticipated at the time of entry to the study., sensitive to macrolide or cephalosporin antibiotics or if they had evidence or a history of significant hematologic, renal, hepatic, or cardiac disease or any other underlying condition that may have affected drug absorption, cystic fibrosis, as well as those with COPD, chronic bronchitis, or bronchiectasis in the absence of acute infection, drug or alcohol dependence.
Davies, 1999[7]	History of increased breathlessness and at least two of the following symptoms for 24 h or more: increased cough frequency or severity, increased sputum volume or purulence, and increased wheeze, aged 40–80 years, history of at least 20 pack-years of cigarette smoking, and physiological evidence of airflow limitation with initial FEV1< 70% predicted and FEV1/FVC ratio < 75%.	Personal or family history of asthma or atopy, uncontrolled left-ventricular failure, clinical or radiological evidence of pneumonia, received oral corticosteroids within 1 month of presentation, or if arterial blood pH on admission was less than 7·26.
De Jong, 2007[98]	Age of >40 years, a history of at least 10 pack-years of cigarette smoking, and evidence of airflow limitation. Airflow limitation was defined as an FEV1/FVC ratio of< 70% and an FEV1 of <80% predicted (GOLD severity stage II).	Excluded were patients who had signs of a very severe exacerbation on hospital admission (arterial pH <7.26 or Paco2 > 9.3 kPa), with significant or unstable comorbidity, who had a history of asthma, had participated in another study within the 4 weeks before hospital admission, were previously randomized into this study, had clinically significant findings on chest radiography other than fitting with signs of COPD, a known hypersensitivity to prednisolone, or who were known to be totally noncompliant.

Author, Year	Inclusion Criteria	Exclusion Criteria
Ding, 2016[73]	60 - 80 years old, meet the diagnostic criteria of COPD: a. based on the comprehensive consideration of the clinical presentations, exposure to risk factors, signs, and other laboratory results ;b. show the major COPD symptoms (chronic cough, expectoration, and/or dyspnea) and the exposure to risk factors; c. to exhibit incomplete reversible airflow (FEV1/FVC is <70% after application of a bronchodilator), the patients will be diagnosed with incomplete reversible airflow limitation; and met the AECOPD diagnostic criteria: a) to possess a history of COPD (the patient has been clearly diagnosed with COPD; with typical clinical COPD presentations, and the pulmonary functions during the hospitalization confirmed COPD); b) to display unusual continuous exacerbation that required a change in the routine medication; c) to show cough, expectoration, dyspnea, and/or wheeze exacerbated, and to have an increased amount of expectoration, or to have a short-term change in the sputum, which can be accompanied with evident aggravation of inflammatory (infection) symptoms (such as fever).	1) to possess serious disease that required invasive mechanical ventilation (patients with excessive respiratory secretion that are not able to use non-invasive mechanical ventilation, or with the PaCO2 >70 mmHg) (the PaCO2 level was accessed according to the safety profiles of the study); 2) history of acute exacerbation or received systemic application of corticosteroids within the past month 3)diabetes cardiac, cerebral, renal, or liver diseases that required hospitalization; 4)history with pneumothorax, pulmonary embolism, pneumonia, or other respiratory diseases; and 5) included in this study before.
Du, 2018[28]	A clinical diagnosis of COPD according to GOLD (Global Initiative for Chronic Obstructive Lung Disease) - clinical examination and FEV1/FVC <0.70, as measured on first admission.	Presence of pulmonary diseases (except COPD for the patients), infective and inflammatory diseases, neoplastic pathologies, renal, gastrointestinal, endocrine and hepatic diseases, and excessive alcohol consumption (≥40 g/day).
Duffy, 2005[29]	Clinical diagnosis of COPD presenting to the emergency department of University Hospital Aintree were considered eligible if they complained of increased breathlessness and two or more of the following symptoms for at least 24 hours: increased cough frequency or severity, increased sputum volume or purulence, increased wheeze. Patients were aged 40–80 years with a smoking history of at least 20 pack years, an initial FEV1 of 70% predicted, and FEV1/FVC ratio of 70% predicted for age.	Clinical history of asthma or atopy, uncontrolled cardiac disease, advanced malignancy, clinical or radiological evidence of pneumonia, pneumothorax, or chest wall deformity. In addition, those with an arterial blood pH below 7.32.
Eaton, 2009[30]	COPD by ATS/ERS criteria and exertional dyspnea interfering with daily activity.	Major cognitive dysfunction, comorbidities precluding ability to participate.
Edwards, 2013[31]	Age ≥35 years, COPD, FEV1/FVC ratio <70% and an FEV1 ≤ 50% predicted 20 min after initial treatment with 2.5 mg salbutamol and 500 mg ipratropium bromide by nebulization.	They required intubation or NIV, were unable to perform spirometry or had evidence of pneumothorax, hypotension, and any other serious medical condition that would prevent their participation in the trial or were pregnant.

Author, Year	Inclusion Criteria	Exclusion Criteria
Emerman, 1989[8]	50 years or older with a clinical history of emphysema or chronic bronchitis presenting to ED with acute respiratory distress and had initial spirometry with FEV1 < 70% predicted or FEV/FVC % < 60%.	History of asthma, episodes of respiratory distress before 35 years age, received oral or IV steroids within one month of presentation, pneumonia, acute CHF, or other conditions mandating admission to the hospital.
Giusti, 2016[75]	Purulent sputum, plus at least two of the following signs/symptoms of at least 3-day duration: increased cough, increased dyspnea, and increase in sputum volume, previous antibiotic treatment with any drug with the exclusion of fluoroquinolones, conducted for at least 3 full days with persistence or worsening of symptoms and consequent hospitalization, age ≥ 60 years, FEV1 ≤ 80% and ≥ 30% and ratio FEV1/FVC ≤ 0.7.	Diagnosis of asthma, pulmonary neoplasm, sepsis, tuberculosis, and cystic fibrosis; renal insufficiency or hepatic dysfunction; history of epilepsy, seizures, stroke (in the previous 6 months), or tendinopathy; known deficiencies for the glucose-6-phosphate dehydrogenase activity; drug addiction or alcohol abuse; and hypersensitivity or allergy to fluoroquinolones.
Greening, 2014[33]	Diagnosis of chronic respiratory disease (chronic obstructive pulmonary disease, chronic asthma, bronchiectasis, or interstitial lung disease), self reported breathlessness on exertion when stable (Medical Research Council dyspnea grade 3 or worse), and age 40 years or greater.	Inability to provide informed consent; concomitant acute cardiac event; presence of musculoskeletal, neurological, or psychiatric comorbidities that would prevent the delivery of the rehabilitation intervention; and more than four emergency admissions to hospital for any cause in the previous 12 months.
Greulich, 2014[34]	COPD patients hospitalized due to severe COPD exacerbations.	NR
Gunen, 2007[9]	Only patients with level II exacerbation.	COPD hospitalized for specific reasons, e.g. pneumonia, PE, CHF and pneumothorax etc., as the cause of exacerbation. With a risk of imminent RF requiring mechanical ventilation or direct admission to the ICU (level III exacerbation).Patients who had utilized systemic corticosteroids or had an exacerbation in the preceding month.
Hamacher, 1995[76]	18 years or older with an acute bacterial exacerbation of chronic bronchitis requiring a parenteral antibiotic.	Pregnant or breastfeeding women; patients with hyper-sensitivity to any beta-lactam antibiotic; patients who had received other investigational agents within the previous 28 days or had entered the study previously; cystic fibrosis; a history of seizures; severe hepatic failure ; neutropenia (neutrophil count < 1 x 109/ L) ; severe underlying disease such that the patient was unlikely to complete at least 48 h of study drug therapy; previous antibiotics in the two days before randomized treatment unless the organism had been shown to be either resistant or still present.
Hasani, 1998[77]	12 patients with COPD during exacerbation.	NR.
Hassan, 2015[10]	Type 1 exacerbation of COPD (defined as an increase in dyspnea, sputum purulence and increased sputum volume).	Received antibiotic treatment during the last 2 weeks or had another disease as left ventricular failure, stroke, pneumonia, pneumothorax, cancer, coma, allergy to quinolone derivatives, or concomitant infection requiring systemic antibacterial therapy.

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He, 2015[35]	Reported a limitation in daily activities due to dyspnea on exertion, as categorized by mMRC dyspnea grade >0.	Any disease not associated with COPD (e.g., uncontrolled HF, sever lower limb arthritis, and symptomatic peripheral vascular disease, which may affect the outcome of dyspnea or exercise tolerance), severe orthopedic or neurological disorders limiting exercise performance, unstable cardiac disease.
Kirsten, 1998[37]	Patients with severe COPD within a referral hospital after an acute exacerbation of their disease.	NR.
Kodric, 2009[36]	COPD patients, hospitalized with an acute exacerbation.	Positive bronchodilator reversibility test or any other chest disease likely to bias results.
Koutsogiannis, 2000[65]	Chronic obstructive airways disease.	Inability to perform spirometry, requirement for salbutamol or adrenaline infusion, requirement for CPAP or intubation, the presence of a pneumothorax, pneumonia or cardiac failure on CXR and asthma.
Kurzaj, 2013[38]	COPD and treated of worsening of the symptoms of their disease.	NR.
Lellouche, 2016[39]	Hospitalized for an acute exacerbation of COPD in whom oxygen therapy was prescribed, patients aged ≥ 40 years with a past or current smoking history of at least 10 pack-years. Maintain an SpO2 of ≥ 92% with supplemental oxygen at a maximum flow rate of 8 L/min.	Admitted for 24 hours, infected with multidrug-resistant bacteria, on intermittent NIV (including CPAP for obstructive sleep apnea), cognitive impairment.
Leophonte, 1998[78]	40 years or older, chronic obstructive bronchitis, FEV1/FVC <70%, sputum production during 3 consecutive months for 2 or more years, acute exacerbation (dyspnea or increased sputum volume/purulence [gram stain sputum with >25 PMNs]).	Hypersensitivity or intolerance to quinolone or beta lactams, hospitalized, any antibiotic use longer than 24 hours in the prior 72 hours, AECOPD severe enough to warrant IV antibiotics, cystic fibrosis, radiograph evidence of pneumonia, significant gastrointestinal condition to preclude oral absorption of pills, AIDS, epilepsy, seizures, recent drug or alcohol abuse or dependence or chronic prednisolone >=10 mg daily use.
Leuppi, 2013[79]	AECOPD (2 of the following: change in baseline dyspnea, cough, or sputum quantity or purulence); ≥40 years old, smoking ≥ 20 pack years, FEV1/FVC ≤ 70%.	Asthma, FEV1/FVC >70%, radiological diagnosis of pneumonia, estimated survival <6 months due to severe comorbidity, pregnancy or lactation, inability to give written informed consent.
Liao, 2015[40]	Moderate exacerbation COPD, older than 65 years, clear consciousness, shortness of breath or dyspnea that was not caused by heart disease, pneumothorax, or pulmonary edema, received bronchodilator aerosol therapy or antibiotic treatment, had not been treated with an antitussive.	Systolic blood pressure lower than 90 mmHg, blood oxygen concentration lower than SpO2 =90%, unstable psychological status, hemoptysis, pneumothorax, pulmonary edema.

Author, Year	Inclusion Criteria	Exclusion Criteria
Llor, 2009[80]	Spirometrically-diagnosed patients older than 40 years with COPD, without criteria of hospitalization and Anthonisen's types I or II exacerbations.	Current chronic treatment with systemic steroids at any dose, severe respiratory impairment requiring hospital referral, evidence of a new pulmonary infiltrate on chest radiography, suspected or known history of hypersensitivity to β-lactam antibiotics, administration of antibiotics within the previous four weeks, documented evidence of bronchiectasis, AIDS, another immunosuppressive condition or patients receiving treatment with immunosuppressive drugs, cystic fibrosis, or patients participating in another clinical trial within the last year.
Llor, 2012[11]	≥ 40 years old, mild to moderate COPD (smoking history ≥ 10 pack years, FEV1/FVC <70%, post bronchodilator FEV1>50% predicted) and presence of exacerbation (increase of dyspnea, sputum volume or sputum purulence).	Antibiotic use in prior 2 weeks, bronchial asthma, cystic fibrosis, bronchiectasis other than COPD, active neoplasm, tracheotomy, need for hospital admission, immunosuppression, hypersensitivity to beta lactams, clavulanate or lactose, institutionalization, or inability to provide informed consent.
Mahmoud Abd El Hafiz, 2013[41]	COPD with a history of ≥ 2 exacerbations/year in 2 years prior to enrollment. An age between 40 and 70 years; a post bronchodilator FEV1/FVC <70% of predicted; an FEV1 reversibility <12% of the predicted value, 15 min after 400 mcg (4 puffs) of Salbutamol; and to be currently experiencing an AECOPD.	Allergy or intolerance to NAC, cystic fibrosis, bronchiectasis, history of infection or active infection by TB, history of active peptic ulcer.
Maltais, 2002[12]	> 50 ye old, had a smoking history of at least 20 pack-years, according to the attending physician had to be treated in hospital.	If they had a personal history of asthma, allergic rhinitis, or atopy; were exposed to systemic corticosteroids, in the preceding month; used more than 1,500 g/d of inhaled beclomethasone equivalent; were at risk of imminent acute respiratory failure requiring mechanical ventilation or admission to the intensive care unit (pH 7.30 and/or PaCO2 70 mm Hg, and/or PaO2 50 mm Hg despite supplemental oxygen); or if a specific cause for the exacerbation, such as pneumonia, pneumothorax, or HF.
Mirici, 2003[81]	If they had moderate to severe acute attacks of COPD.	Exposure to systemic corticosteroids in the preceding month; presence of asthma, allergic rhinitis, atopy or any systemic disease (such as DM or hypertension); and being at risk of acute RF requiring mechanical ventilation.
Moayyedi, 1995[66]	Emergencies to acute medical units with diagnosis of acute exacerbation of COPD, not taking regular nebulized bronchodilators at home. All over 45 years and had smoking history more than 10 pack-years. All had a FEV1 < 65% predicted when well and history of exertional dyspnea from respiratory disease over three years.	History suggestive of asthma (childhood respiratory disease, atopy, night time wheezing) and a peripheral eosinophilia of > 10%. Patients with a > 20% (at least 200 ml) reversibility of FEV, to 400 mcg of inhaled salbutamol on the day of discharge.

Author, Year	Inclusion Criteria	Exclusion Criteria
Moretti, 2015[42]	Aged between 38 and 75 years admitted with an acute exacerbation of COPD, fever, cough, and purulent sputum in the previous 24 hours.	Pneumonia, acute heart failure, bronchiectasis, asthma (as the primary diagnosis), acute respiratory acidosis needing noninvasive ventilation, AECOPD treated with antibiotics or systemic corticosteroids in the previous 4 weeks, or any other medical or personal problems that in the opinion of the investigator would interfere with the conduct of the study.
Mukerji, 2015[43]	Above age of 35 years, who had a previously documented diagnosis of COPD by either their general practitioner or in-hospital respiratory specialists. Non-infective and infective cause of AECOPD.	Patients requiring mechanical ventilation or NIV at presentation, anyone who was unable to do spirometry or had evidence of pneumothorax or hypertension or any other serious medical condition that would prevent their participation. Responders or 'asthma-type' COPD patients, history of asthma.
Niewoehner, 1999[13]	50 or older, history 30 pack-years or more smoking, either FEV1 1.50 L or less or inability to undergo spirometry due to dyspnea.	Diagnosis of asthma, use of systemic glucocorticoids within the preceding 30 days, coexisting medical conditions that made survival for at least 1 year unlikely.
Ogasawara, 2018[44]	Clinically diagnosed as COPD according to the GOLD criteria and hospitalized for exacerbation of COPD or pneumonia, planned to receive pulmonary rehabilitation during the hospitalization, and able to eat and drink safely without dysphagia.	Patients who had a history of severe drug allergy, patients who took oral nutritional supplements during the trial, patients regarded as inadequate to receive additional nutrition therapy because of uncontrolled diabetes and/or dyslipidemia, and patients who refused pulmonary rehabilitation.
Oncu, 2017[45]	Diagnosed with AECOPD by independent thoracic physicians.	Other pulmonary disease, who were not eligible as a result of cardiology consultation, another chronic disease/condition drug addicts, applied acupuncture/TENS previously, smoked during the last four hours prior to the pulmonary function test used long-term bronchodilator in the last 12 hours, and conditions that prevented six-minute walk test.
Osadnik, 2014[46]	Hospitalized due to an AECOPD were screened by study personnel, and those with evidence of sputum expectoration or a history of chronic sputum Production ('regularly expectorated sputum on most days') were recruited from respiratory units within 48h of admission.	A respiratory condition deemed more significant than COPD (e.g., clinical history of primary bronchiectasis, asthma or lung cancer requiring active therapy) even if coexistent with COPD, if they had established airway clearance routines, were breathing via an artificial airway or PEP therapy was contraindicated (undrained pneumothorax; significant haemoptysis; recent facial, oral, esophageal or skull surgery/trauma; surgical or nonsurgical lung volume reduction procedures, lung transplantation or pneumonectomy within the last 6 months).
Perri, 1985[67]	Reversible chronic obstructive lung disease with at least a 15% greater FEV1 in relation to their CECA predicted values after 200 mcg (2 puffs) of salbutamol administered by aerosol.	NR.

Author, Year	Inclusion Criteria	Exclusion Criteria
Petitpretz, 2007[82]	Age ≥45 years, candidate for outpatient management and diagnosis of AECOPD defined as: current or former smoking activity; history of chronic bronchitis characterized by cough and sputum production on most days for 3 consecutive months and for >2 consecutive years; chronic obstructive bronchitis confirmed by lung function test performed in a stable condition in the previous 12 months showing a FEV1/FVC ratio of <70% and an FEV1 in the range of 35–80% of the predicted value, and no significant reversibility following B2-agonist therapy (<200 mL and <15% increase in FEV1); at least three exacerbations during the previous year; a current acute exacerbation characterized by the presence of the three Anthonisen's criteria of recent increase in sputum volume, sputum purulence and dyspnea; and no evidence of pneumonia on chest radiography performed within 48 h prior to or no later than 72 h after initiating the study drug.	Significant reversibility following B2-agonist therapy or failure to perform this test and FEV1/FVC ≥70% or failure to measure lung function.
Phillips, 1993[83]	18 years or older, ≥ 40 kg, AECOPD (cough, fever, or increased sputum production/purulence), absence of infiltrate on chest radiograph), hospitalized and outpatients were included.	Severe respiratory infection requiring IV antibiotics, pregnant, breastfeeding, hypersensitivity to cephalosporins, anaphylaxis or severe reaction to penicillins, antibiotics in prior 5 days, neutropenic, creatinine >2.5, hepatic dysfunction, immune or neoplastic disease, severe vascular insufficiency, gastro-intestinal disorder that would impair oral absorption, enrolled in another investigational protocol, prior enrollment in a cefpodoxime protocol.
Pourrashid, 2018[47]	AECOPD in the emergency ward and Vitamin D deficiency (serum 25(OH) D < 20 ng/mL).	Serum 25(OH)D < 5 ng/mL, vitamin D supplementation within six month prior to study, use of maintenance dose of oral corticosteroids within three months prior to study, diagnosed asthma, osteoporosis, renal failure (serum creatinine ≥ 2.5 mg/dL), nephrolithiasis, uncompensated liver failure (Child-pugh class B, C), hypercalcemia (ionized calcium > 1.3 mmol/L), conditions associated with pathological 1-alpha hydroxylase activity such as sarcoidosis, lymphoma or multiple myeloma, coagulopathy (platelet count < 30,000 per mm^3 or international normalized ratio > 3), contraindication for intramuscular administration, pregnancy, lactation, and immuno-compromised patients.

Author, Year	Inclusion Criteria	Exclusion Criteria
Rhee, 2015[84]	40 years old or older, moderate exacerbation of COPD; post-bronchodilator FEV1/FVC < 0.7; purulent sputum or increased volume of sputum.	Pregnant women, received systemic antibiotics and/or antifungal agents within the last 72 hours, pneumonia, underlying septic shock, bronchiectasis, lung abscess, active tuberculosis, pulmonary malignancy, cystic fibrosis, empyema, or asthma; kidney or liver disease with abnormal laboratory test results, organic gastrointestinal disorder; absolute neutrophil count <1,000 cells/ mm^3; chronic hepatitis B or C; immunocompromised patients, history of hypersensitivity to fluoroquinolone antibiotics; history of seizure or anti-seizure medications; history of ventricular arrhythmia; and history of corrected QT prolongation or treatment with medication that prolongs the corrected QT interval.
Rice, 1987[48]	Diagnosis of COPD consistent with FEV1 >2 SD below predicted and FEV1/FVC ratio <60%.	Clinical diagnosis of asthma, readily reversible episodes of wheezing and dyspnea separated by asymptomatic intervals, or bronchodilator response of a >30% increase in FEV1 from previous spirometry. Left ventricular failure and pneumonia.
Rizzato, 1998[85]	Admitted to hospital for AECOPD, max value of FEV1<70% predicted, marked respiratory distress.	Drug sensitivity, pregnant or nursing, drug addicts, alcoholics, HIV positive, cognitive impairment, clinically impaired diabetes, active peptic ulcer, untreated active tuberculosis, systemic mycosis.
Roede, 2007[86]	Aged ≥ 18 years who fulfilled the clinical criteria for COPD, and who presented with purulent sputum and a type 1 exacerbation, increased dyspnea, increased volume and purulence of sputum, or two of these criteria in a patient with chronic HF and a chest radiograph that showed no evidence of pneumonia.	Patients with a history of allergy to amoxicillin–clavulanic acid, neutropenia (<1.0 x10^9⁄L), agammaglobulinemia, cystic fibrosis or bronchiectasis, a life-expectancy of <1 month, previous treatment with an effective antimicrobial agent for >24 h before admission, or any other infection necessitating the administration of systemic antibiotics. Patients admitted to an ICU and patients who required ventilation.
Ruiz Gonzalez, 2007[87]	Aged >40 years, with a diagnosis of COPD and were admitted to the emergency room with a primary diagnosis of an acute exacerbation. Spirometry that met criteria for COPD defined as FEV1 to FVC ratio ≤70%, and FEV1 ≤ 80% predicted, a severe or Anthonisen's type 1 exacerbation, worsening of dyspnea, increase in sputum volume and increase in sputum purulence; and a CXR without any new infiltrates.	Previous adverse reaction to study drugs, pregnancy or lactation, syndrome of QT prolongation, severe renal or hepatic impairment, lung disease other than COPD.
Sanjari, 2015[49]	Ex-smokers with a history of chronic cough and expectoration who also had exertional dyspnea and admitted with the diagnosis of COPD exacerbation.	Unable to perform spirometry, A history of asthma symptoms, existence of other respiratory disorders including bronchial carcinoma, a history of hospitalization (within 4 weeks) for COPD, any medical condition which needed more invasive respiratory support, symptoms of lower respiratory tract infection or other kinds of simultaneous systemic disease such as hypercalcemia, renal failure, hyperparathyroidism, malignancy, history of renal stone, cardiac arrhythmia, or patients who were using lithium.

Author, Year	Inclusion Criteria	Exclusion Criteria
Saudny-Unterberger, 1997[50]	Diagnosis of COPD, and a FEV1 ≤ 60% of the predicted.	Required mechanical ventilation, had a gastrointestinal tract disorder, had active cancer or other conditions predisposing to weight loss, terminally ill, unable to communicate in English or French, suffered from mental confusion or followed a special diet.
Sayiner, 2001[88]	COPD, all current or ex-smokers with a smoking history ≥ 20 pack-years and severe airway obstruction (FEV1 35% predicted), who presented with an exacerbation necessitating hospitalization.	Personal or family history of asthma, atopy, allergic disease, presence of eosinophilia, use of systemic steroids within the preceding month, presence of severe hypertension, uncompensated CHF or uncontrolled (or difficult to control) DM, and RF necessitating mechanical ventilation therapy.
Seidenfeld, 1984[51]	Met ATS chronic bronchitis guidelines.	Temp >37.5℃, obvious cardiac rhythm disturbance, acute pneumonia, acute HF.
Skorodin, 1995[52]	35 years or older who presented to ED with AECOPD, provided they met the diagnostic criteria for chronic bronchitis and/or emphysema as defined by the ATS.	Temperature greater than 37.9°C, systolic blood pressure less than 100 mm Hg, history of kidney disease, and clinical evidence of pneumonia.
Solooki, 2014[53]	40 years or older, COPD exacerbation to emergency department.	Contraindication for use of IV magnesium sulfate, unable to perform spirometry, presence of pneumonia, oral temperatures of 38 °C or more and systolic blood pressure less than 100 mmHg.
Soltaninejad, 2016[54]	Older than 40 years and known case of COPD.	History of HF (ejection fraction <40%), renal failure, ongoing ischemia, hearing problems, lung cancer, lung abscess, bronchiectasis, lung resection surgery, and hypersensitivity to aminoglycosides.
Stallberg, 2009[89]	≥10 pack year smoking history, age ≥ 40 years old, moderate COPD GOLD stage IIA or IIB, established diagnosis of COPD for ≥ 6 months at start of study, exacerbation in the week prior (increased dyspnea, sputum volume, or sputum purulence), primary care physician thought that oral steroids were clinically indicated.	Mild exacerbation treated with antibiotics and/or increased bronchodilators alone, hypoxemia, admitted to hospital, asthma, FEV1/FVC >70%, AECOPD in prior 30 days, SaO2 <92% after initial acute treatment, required oxygen, inhaled corticosteroid >1000 mcg/day at study entry, use of non-selective beta antagonist.
Sun, 2015[90]	Patients with AECOPD meeting the GOLD diagnostic criteria.	A personal history of asthma, cystic fibrosis, diffuse pan bronchiolitis (DPB), obliterative bronchiolitis, allergic rhinitis, or atopy; complicated with acute RF, acidosis, cancer or serious heart, liver, kidney, and gastrointestinal diseases; or were at risk of admission to the ICU, exposed to corticosteroids in past 4 weeks, more than 50 years.
Tang, 2012[55]	AECOPD had to be admitted into the hospital, able to walk independently before admission, have spontaneous ventilation without any ventilator assistance, receive medical clearance to participate, able to communicate in English, and able to provide informed consent.	NR

Author, Year	Inclusion Criteria	Exclusion Criteria
Thompson, 1996[14]	History of cigarette smoking (≥ 20 pack-year), airflow obstruction, diagnosis or chronic bronchitis or emphysema as defined by the ATS.	Family or personal history of asthma; atopy, allergic rhinitis, or nasal polyposis; or a history of pulmonary disease other than COPD; positive skin test to common environmental allergens, systemic contortionists used in last month, uncompensated CHF, pneumonia, fever > 38.5°C, acidemia (arterial pH< 7.35); hospital admission for any reason; or inability to return for followup appointments.
Torres-Sanchez, 2017[56]	AECOPD according to (ATS) criteria. Age 65 or older. Patients with COPD who scored over 3 in the Brief Frailty Index.	Psychiatric or cognitive disorders, progressive neurological or musculoskeletal disorders, sever orthopedic problems, organ failure, cancer, or inability to cooperate. Experienced another exacerbation of COPD in the previous month.
Torres-Sanchez, 2017[57]	COPD according to the criteria of GOLD, hospitalized due to acute exacerbation of COPD.	Severe comorbidities "unstable cardiovascular disease, orthopedic diseases in the upper and lower limbs, motor sequelae from neurological or visual disorders that interfere with the ability to perform physical exercise, cognitive impairment that interfere with the evaluation and the treatment".
Troosters, 2010[58]	Diagnosis of AECOPD, age <85 years.	Hospitalization within the previous 14 days, current participation in rehabilitation program, locomotor or neurological condition or disability limiting the ability to perform exercise, lung transplantation or lung volume reduction surgery foreseen within 1 month after discharge.
Goktalay, 2013[32]	Stage 3–4 COPD according to the GOLD criteria and hospitalized for infective exacerbations of the COPD.	Need for INV, bronchiectasis, active lung tuberculosis, chest wall trauma, thoracic or abdominal operation in the last three months, a diagnosis of PE in the last three months, myocardial infarction in the last six months, and thrombocytopenia (<50,000/mm^3) plus exacerbation secondary to cardiovascular causes and non-infective exacerbations.
Tumer, 2009[59]	Male patients hospitalized with acute exacerbation of COPD.	NR
Ucar, 2014[91]	Moderate or severe COPD exacerbation, ≥ 40 years, ≥ 10 pack-year smoking history, required hospitalization for COPD exacerbation.	Asthma, allergic rhinitis, atopy, any systemic disease (such as diabetes or hypertension), prior steroid use in past month, used >1500 mcg/day of inhaled beclomethasone equivalent, admitted to the ICU, pH<7.30, PaCO2>70mmHg, PaO2 < 50mmHg despite supplemental oxygen, or if he had a specific cause of the exacerbation diagnosed (pneumonia, pneumothorax, HF, etc.)
Umut,1999[92]	COPD diagnosis was made according to the ATS criteria.	Pregnancy, known allergy to antibiotics, antibiotic therapy 6 weeks prior to study, active tuberculosis, immunosuppression, liver and kidney insufficiency, empyema, lung abscess, aspiration pneumonia, need to use parenteral antibiotics.

Author, Year	Inclusion Criteria	Exclusion Criteria
Van Velzen, 2017[15]	45 years or older, smoking history of 10 pack-years; clinical diagnosis of mild to severe COPD, last exacerbation in the three years, exacerbation had to have ended at least 4 weeks before and symptoms had returned to baseline.	Poor mastery of the Dutch language, poor cognitive functioning, known allergy to doxycycline, pregnancy, life expectancy of shorter than one month, fever, admission to hospital, current antibiotics or use in previous 3 weeks.
Van Zanten, 2007[93]	Ninety-three consecutive patients aged ≥ 18 years (range 34–76 years) requiring hospital admission and antibiotic treatment for moderate to severe acute exacerbations of COPD (GOLD classes 2–4).	Suspected or proven resistance to cefotaxime, administration of antibiotics in the preceding 48 h, allergy to β-lactam antibiotics, bilirubin concentrations >20 μmol l^{-1}, serum creatinine concentrations >120 μmol and whole blood count<3.0 × 10^9 l^{-1}.
Vermeeren, 2004[60]	Admitted to the hospital for an exacerbation of COPD, recent increase in breathlessness, cough and sputum production of sufficient severity to warrant hospital admission, judged by an independent chest physician. Criteria for nutritional intervention were a BMI ≤ 22 kg/m^2 or a BMI ≤ 25 kg/ m^2 and >5% weight loss in 1 month, or > 10% weight loss in 6 months prior admission to the hospital.	Patients with DM type 1, thyroid, intestinal diseases, and carcinoma.
Wang, 2016[16]	Patients admitted to hospital with AECOPD who were 40 years of age and who had a PCT level <0.1 ng/ml.	Fever (≥ 38.0°C), tracheal intubation within 24 h after hospital admission, a PCT level of ≥ 0.1 ng/ml on admission, pneumonia, chronic renal failure, history of malignant disease, immunosuppressive therapy.
Whitlock, 1995[94]	Between 35-75 years old, acute bacterial exacerbation of COPD.	Pneumonia; acute bronchitis or chronic bronchitis with concurrent bronchiectasis or active bronchial asthma; neutrophil function disorders, cytopenias, or bleeding disorders; clinically significant renal or hepatic dysfunction; clinically significant cardiovascular disorders; any condition that could interfere with evaluation of therapeutic response or increase the risk of an adverse event; alcohol or drug dependence; significant psychiatric disorders; hypersensitivity to any of the study drugs; infections caused by organisms resistant or likely to be resistant to study drugs; use of antibiotics within 72 hours of enrollment; and use of investigational drugs within the previous 4 weeks. Breastfeeding women.
Willaert, 2002[95]	Patients with a clinical history of COPD who presented with an acute exacerbation.	There was a personal or family history of asthma (defined as episodic wheezing or dyspnea that rapidly improved with treatment) or atopy, INV or NIV assisted ventilation was deemed necessary according to the attending casualty physician, the patient was unable to successfully use a MDI as a device for administering bronchodilators.

Author, Year	Inclusion Criteria	Exclusion Criteria
Wilson, 2012[96]	Outpatients with moderate-to severe COPD and chronic bronchitis suffering from an investigator-evaluated Anthonisen type I exacerbation and who were considered by the investigator to require antibiotic therapy.	NR
Woodruff, 2011[61]	Over 45 years old, with an admitting diagnosis of AECOPD, 10 or more pack-years, FEV1 < 60% predicted or inability to perform spirometry due to dyspnea.	Uncontrolled systemic disease; hypersensitivity to zileuton; Asthma; Lobar pneumonia or pulmonary edema; Interstitial lung disease; predicted survival of less than 30 days; History of liver disease; current use of theophylline; incarceration; institutionalization; pregnant; history of a suicide attempt; prior inpatient admission for a psychiatric disorder; bipolar disorder.
Xiong, 2008[62]	Diagnosis is consistent with the standard of the GOLD of 2006, no application of glucocorticosteroid systematically in 6 months, no systemic infection in 2 weeks before the study, no application of β2-receptor agonist or antihistamine drugs in 24 hours, no any other chronic heart or lung disease or endocrine disease, no need of mechanical ventilation.	NR
Yohannes, 2003[63]	60 years old and older, inpatient admitted with AECOPD.	Terminal illness, current participation in any other research project, uncontrolled heart failure, major cardiac arrhythmia. History of nondepressive psychotic illness, history of poor compliance with medical therapy, acute/chronic confusion (Hodkinson Abbreviated Mental Test score <7/10), carbon dioxide retention judged by the patient's supervising consultant to be severe enough to prevent oxygen supplementation, limitation of exercise capacity by nonrespiratory disability (e.g., musculoskeletal problems), inability to use co-ordinate frame, intolerance of oxygen mask or nasal cannula.
Yoon, 2013[97]	Older than 18 years with AECOPD.	Radiographic evidence of pneumonia, bronchiectasis, cystic fibrosis, tuberculosis, or lung cancer. Patients with serious renal dysfunction, a history of seizure, a history of allergy or other side effects to quinolone, cephalosporin, or penicillin, a history of antibiotic therapy during the previous 48 hours, pregnancy or possibility of pregnancy, and lactating women.
Zuin, 2005[64]	History of COPD with at least two exacerbations in the previous 2 years, post-bronchodilator FEV1 between 40% and 70% of predicted.	Serious concomitant diseases (cardiac, hepatic, renal or cancer) or α-1-antitrypsin deficiency.

AECB = acute exacerbation of chronic bronchitis; ECOPD = exacerbation of chronic obstructive pulmonary disease; ATS = American Thoracic Society; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CPAP: continuous positive airway pressure; CXR = chest x-ray; DM = diabetes mellitus; ED = emergency department; EKG = electrocardiogram; EPA = eicosapentaenoic acid; ERS = European Respiratory Society; FEV1 = forced expiration volume in 1 second; FVC = forced vital capacity; GOLD = global initiative for chronic obstructive lung disease; HF = heart failure; ICU = intensive care unit; IHD = ischemic heart disease; INV = invasive ventilation; KPA = kilopascal; mMRC = modified medical research council; NIV = noninvasive ventilation; NT-proBNP = N-terminal pro b-type natriuretic peptide; NYHA = New York Heart

Association; ONS = oral nutrition supplementation; PaCO2 = partial pressure of carbon dioxide in arterial blood; Pao2 = partial pressure of oxygen in arterial blood; PE = pulmonary embolism; PEF = peak expiratory flow; pH = potential of hydrogen; RF = respiratory failure; TLC = total lung capacity; VC = vital capacity; WBC = white blood cell count.

Appendix J. Sensitivity Analysis

Table J.1. Sensitivity Analysis

Comparison	Outcome	Method	OR	95% CI	I^2
Systemic Antibiotics versus Placebo or Management without Systemic Antibiotics	Clinical Cure Longest Followup	Profile Likelihood	1.56	0.84, 2.21	0.00%
		HKSJ	1.53	0.81, 2.88	0.20%
		DL	1.50	1.01, 2.24	20.33%
Systemic Corticosteroids vs Placebo	Mortality End of Intervention	Profile Likelihood	1.61	0.47, 6.18	0.00%
		HKSJ	1.61	0.22, 11.75	0.00%
		DL	1.61	0.47, 5.47	0.00%
Systemic Corticosteroids vs Placebo	FEV1 % Predicted End of Intervention	Profile Likelihood	4.64	1.00, 8.96	0.00%
		HKSJ	4.64	-0.81, 10.09	0.00%

DL = DerSimonian and Laird; HKSJ = Hartung-Knapp-Sidik-Jonkman; OR=odds ratio; CI=confidence interval

Appendix K. Appendix References

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