Management of COPD exacerbations:
A European Respiratory Society/American Thoracic Society (ERS/ATS) guideline

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ABSTRACT

Background: This document provides clinical recommendations for treatment of chronic obstructive pulmonary disease (COPD) exacerbations. It represents a collaborative effort between the European Respiratory Society (ERS) and the American Thoracic Society (ATS).

Methods: Comprehensive evidence syntheses, including meta-analyses, were performed to summarize all available evidence relevant to the task force's questions. The evidence was appraised using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach and the results were summarized in evidence profiles. The evidence syntheses were discussed and recommendations formulated by a multi-disciplinary task force of COPD experts.

Results: After considering the balance of desirable (benefits) and undesirable consequences (burden, adverse effects, cost), quality of evidence, feasibility, and acceptability of various interventions, the task force made 1) a strong recommendation for non-invasive mechanical ventilation of patients with acute or acute-on-chronic respiratory failure, 2) conditional recommendations for oral corticosteroids in outpatients, oral rather than intravenous corticosteroids in hospitalised patients, antibiotic therapy, home-based management, and the initiation of pulmonary rehabilitation with three weeks after hospital discharge, and 3) a conditional recommendation against the initiation of pulmonary rehabilitation during hospitalisation.

Conclusion: The task force provided recommendations related to corticosteroid therapy, antibiotic therapy, non-invasive mechanical ventilation, home-based management, and early pulmonary rehabilitation in patients having a COPD exacerbation. These recommendations should be reconsidered as new evidence becomes available.

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EXECUTIVE SUMMARY

Chronic obstructive pulmonary disease (COPD) exacerbations are episodes of increased respiratory symptoms, particularly dyspnea, cough, and sputum. The European Respiratory Society (ERS) and American Thoracic Society (ATS) collaborated to develop guidelines that address questions regarding the treatment of COPD exacerbations that are not clearly answered by current guidelines. Key recommendations from the guidelines include the following:

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

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

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

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

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

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

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

INTRODUCTION

The chronic and progressive course of COPD is often punctuated by “exacerbations”, defined clinically as episodes of increasing respiratory symptoms, particularly dyspnea, cough, sputum production, and increased sputum purulence. COPD exacerbations have a negative impact on the quality of life of patients with COPD (1,2), accelerate disease progression, and can result in hospital admissions and death (3,4).

Evidence-based clinical practice guidelines have been developed by other organizations that recommend inhaled bronchodilator therapy for patients having a COPD exacerbation, as well as supplemental oxygen for hypoxemic patients (5). They also make recommendations related to systemic steroids, antibiotic therapy, non-invasive mechanical ventilation, and home-based management. The purpose of our guidelines is to update the latter recommendations and to also address specific questions regarding the treatment of COPD exacerbations that are not answered by existing guidelines. For six questions, we employed a systematic review of the literature followed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to develop treatment recommendations:

Question #1: Should oral corticosteroids be used to treat ambulatory patients who are having a COPD exacerbation?

Question #2: Should antibiotics be used to treat ambulatory patients who are having a COPD exacerbation?

Question #3: Should intravenous or oral corticosteroids be used to treat patients who are hospitalized with a COPD exacerbation?

Question #4: Should non-invasive mechanical ventilation be used in patients who are hospitalized with a COPD exacerbation associated with acute or acute-on-chronic respiratory failure ?

Question #5: Should a home-based management program ("hospital-at-home") be implemented in patients with COPD exacerbations?

Question #6: Should pulmonary rehabilitation be implemented in patients hospitalized with a COPD exacerbation?

The target audience of these guidelines is specialists in respiratory medicine who manage adults with COPD. General internists, primary care physicians, emergency medicine clinicians, other health care professionals, and policy makers may also benefit from these guidelines. These guidelines provide the basis for rational decisions in the treatment of COPD exacerbations. Clinicians, patients, third-party payers, stakeholders, or the courts should never view the recommendations contained in these guidelines as dictates. Though evidence-based guidelines can summarize the best available evidence regarding the effects of an intervention in a given patient population, they cannot take into account all of the unique clinical circumstances that may arise when managing a patient.

While the focus of these guidelines is the treatment of COPD exacerbations, the task force has also provided a narrative review in the online supplement that answers the following complementary questions: what is the optimal approach to diagnose a COPD exacerbation; what are the conditions to include in the differential diagnosis; what tests are required to assess the severity of a COPD exacerbation; and how should a patient be followed during recovery from a COPD exacerbation?

METHODS

Group composition

The task force co-chairs (JAW, JAK) were selected by the European Respiratory Society (ERS) and American Thoracic Society (ATS). They led all aspects of project management and selected the panellists, which included 11 clinicians with experience in COPD management and research. In addition, there were two methodologists (TT, DR) and a clinician-methodologist (KCW). The lead methodologist (TT) identified and collected the evidence, performed the evidence syntheses, constructed the evidence profiles, and ensured that all the methodological requirements were met, with assistance from the other methodologists. The

co-chairs and panelists discussed the evidence and formulated the recommendations; the methodologists did not participate in the development of recommendations. All panel members were required to disclose their conflicts of interest. At least 50% of the co-chairs and 50% of the panel were required to be free from conflicts of interest. Individuals with potential conflicts of interest took part in the discussions about the evidence but did not participate in the formulation of recommendations.

Formulation of questions

Task force members compiled a list of issues that they considered important and relevant to the treatment of COPD exacerbations. The questions were rephrased by the lead methodologist using the Population, Intervention, Comparator, and Outcomes (PICO) format (6). Discussion and consensus among the co-chairs and panelists was used to identify the six questions that would be addressed in the guideline.

Rating the importance of outcomes

After choosing the questions, the task force identified outcomes that they considered relevant to each question. They rated the importance of each outcome using a scale from 1 to 9 (a rating of 1 to 3 was assigned to outcomes of low importance for decision-making, 4 to 6 to outcomes important for decision-making, and 7 to 9 to outcomes critically important for decision-making). A teleconference was convened during which the ratings were discussed and some additional outcomes were rated. At the conclusion of the teleconference, all outcomes were categorized as “not important”, “important”, or “critical” for decision-making.

Literature searches

Our literature searches used the National Institute of Health and Clinical Excellence (NICE) guidelines as a starting point (5,7). For questions that were addressed in the 2004 NICE guidelines, we conducted literature searches in Medline, Embase, and the Cochrane Database of Systematic Reviews beginning in 2003. For questions that were addressed in the 2010 NICE guidelines, we conducted literature searches in the same databases beginning in 2009. Initial searches were conducted in January 2012 and then updated in June 2012, February 2013, and September 2015. We used the same or similar search strategies as those used by NICE. To search Embase and Medline, we searched only the English speaking literature using the search

strategy shown in the online supplement, whereas to search the Cochrane Database of Systematic Reviews, we used the search term, “chronic obstructive pulmonary disease”.

Study selection

The lead methodologist screened the titles and abstracts of the retrieved studies and excluded studies on the basis of the pre-defined study selection criteria shown in the online supplement. For those studies that could not be excluded by the title and abstract, we obtained the full text of the studies and then included or excluded the studies on the basis of our full text review. In cases of uncertainty, the opinions of the co-chairs and panelists were obtained and decisions were reached by discussion and consensus. We also screened the reference lists from recent and systematic reviews to ensure that our literature review had not missed relevant studies.

Evidence synthesis

Study characteristics, types of participants, interventions, the outcomes measured, and results were extracted from each study. If the data was amendable to pooling, effects were estimated via meta-analysis using Review Manager (8). For the meta-analyses, the random effects model was utilized unless otherwise specified. Dichotomous outcomes were reported as relative risks and continuous outcomes were reported as mean differences unless otherwise specified. The lead methodologist appraised the quality of evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach (9).

The lead methodologist used GRADEpro to develop evidence profiles that summarized the findings for each outcome and the rationale for the quality of evidence appraisal (10). Thresholds for clinically important changes (used to judge imprecision) included the following relative risk reductions: mortality 15%, exacerbations 20%, hospitalizations 20%, treatment failure 20%, and adverse events 15%. They also included the following absolute reductions: St. George’s Respiratory Questionnaire score change of 4 points and a forced expiratory volume in one second change of 100 mL. The thresholds for clinically important relative risk reductions were based upon the task force’s collective clinical experience and, for consistency, were chosen to be similar to the thresholds used to develop the NICE guidelines on COPD (7). The thresholds for clinically important absolute risk reductions were based upon published literature (11).

Formulating and grading recommendations

The evidence profiles were sent to the task force members for review. Using an iterative consensus process conducted face-to-face, via teleconference and via email, recommendations were formulated on the basis of the following considerations: the balance of desirable (benefits) and undesirable consequences (burden, adverse effects, cost) of the intervention, the quality of evidence, patient values and preferences, and feasibility (12).

A strong recommendation was made for an intervention when the panel was certain that the desirable consequences of the intervention outweigh the undesirable consequences, just as a strong recommendation would have been made against an intervention if the panel was certain that the undesirable consequences of the intervention outweigh the desirable consequences. A strong recommendation indicates that most well-informed patients would choose to have or not to have the intervention.

A conditional recommendation was made for an intervention when the panel was uncertain that the desirable consequences of the intervention outweigh the undesirable consequences, just as a conditional recommendation would have been made against an intervention if the panel was uncertain that the undesirable consequences of the intervention outweigh the desirable consequences. Reasons for uncertainty included low or very low quality of evidence, the desirable and undesirable consequences being finely balanced, or the underlying values and preferences playing an important role. A conditional recommendation indicates that well-informed patients may make different choices regarding whether to have or not have the intervention.

Manuscript preparation

The initial draft of the manuscript was prepared by the co-chairs, methodologists, and one panellist (MM). The panel members wrote the content for the online supplement, which was collated and edited by the co-chairs. Both the manuscript and the online supplement were reviewed, edited, and approved by all panel members prior to submission.

RESULTS

Question #1: Should oral corticosteroids be used to treat patients whose COPD exacerbation is mild enough to be treated as an outpatient (i.e., ambulatory patients)?

Summary of the evidence

We identified three relevant systematic reviews (13-15), which identified two trials that evaluated the effects of oral corticosteroids in ambulatory patients having a COPD exacerbation (16,18). Our own systematic review identified a third clinical trial (18). These three trials in a total of 204 patients informed the task force's judgments (16-18). The first trial enrolled 27 ambulatory patients who were having a COPD exacerbation, defined as subjective worsening of baseline cough or dyspnea for more than 24 hours, requiring a hospital visit, and at least one of the following: a 25% increase in beta-agonist use, increased sputum production, or increased sputum purulence (17). The patients were randomly assigned to receive a tapering dose of prednisone or placebo for nine days and then followed the patients for 14 days following the completion of the tapering dose. The second trial enrolled 147 patients who were being discharged from the emergency room after being seen for a COPD exacerbation, defined as having at least two of the following: a recent increase in breathlessness, sputum volume, or sputum purulence (16). The patients were randomly assigned to receive either 40 mg of oral prednisone or placebo for ten days and then followed the patients for 30 days from the initiation of treatment. The most recent trial randomly assigned 30 ambulatory patients who were having a COPD exacerbation to receive 30 mg of oral prednisolone or placebo for 14 days and then followed the patients during the treatment course only (18).

The task force identified a priori four outcomes as "critical" to guide treatment recommendations: treatment failure (composite of unscheduled visit to the physician, return to the emergency department because of worsening respiratory symptoms, hospitalisation, or un-masking of study medication due to worsening respiratory symptoms), hospital admissions, mortality, and time next COPD exacerbation. Change in quality of life and serious adverse events were considered "important" outcomes to guide treatment recommendations.

When the data were pooled via meta-analysis (**see Evidence Profile #1**), oral corticosteroids caused a trend toward fewer hospital admissions (7.9% vs. 17%, RR 0.49, 95% CI 0.23-1.06). There was no significant difference in treatment failure (26.5% versus 42.4%, RR 0.69, 95% CI 0.22-2.19) or mortality (1.1% vs. 1.1%, RR 0.99, 95% CI 0.06-15.48). The effect on treatment failure would be clinically important if real, but there were too few events to confirm or exclude the effect and the analysis was limited by severe heterogeneity of uncertain cause, as sensitivity analyses failed eliminate the heterogeneity. Data regarding length of hospital stay or time to next exacerbation were not reported in the three studies. Patients who received oral corticosteroids had better lung function, measured as the forced expired volume in the first second (FEV1; mean difference 0.16 L higher, 95% CI 0.04-0.28 L higher), but no significant difference in quality of life measured by the Chronic Respiratory Questionnaire (CRQ) score (mean difference 0.38 higher, 95% CI 0.09 lower - 0.85 higher), or serious adverse effects (2.2% vs. 1.1%, RR 1.97, 95% CI 0.18-21.29).

Benefits: Oral corticosteroids improved lung function in ambulatory patients having a COPD exacerbation. There was also a trend toward fewer hospitalizations.

Harms: Various adverse effects were reported in the studies, including seizures, insomnia, weight gain, anxiety, depressive symptoms, and hyperglycemia. However, it is unclear whether the methods used to assess harms were similar across the studies and there were too few serious adverse events reported to adequately evaluate the difference in the risk of harms with oral corticosteroids versus placebo in patients with COPD exacerbations treated in the ambulatory setting.

Other considerations: There was no information in any of the trials regarding the time to next exacerbation and inadequate information to have confidence regarding the effects of systemic corticosteroids on several outcomes considered critical or important to decision making (hospitalization, mortality, serious adverse events)**.**

Conclusions and research needs: A course of oral corticosteroids for 9 to 14 days in outpatients with COPD exacerbations improves lung function and causes a trend toward fewer hospitalisations. No effect on treatment failure, mortality, or adverse effects has been demonstrated, although there were too few events in the trials to definitively confirm or

exclude an effect on any of these outcomes. The task force judged that the benefits of oral corticosteroids likely outweigh the adverse effects, burdens, and costs, but was uncertain due to its very low confidence in the accuracy of the estimated effects.

Phenotypic identification of responders to oral corticosteroids is an area of research that should be explored. There are some data suggesting that patients with an elevated blood eosinophil count will respond more to oral corticosteroids than patients with a low blood eosinophil count. One randomized trial found that patients whose blood eosinophil count was ≥2% had greater improvement in their health-related quality of life and faster recovery after receiving oral corticosteroids compared to placebo. In contrast, in patients whose blood eosinophil count was <2% there was s significantly greater improvement in health-related quality of life in patients receiving placebo (19). Another study pooled data from three randomized trials of patients with a COPD exacerbation and found that systemic steroid-treated patients with a blood eosinophil count ≥2% have a treatment failure rate of only 11%, compared with a treatment failure rate of 66% among those in placebo arm. However, among patients with blood eosinophils <2% the rate of failure was 26% with prednisone and only 20% with placebo (20). Larger randomised controlled trials with stratification by blood eosinophil count are needed. Several studies suggest that an even shorter duration of systemic corticosteroid treatment (e.g., 3 days [21], 5 days [22], or 7 days [23]) may be as effective as longer courses in hospitalised patients with exacerbations of COPD; similar studies need to be performed in ambulatory patients. Finally, effectiveness studies conducted in real-life situations should be conducted to confirm the findings of efficacy trials.

What others are saying: The 2010 NICE Guidelines (5) concluded that, in the absence of significant contraindications, oral corticosteroids should be used in conjunction with other therapies in all patients admitted to hospital with an exacerbation of COPD and considered in patients in the community who have an exacerbation with a significant increase in breathlessness that interferes with daily activities. The 2014 GOLD Strategy document (24) concluded that “systemic corticosteroids are beneficial in the management of COPD. They shorten recovery time, improve lung function and hypoxemia, and may reduce the risk of early relapse, treatment failure, and length of hospital stay. A dose of 30-40 mg prednisone per day for 5 days is recommended”.

ATS/ERS recommendation:

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

Remarks:

The task force defines a short course of oral corticosteroids as 14 days or less.

Values and preferences:

This recommendation places a high value on a reduction in treatment failure and a lower value on the uncertainty regarding the potential for adverse events.

Question #2: Should antibiotics be administered to ambulatory patients who are having a COPD exacerbation?

Summary of the evidence

We identified three systematic reviews (25-27), which included four trials that evaluated antibiotic therapy in ambulatory patients with COPD exacerbations (28-31). Our own systematic review identified an additional relevant trial that was not included in the published systematic reviews (32). We pooled two of the five trials (28,32) that enrolled a total of 483 participants via meta-analysis to inform the task force's judgments (**see Evidence Table #3**). The remaining three trials were excluded because the diagnosis of COPD was inadequately established among patients enrolled (29); data on treatment failure were measured on day 5 (31) and the panel believed that five days are not enough to judge whether an exacerbation has resolved (33); and, publication was as an abstract only (30).

The task force identified a priori six outcomes as "critical" to guide treatment recommendations: treatment failure (composite of death, no resolution or deterioration), adverse events, time to next COPD exacerbation, hospitalization, length of hospital stay, and death.

Among the trials that were pooled, one randomly assigned 310 ambulatory patients who were having a COPD exacerbation to receive placebo or amoxicillin/clavulanate for 8 days (32), while the other randomly assigned 116 similar patients to receive placebo or any one of the following for 7 to 10 days: trimetoprim/sulfamethoxazole, amoxicillin, or doxycycline (28). Antibiotic therapy decreased treatment failure (27.9% vs. 42.2%, RR 0.67, 95% CI 0.51-0.87); this effect was driven entirely by lack of resolution and deterioration, since no deaths were reported. It also prolonged the time to the next exacerbation (difference of medians 73 days, p=0.015). There was a trend toward more adverse events among patients who received antibiotic therapy (14.6% vs. 7.9%, RR 1.84, 95% CI 0.95-3.57), although most of the adverse events were described as mild. Data regarding hospitalization, length of hospital stay, and death were not reported.

Benefits: Antibiotic therapy reduced the risk of treatment failure and increased the time between COPD exacerbations.

Harms: Patients who received antibiotic therapy had a trend toward more adverse events, most of which were mild gastrointestinal side effects (e.g., diarrhea).

Other considerations: In this evaluation of ambulatory exacerbations, there was no information in either trial about several outcomes of interest to the task force; specifically, the hospital admission rate, length of hospital stay, and mortality.

Conclusions and research needs: The use of antibiotics in ambulatory patients with exacerbations of COPD reduces the treatment failure rate, and increases the time to the next exacerbation. However, the majority of patients avoided treatment failure even in the placebo group (58%), suggesting that not all exacerbations require treatment with antibiotics. Effectiveness studies should be conducted in real-life situations to confirm the findings of efficacy trials. Identifying biomarkers of bacterial infection may allow the patient population that definitively requires antibiotic treatment to be more precisely selected (34). Additional research is needed to identify patients in whom antibiotic therapy is needed.

What others are saying: The 2010 NICE Guidelines (5) advise that antibiotics should be used to treat exacerbations of COPD associated with purulent sputum. However, the recommendation is not specific for ambulatory patients with COPD exacerbations. The 2014 GOLD Strategy document (24) state that antibiotics should be given to patients with COPD exacerbations who fulfil certain criteria; again, the recommendation is not specific to ambulatory patients having an exacerbation of COPD.

ATS/ERS recommendation:

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

Remarks:

Studies suggest that episodes that present with purulent sputum are most likely to benefit from antibiotic treatment; however, there may be other considerations (e.g., disease severity) when deciding whether or not to prescribe an antibiotic (24).

Values and preferences:

This recommendation places a high value on a reduction in treatment failure and extending the time between exacerbations, and a lower value on avoiding adverse events.

Question #3: Should intravenous or oral corticosteroids be used to treat patients who are hospitalized with a COPD exacerbation?

Summary of the evidence:

There is evidence supporting the use of systemic corticosteroids in patients with severe exacerbations of COPD treated in the hospital (5,24). However the need of high dosis intravenous corticosteroids for admitted patients with severe exacerbations may not have a higher efficacy and can potentially be associated to a higher risk of adverse events; therefore we searched for evidence comparing both routes of administration of corticosteroids in this population of patients.

We did not identify any systematic reviews comparing intravenous corticosteroids with oral corticosteroids in hospitalized patients with COPD exacerbations. Our own systematic review identified two trials in a total of 250 patients hospitalized with a COPD exacerbation (35,36). One trial randomly assigned 210 hospitalized patients with COPD exacerbations to receive either 60 mg of intravenous prednisolone plus oral placebo or 60 mg of oral prednisolone plus intravenous placebo for five days (35). Both groups received an oral prednisolone taper following the five days of full dose therapy (total duration 10 days). The other trial randomly assigned 40 patients to receive either 32 mg per day of oral methylprednisolone for seven days or 1 mg/kg per day of intravenous methylprednisolone for four days followed by 0.5 mg/kg per day of intravenous methylprednisolone for three days (total duration 10 days) (36).

The task force identified a priori five outcomes as "critical" to guide treatment recommendations: treatment failure (composite of death, admission to the intensive care unit, readmission to the intensive care unit due to COPD, or intensification of pharmacologic therapy), mortality, readmission to the hospital, length of hospital stay, and time next COPD exacerbation. Adverse events were considered "important" outcomes to guide treatment recommendations.

When the trial results were pooled (**see Evidence Profile #2**), there were no significant differences in treatment failure (53.5% for intravenous vs. 49.6% for oral corticosteroids, RR 1.09, 95% CI 0.87-1.37), mortality (5.5% for intravenous vs. 1.7% for oral corticosteroids, RR 2.78, 95% CI 0.67-11.51), hospital readmissions (14.2% for intravenous vs. 12.4% for oral corticosteroids, RR 1.13, 95% CI 0.60-2.13), or length of hospital stay (mean difference of 0.71 more days with intravenous steroids than oral steroids, 95% CI ranged from 1.35 fewer days to 2.78 more days). Data regarding time to next exacerbation were not reported in the studies.

One trial demonstrated an increased risk of mild adverse effects in the intravenous corticosteroids group (70% vs. 20%, RR 3.50, 95% CI 1.39-8.8) (36), which were easily treated with appropriate medications. Of note, the intravenous arm used a higher dose of corticosteroids than the oral arm; therefore, it is unknown whether the increased incidence of adverse effects was due to the route of administration or the dose. Neither trial reported any serious adverse effects.

Benefits: Among outcomes that are known to be improved by corticosteroids therapy (i.e., reduced treatment failure), there were no differences between oral and intravenous therapy.

Harms: Only one study (which enrolled a total of 40 participants) reported the frequency of adverse events, which were numerically higher in the group treated with intravenous corticosteroids than with oral corticosteroids (e.g., 11 vs. 4 developed hyperglycemia, 3 vs. 0 had worsening of hypertension, respectively) (36). However, these assessments were not performed masked to treatment assignment and there were too few events to make definitive conclusions about the relative risk of adverse events with either therapy. A large observational study of 80,000 non-ICU patients hospitalized with COPD exacerbations suggests that >90% of practitioners in the U.S. favor use of intravenous over oral corticosteroids in this population (37). Interestingly, patients in this study treated with intravenous corticosteroids had a longer length of stay and higher cost compared to those treated with oral corticosteroids without clear evidence of benefit (assessed using the composite outcome of death, need for mechanical ventilation, or 30-day readmission) (38).

Other considerations: There was no information in either trial about one of the outcomes of interest to the task force – the time to next exacerbation**.** There was a serious risk of bias due to lack of blinding for most outcomes and the number of events and patients were small for all outcomes; these features decreased the panel's confidence in the estimated effects.

Conclusions and research needs: Treatment failure, hospital readmissions, and length of hospital stay are not significantly different among patients who receive oral or intravenous corticosteroids; however, the results indicate that intravenous therapy might increase the risk of adverse effects. No effect on mortality has been shown, although there were too few deaths in the trials to definitively confirm or exclude an effect on mortality. Since the studies did not employ a non-inferiority design and the confidence intervals indicate imprecision for both benefits and harms, we cannot conclude that both intravenous and oral corticosteroids confer similar benefits and harms. There is therefore insufficient evidence to support one method of administration over the other. An adequately powered non-inferiority trial comparing the relative harms and benefits of intravenous vs. oral corticosteroids in this population is needed, particularly given the potential for increasing the length of stay and health care costs with intravenous therapy, as observed in the observational study.

What others are saying: The 2010 NICE Guidelines (5) did not compare oral and intravenous corticosteroids. The 2014 GOLD Strategy document (24) say that the oral prednisolone is preferable.

ATS/ERS recommendation:

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

Remarks:

Intravenous corticosteroids should be administered to patients who are unable to tolerate oral corticosteroids. Foregoing corticosteroid therapy in patients who cannot tolerate oral therapy is not an option due to the benefits of corticosteroid therapy.

Values and preferences:

This recommendation places a high value on the simplicity of providing oral compared to intravenous corticosteroids and the potential to reduce healthcare expenditures with oral therapy, rather than convincing evidence about benefits or harms supporting one form of administration over the other.

Question #4: Should non-invasive mechanical ventilation be used in patients who are hospitalized with a COPD exacerbation associated with acute or acute-on-chronic respiratory failure?

Summary of the evidence

We identified a systematic review (39) that included 14 randomized trials that evaluated the effects of non-invasive mechanical ventilation (NIV) on patients with acute respiratory failure due to a COPD exacerbation (40-53). Our own systematic review identified an additional seven relevant trials (54-60). These 21 trials formed the evidence base that was used to inform the task force's judgments. Many of the trials excluded patients with any of the following: inability

to cooperate, protect the airway, or clear secretions; severely impaired consciousness; facial deformity; high aspiration risk; or recent esophageal stenosis.

The task force identified a priori five outcomes as "critical" to guide treatment recommendations: death, intubation, length of hospital stay, length of ICU stay, and nosocomial pneumonia. Complications of treatment (e.g., aspiration, barotrauma) and pH one hour after intervention were considered "important" outcomes.

All of the trials enrolled hospitalized patients with respiratory failure due to a COPD exacerbation. In the overwhelming majority of the studies, the patients had confirmed acute or acute-on-chronic hypercapnic respiratory failure; a few of the studies did not specify that the respiratory failure was hypercapnic. Most the trials compared usual care plus NIV or usual care alone, although a few assigned patients to usual care plus NIV or usual care plus sham NIV. Due to the nature of the intervention, most of the trials were not blinded to the patients, caregivers, or assessors.

When the trials were pooled via meta-analysis (**see Evidence Table #4**), patients who received NIV had a lower mortality rate (7.1% vs. 13.9%; RR 0.54, 95% CI 0.38-0.76), were less likely to require intubation (12% vs. 30.6%; RR 0.43, 95% CI 0.35-0.53), had a shorter length of hospital stay (mean difference 2.88 days fewer, 95% CI 1.17-4.59 days fewer) and ICU stay (mean difference 4.99 days fewer, 95% CI 0-9.99 days fewer), and had fewer complications of treatment (15.7% vs. 42%; RR 0.39, 95% CI 0.26-0.59). There was no difference in the pH after one hour (mean difference 0.02, 95% CI 0.01-0.06). When we repeated the analyses using only the studies that had confirmed acute or acute-on-chronic hypercapnic respiratory failure, the results were essentially the same.

Benefits: NIV reduced the need for intubation, mortality, complications of therapy, and length of both hospital stay and ICU stay in patients with acute or acute-on-chronic respiratory failure due to a COPD exacerbation.

Harms: There were no reports of adverse consequences; to the contrary, complications of therapy were reduced in patients who received NIV.

Other considerations: Most of the trials had a serious risk of bias due to uncertain allocation concealment and lack of blinding. For some outcomes, the estimated effects were inconsistent across studies or the number of events and patients were small, diminishing confidence in the estimated effects. Some trials that enrolled our population of interest were not included in our analysis because the outcomes were unclearly or incompletely reported. Similarly, one of the outcomes of interest, the rate of nosocomial pneumonia, could not be assessed because the data was either not reported or incompletely reported. These considerations contributed to grading the quality of evidence as low.

Conclusions and research needs: Use of NIV in patients with acute or acute-on-chronic respiratory failure due to a COPD exacerbation reduces the need for intubation, mortality, complications of therapy, length of hospital stay, and length of ICU stay. Future research will determine strategies for optimizing the delivery of NIV, including the optimal technique NIV ventilation and type of interface selection. We need studies to address how to titrate and wean patients from NIV ventilation, and how to better determine which physiological effects should be expected during the application of NIV that predict treatment success or failure. The efficacy of home NIV in patients following a COPD-related hospitalization when NIV was utilized to treat acute-on-chronic respiratory failure is also an area that requires additional study. Recent data has reported conflicting outcomes regarding home NIV in the severe COPD outpatient population (61-64). Effectiveness studies should be conducted in real-life situations to confirm the findings of efficacy trials. Other research opportunities are related to decision-making about whether or when to intubate or not, as well as the use of NIV by health care providers, patients, and family members.

What others are saying: The 2010 NICE Guidelines (5) did not discuss the use of NIV in COPD exacerbations. In the 2004 NICE Guidelines, however, it was stated that NIV should be used as the treatment of choice for persistent hypercapnic ventilatory failure during exacerbations despite optimal medical therapy. The 2014 GOLD Strategy document (24) state that, in patients with acute respiratory failure due to a COPD exacerbation, NIV improves respiratory acidosis and decreases the intubation rate, mortality, respiratory rate, severity of breathlessness, complications (e.g., ventilator associated pneumonia), and length of hospital stay. They recommend the use of NIV in patients with a) respiratory acidosis or b) severe

dyspnea with clinical signs suggestive of respiratory muscle fatigue, increased work of breathing, or both, such as use of respiratory accessory muscles, paradoxical motion of the abdomen, or retraction of the intercostal spaces.

ATS/ERS recommendation:

For hospitalized patients with acute or acute-on-chronic hypercapnic respiratory failure due to a COPD exacerbation, we recommend the use of NIV (strong recommendation, low quality of evidence).

Remarks:

The strong recommendation despite the panel's low confidence in the estimated effects reflects the panel's consensus opinion that the overwhelming majority of patients would want NIV given the possibility of one or more important clinical benefits with minimal risk of harm. Many of the trials excluded patients with any of the following: inability to cooperate, protect the airway, or clear secretions; severely impaired consciousness; facial deformity; high aspiration risk; or recent esophageal stenosis.

Values and preferences:

This recommendation places a high value on reducing mortality and the need for invasive mechanical ventilation and a lower value on the burdens associated with NIV.

Question #5: Should a home-based management program ("hospital-at-home") be implemented in patients with COPD exacerbations?

Summary of the evidence

A home-based management program involving nurses and potentially other healthcare professionals (e.g., physicians, social worker, physical therapists), also known as "hospital-at-home", offers the option of an early assisted hospital discharge or an alternative to hospitalization in patients presenting to the emergency department with a COPD exacerbation. Clinical trials have compared home-based management to usual care in patients with COPD exacerbations who meet other additional eligibility criteria (e.g., absence of

impaired level of consciousness, decompensated heart failure or other acute condition, or need for mechanical ventilation). We found a systematic review (65) that included eight relevant trials (66-73). Our own systematic review identified one additional trial (74). These nine trials formed the evidence base that was used to inform the task force's judgment. All of the trials enrolled patients who presented with COPD exacerbations; five trials evaluated hospital admission versus discharge to a hospital-at-home from the emergency department (67-69,71,72), three trials assessed ongoing hospital admission versus discharge to a hospital at home following an initial hospitalization (66,73,74), and in one trial the setting of the discharge could not be determined (70). Four trials were conducted in the United Kingdom (66,67,71,73), four trials were conducted in other European countries (68,70,72,74), and one trial was conducted in Australia (69).

The task force identified a priori three outcomes as "critical" to guide treatment recommendations: death, hospital readmission, and time to first readmission. Hospital acquired infections and quality of life were considered "important" outcomes.

When the trials were pooled via meta-analysis (**see Evidence Table #5**), home-based management reduced hospital readmissions (26.8% vs. 34.2%, RR 0.78, 95% CI 0.62-0.99) and was associated with a trend toward lower mortality (5.6% vs. 8.5%, RR 0.66, 95% CI 0.41-1.05). There was no difference in the time to first readmission (mean difference of 8 days longer among patients in the home-based management group, 95% CI 19.7 days longer to 3.7 days shorter). No data were reported on hospital acquired infections or quality of life.

The task force raised the possibility that a home-based management may have different effects among patients who are discharged from the emergency department compared to patients who are discharged following an initial hospitalization. To address these concerns, a post hoc stratified analysis was performed (**see Evidence Table #5**); the results of these analyses did not provide convincing evidence to indicate differential effects among patients discharged from different locations or to exclude the possibility of heterogeneity of treatment effects.

Benefits: Utilization of a home-based management model reduced the number of hospital readmissions and, possibly, mortality in patients with COPD exacerbations. .

Harms: Adverse events were not an outcome reported in any of the included trials; therefore, there exists no data regarding the potential harms of the home-based management model.

Other considerations: For most of the outcomes, the number of events and patients in the trials were small, diminishing confidence in the estimated effects. There was no information reported for one outcome of interest to the task force, the rate of hospital-acquired infections. In addition, there was insufficient information to draw conclusions regarding another outcome of interest, quality of life (i.e., among the three trials that reported quality of life, one did not provide standard deviations, another only provided St. George's Respiratory Questionnaire scores for a subgroup of participants, and a third measured generic health-related quality of life using the EuroQoL-5D scale). Moreover, the eligibility criteria varied across studies and the capacity of health systems to deliver home-based care for this population may vary.

Although not pre-specified by the task force as outcomes of interest, it is worth noting that four trials reported costs and three reported patient and provider satisfaction. Among the trials that evaluated costs, two found lower costs for hospital at home programs (69,72), one found a trend toward lower costs (68), and one found no difference (75). Among the three trials that evaluated patient and provider satisfaction, all reported no differences (71,72,76). While no differences in overall satisfaction were found, the majority of patients indicated that they would prefer home treatment if they were allowed to choose.

Conclusions and research needs: The home-based management program model in patients with a COPD exacerbation reduces hospital admissions, making it a safe and effective way of discharging patients with additional home-based support in appropriately selected patients. This may increase the availability of hospital beds and reduce pressure on clinicians to discharge patients whose readiness is uncertain. The home-based model might also reduce mortality; however, there were too few deaths in the trials to definitively confirm or exclude an effect.

One of the major research needs for home-based management is the development of algorithms to screen patients to determine which are or are not appropriate for home-based

care. Some studies suggest that home treatment of COPD exacerbations should be considered in all patients unless there are mental status changes, confusion, hypercarbia, refractory hypoxemia, serious co-morbid conditions, or inadequate social support. However, these criteria need to be prospectively evaluated to define the most appropriate selection criteria. The feasibility of home-based administration of medications for COPD exacerbations (i.e., systemic corticosteroids, antibiotics, nebulized bronchodilators, supplemental oxygen) may vary by patient characteristics (e.g., ability to carry out activities of daily living, level of social support) or by the capacity of the health system or home health agency. Studies are needed to define the patient selection criteria and key elements of the home-based program (e.g., nurse or interprofessional teams that include a physician, respiratory therapist, or social worker; treatment plan at home; criteria for treatment failure at home and need for hospitalization). Finally, studies are needed to prospectively evaluate the potential for heterogeneity of treatment effects according to whether the home-based management program is intended to avoid a hospitalization or to facilitate early discharge from the hospital to home. Many of these studies may be best conducted as effectiveness studies in real-life situations; at a minimum, effectiveness studies should be conducted to confirm the findings of efficacy trials.

What others are saying: The 2010 NICE guidelines (5) did not include a section on home-based management of patients with COPD exacerbations, but referred to it briefly as something that respiratory nurse specialists might be involved in. The 2014 GOLD strategy document (24) stated that “hospital at home represents an effective and practical alternative to hospitalisation in selected patients with exacerbations of COPD without acidotic respiratory failure." However, the exact criteria for this approach as opposed to hospital treatment remain uncertain and will vary by health care setting. Treatment recommendations are the same for hospitalised patients”.

ATS/ERS recommendation:

For patients with a COPD exacerbation who present to the emergency department or hospital, we suggest a home-based management program (“hospital-at-home”; conditional recommendation, moderate quality of evidence).

Remarks:

Appropriately selected patients may include those who do not have acute or acute-on-chronic ventilatory respiratory failure, respiratory distress, hypoxemia requiring high-flow supplemental oxygen, an impaired level of consciousness, cor pulmonale, a need for full-time nursing care, other reasons for hospitalization (e.g., myocardial ischemia), housing or food insecurity, poor social support, or active substance abuse.

Values and preferences:

This recommendation places a high value on reducing hospital readmissions, improving patient safety, and potentially also decreasing mortality, and a lower value on the burdens of caring for acutely ill patients at home.

Question #6: Should pulmonary rehabilitation be implemented in patients hospitalized with a COPD exacerbation?

Summary of the evidence

We identified a systematic review (76) that included nine trials that randomly assigned hospitalized patients with COPD exacerbations to early pulmonary rehabilitation plus usual care or usual care alone (78-86). The pulmonary rehabilitation programs all included physical exercise that was initiated within three weeks of initiating treatment for a COPD exacerbation treatment; in five trials, pulmonary rehabilitation was initiated during the hospitalization (78,80,81,84,86) and, in three trials, pulmonary rehabilitation was initiated following discharge (82,83,85). We excluded one of the trials because the patients had already completed a pulmonary rehabilitation program in the past and the trial assessed a repeat program (79).

Our own systematic review identified five additional relevant randomized trials (87-91), with 2 studies enrolling hospitalized patients (90,91) and 3 studies enrolling patients up to 8 weeks after hospital discharge (87-89). Each trial implemented pulmonary rehabilitation differently: health education and exercise training beginning within two months following hospital discharge (87); training in breathing techniques and physical exercise, beginning two to three weeks after hospital discharge (88); strength and aerobic exercise training, chest physiotherapy for secretion drainage, breathing retraining, nutrition, and psychosocial support beginning within two weeks after discharge (89); twice daily exercise training of varying

intensity initiated during hospitalization (90); and, progressive strength and aerobic exercise initiated within 48 hours of admission (91).

These 13 trials formed the evidence base used to inform the task force's decisions. The task force identified a priori three outcomes as "critical" to guide the formulation of treatment recommendations: death, hospital readmission, and quality of life. Exercise capacity was considered an "important" outcome.

Pooling the trials via meta-analysis (**see Evidence Table #6**) suggested that pulmonary rehabilitation following admission for an exacerbation may have reduced hospital readmissions (44.6% vs. 51.3%; RR 0.56, 95% CI 0.33-.93), improved quality of life as measured by a change in the St. George's Respiratory Questionnaire score (mean difference -11.75, 95% CI -19.76 to -3.75), and improved exercise capacity as measured by the six-minute walking test (mean difference +88.89 m, 95% CI +26.67 m to +151.11 m). However, these estimates were uncertain due to inconsistent results for across trials (I^2=73% for hospital readmissions, I^2=70% for quality of life, and I^2=97% for exercise capacity). With respect to mortality, we excluded one trial from the mortality analysis because the panel decided that its measurement of deaths in the ICU was potentially misleading (84); when the remaining trials were pooled, there was no significant difference among those who did or did not receive pulmonary rehabilitation (19.6% vs. 14.1%; RR 1.44, 95% CI 0.97 to 2.13; I^2=0% for mortality).

The panel hypothesized that differences in the timing of the initiation of pulmonary rehabilitation may have been the cause of the inconsistent results across trials. To test this hypothesis, a post hoc stratified analysis was performed. Patients who initiated pulmonary rehabilitation during their hospitalization had increased mortality (23.8% vs. 15.6%; RR 1.54, 95% CI 1.03 to 2.29), increased exercise capacity (mean difference +107.92 m, 95% CI +17.57 m to +198.27 m), and no difference in hospital readmissions (52.9% vs. 52.9%; RR 0.74, 95% CI 0.39-1.40), although all outcomes except mortality continued to have serious heterogeneity. The effect of pulmonary rehabilitation initiated after hospital discharge (up to 3 weeks after discharge) on mortality was uncertain due to the wide confidence interval (2.0% vs. 7.8%; RR 0.37, 95% CI 0.06 to 2.29). However, pulmonary rehabilitation initiated after hospital discharge (up to 3 weeks after discharge) reduced hospital readmissions (21.5% vs. 46.8%; RR 0.37, 95% CI 0.14 to 0.97) and improved quality of life (mean difference -11.75, 95% CI -19.76

to -3.75). Similarly, pulmonary rehabilitation initiated after hospital discharge (up to 8 weeks after discharge) increased exercise capacity (mean difference +57.47 m, 95% CI +20.04 m to +94.89 m). Again all outcomes except mortality continued to have serious heterogeneity. It is important to recognize, however, that the inconsistency across trials reflect variable magnitudes of effect (i.e., some studies showed a large benefit while others found a small benefit) and not differences in the direction of the effect.

Four of the trials evaluated adverse outcomes, three of which detected none (78,80,82). The remaining trial reported that 6 out of 32 patients (19%) had at least one adverse event (2 events occurred in two patients in the control group, whereas 11 events occurred in 4 patients in the exercise groups) (90). Only one of these adverse events was considered to be serious; a patient in one of the experimental groups had an episode of atrial fibrillation with accompanying chest pain.

Benefits: Pulmonary rehabilitation initiated during hospitalization increased exercise capacity. Pulmonary rehabilitation initiated within three weeks following discharge reduced hospital readmissions and improved quality of life. Pulmonary rehabilitation initiated within eight weeks following discharge increased exercise capacity.

Harms: Pulmonary rehabilitation initiated during hospitalization increased mortality. Other serious adverse events occurring during pulmonary rehabilitation were rare.

Other considerations: The reliability of the estimated effects for all outcomes other than mortality is limited by inconsistency across trials in both the primary analysis and the stratified analysis. In addition to inconsistency, confidence in the estimated effects for all other outcomes was reduced because all of the trials had a risk of bias due to uncertain allocation concealment, lack of adherence to the intention-to-treat principle, and/or lack of blinding.

Conclusions and research needs: Pulmonary rehabilitation implemented during hospitalization increases mortality. Pulmonary rehabilitation implemented within three weeks after discharge following a COPD exacerbation reduces hospital admissions and improves quality of life, while pulmonary rehabilitation implemented within eight weeks after discharge increases exercise

capacity. Research is needed to identify the interventions that provide the greatest benefits; some studies suggest that a combination of regular exercise with breathing technique training may be best, but additional investigations are needed. Studies employing methodologies of implementation science (also known as knowledge translation) are needed to test strategies that systematically target barriers and facilitators of integrating pulmonary rehabilitation into the care of patients with COPD exacerbations after hospital discharge.

What others are saying: The 2010 NICE guidelines concluded that "pulmonary rehabilitation should be made available to all appropriate people with COPD including those who have had a recent hospitalization for an acute exacerbation" (5).

ATS/ERS recommendations:

1. For patients who are hospitalized with a COPD exacerbation, we suggest the initiation of pulmonary rehabilitation within three weeks after hospital discharge (conditional recommendation, very low quality of evidence).
2. For patients who are hospitalized with a COPD exacerbation, we suggest NOT initiating pulmonary rehabilitation during hospitalization (conditional recommendation, very low quality of evidence).

Remarks: Early pulmonary rehabilitation refers to a program that consists of physical exercise and education, which begins within three weeks of the start of treatment of the exacerbation.

Values and preferences: This recommendation places a high value on improving clinical outcomes and a lower value on the burden and cost of pulmonary rehabilitation.

SUMMARY

The task force utilized comprehensive evidence syntheses to inform its judgments regarding the balance of benefits versus burdens, adverse effects, and costs; the quality of evidence; the feasibility; and the acceptability of various interventions for COPD exacerbations. A strong recommendation was made for non-invasive mechanical ventilation in patients with acute hypercapnic respiratory failure. Conditional recommendations were made for oral

corticosteroids in outpatients, oral rather than intravenous corticosteroids in hospitalized patients, antibiotic therapy, home-based management of appropriately selected patients, and initiation of pulmonary rehabilitation within three weeks of hospital discharge (Table 1). A conditional recommendation was made against the initiation of pulmonary rehabilitation during hospitalization. These recommendations should be reconsidered as new evidence becomes available.

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Table 1: Recommendations for the treatment of COPD exacerbations

	Recommendation	Strength	Quality of Evidence
1	For ambulatory patients with an exacerbation of COPD, we suggest a short course (14 days or less) of oral.	Conditional	Very low
2	For ambulatory patients with an exacerbation of COPD, we suggest the administration of antibiotics.	Conditional	Moderate
3	For patients who are hospitalized with a COPD exacerbation, we suggest the administration of oral corticosteroids rather than intravenous corticosteroids if gastrointestinal access and function are intact.	Conditional	Low
4	For patients who are hospitalized with a COPD exacerbation associated with acute or acute-on-chronic respiratory failure, we recommend the use of non-invasive mechanical ventilation.	Strong	Low
5	For patients with a COPD exacerbation who present to the emergency department or hospital, we suggest a home-based management program (“hospital-at-home”).	Conditional	Moderate
6	For patients who are hospitalized with a COPD exacerbation, we suggest the initiation of pulmonary rehabilitation within three weeks after hospital discharge.	Conditional	Very low
7	For patients who are hospitalized with a COPD exacerbation, we suggest NOT initiating pulmonary rehabilitation during hospitalization.	Conditional	Very low

Evidence Profile #1

Comparison: **Oral corticosteroids vs. no corticosteroids for ambulatory COPD exacerbations**
Bibliography: **16)** Aaron SD, Vandemheen KL, Hebert P, et al. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. New Engl J Med 2003; 348:2618-2625; **17)** Thompson W, Nielson C, Carvalho P, et al. Controlled Trial of Oral Prednisone in Outpatients with Acute COPD Exacerbation. Am J Respir Crit Care Med 1996; 154:407-412; **18)** Bathoorn E, Liesker JJ, Postma DS, et al. Anti-inflammatory effects of combined budesonide/formoterol in COPD exacerbations. COPD J Chronic Obstructive Pulm Dis 2008; 5:282-290.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oral corticosteroids**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Treatment failure (an unscheduled visit to the physician, a return to the ER because of worsening of dyspnea, hospitalisation, or dyspnea requiring open label CS) (%)												
3	randomised trials	not serious[1]	serious[2]	serious[3]	serious[4]	none	26/98 (26.5%)	42/99 (42.4%)	**RR 0.69** (0.22 to 2.19)	132 fewer per 1000 (from 331 fewer to 505 more)	⊕OOO VERY LOW	CRITICAL
Hospital admission (%)												
3	randomised trials	not serious[1]	not serious	serious[3]	serious[4]	none	8/101 (7.9%)	17/100 (17%)	**RR 0.49** (0.23 to 1.06)	87 fewer per 1000 (from 131 fewer to 10 more)	⊕⊕OO LOW	CRITICAL
Mortality (%)												
2	randomised trials	not serious	not serious	serious[5]	serious[4]	none	1/87 (1.1%)	1/87 (1.1%)	**RR 0.99** (0.06 to 15.48)	0 fewer per 1000 (from 11 fewer to 166 more)	⊕⊕OO LOW	CRITICAL
Time to next exacerbation (days)												
NR[5]	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Change in quality of life (CRQ) (Better indicated by higher values)												

1	randomised trials	not serious	not serious	serious[6]	serious[4]	none	74	64	-	**MD 0.38 higher** (0.09 lower to 0.85 higher)	⊕⊕OO LOW	IMPORTANT
Serious adverse events (%)												
2	randomised trials	not serious	not serious	serious[5]	serious[4]	none	2/89 (2.2%)	1/88 (1.1%)	**RR 1.97** (0.18 to 21.29)	11 more per 1000 (from 9 fewer to 231 more)	⊕⊕OO LOW	IMPORTANT

Abbreviations: CI= confidence interval; ER= emergency room; CS= corticosteroids; RR= relative risk; COPD= chronic obstructive pulmonary disease; CRQ= chronic respiratory disease questionnaire; FEV1= forced expiratory volume in one second; MD= mean difference; NR= not reported.

[1] In one of the trials (Thompson, et al), the steroid group had more patients taking an inhaled corticosteroid than the placebo group; however, the task force did not deem the imbalance serious enough to warrant downgrading the quality of evidence.

[2] In two trials, the estimated effect favored steroids (Aaron, et al. and Thompson, et al.), whereas in one trial the estimated effect favored placebo (Bathoorn, et al).

[3] One of the trials enrolled patients who presented to the emergency department (Aaron, et al.) and, in another trial, more than half of patients were enrolled in the emergency department (Thompson, et al.), suggesting that many of the patients had a more severe exacerbation than those for whom the question is intended.

[4] The ends of the confidence interval lead to opposite clinical actions.

[5] The larger of the trials enrolled patients who presented to the emergency department (Aaron, et al.), suggesting that many of the patients studied had a more severe exacerbation than those for whom the question is intended.

[6] The trial enrolled patients who presented to the emergency department (Aaron, et al.), suggesting that many of the patients studied had a more severe exacerbation than those for whom the question is intended.

Evidence Profile #2

Comparison: Antibiotics vs. no antibiotics for COPD exacerbations
Bibliography: 27) Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Anales de Medicina Interna 1987; 106(2):196–204; **31)** Llor C, Moragas A, Hernandez S, Bayona C, Miravitlles M. Efficacy of antibiotic therapy for acute exacerbations of mild to moderate COPD. Am J Respir Crit Care Med 2012;186:716-23.

Quality assessment							No. of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antibiotics**	**Placebo**	**Relative effect (95% CI)**	**Absolute effect**		
Treatment failure (defined as death or no resolution or deterioration of symptoms after a trial of medication of any duration) (%)												
2	randomised trials	not serious	not serious	not serious	serious[1]	none	60/215 (27.9%)	89/211 (42.2%)	**RR 0.67** (0.51 to 0.87)	139 fewer per 1000 (from 55 fewer to 207 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Adverse Events (%)												
1	randomised trials	not serious	not serious	not serious	serious[1]	none	23/158 (14.61%)	12/152 (7.9%)	**RR 1.84** (0.95 to 3.57)	66 more per 1000 (from 4 fewer to 203 more)	⊕⊕⊕O MODERATE	CRITICAL
Time to next exacerbation (days)												
1	randomised trials	not serious	not serious	not serious	not serious	none	158	152	-	**Diff med = 73 days**[2] Median 233 days (IQR 110-365) with antibiotics vs. 160 days (IQR 66 to 365) with placebo; p=0.015	⊕⊕⊕⊕ HIGH	CRITICAL
Mortality (%)												
NR	-	-	-	-	-	-	-	-	-	-	–	CRITICAL

Length of hospital stay (days)												
NR	-	-	-	-	-	-	-	-	-	-	–	CRITICAL
Hospital admission (%)												
NR	-	-	-	-	-	-	-	-	-	-	–	CRITICAL

Abbreviations: CI= confidence intervals; RR= relative risk; MD= mean difference; MeD= median difference.

[1] Wide confidence intervals; the ends of the confidence interval would lead to different clinical decisions

[2] Patient level data was not reported; therefore, the difference in the medians with 95% CI could not be calculated via a Wilcoxon-Mann-Whitney test.

Evidence Profile #3

Comparison: Intravenous corticosteroids vs. oral corticosteroids for COPD exacerbations
Bibliography: **34)** de Jong YP, Uil SM, Grotjohan HP, Postma DS, Kerstjens HA, and van den Berg JW. Oral or IV prednisolone in the treatment of COPD exacerbations: a randomized, controlled, double-blind study. Chest 2007; 132(6): 1741-1747; **35)** Ceviker Y, Sayiner A, et al. Comparisons of two systemic steroid regimens for the treatment of COPD exacerbations. Pulm Rehab Ther 2014; 27, 179-183.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IV CS**	**Oral CS**	**Relative (95% CI)**	**Absolute (95% CI)**		
Treatment failure (follow up at 90 days; defined as death, admission to the ICU, readmission to the ICU because of COPD, or intensification of pharmacological therapy) (%)												
2	randomised trials	serious[1]	not serious	not serious	serious [2]	none	68/127 (53.5%)	60/121 (49.6%)	**RR 1.09** (0.87 to 1.37)	45 more per 1000 (from 64 fewer to 183 more)	⊕⊕◯◯ LOW	CRITICAL
Mortality (%)												
2	randomised trials	serious[1]	not serious	not serious	serious [2]	none	7/127 (5.5%)	2/121 (1.7%)	**RR 2.78** (0.67 to 11.51)	29 more per 1000 (from 5 fewer to 174 more)	⊕⊕◯◯ LOW	CRITICAL
Readmission to hospital (%)												
2	randomised trials	serious[1]	not serious	not serious	serious [2]	none	18/127 (14.2%)	15/121 (12.4%)	**RR 1.13** (0.60 to 2.13)	16 more per 1000 (from 50 fewer to 140 more)	⊕⊕◯◯ LOW	CRITICAL
Length of hospital stay (days)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IV CS**	**Oral CS**	**Relative (95% CI)**	**Absolute (95% CI)**		
2	randomised trials	serious[1]	not serious	not serious	serious [2]	none	127	121	-	**MD 0.71 days more** (1.35 fewer to 2.78 more)	⊕⊕◯◯ LOW	CRITICAL
Time to next exacerbation (days)												
NR	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Adverse events (%)												
1	randomised trials	serious[1]	not serious	not serious	serious [2]	none	14/20 (70%)	4/20 (20%)	**RR 3.50** (1.39-8.8)	500 more per 1000 (from 192 more to 695 more)	⊕⊕◯◯ LOW	IMPORTANT

Abbreviations: CS= corticosteroids; CI= confidence intervals; RR= relative risk; ICU= intensive care unit; COPD= chronic obstructive pulmonary disease; FEV1= forced expiratory volume in one second; SGRQ= St. George's Respiratory Questionnaire; MD= mean difference; NR= not reported.

[1] One of the trials (Ceviker, et al.) did not blind the patients or clinicians, thereby allowing the possibility of bias due to co-interventions.

[2] Wide confidence intervals; the ends of the confidence interval would lead to different clinical decisions

[3] Higher SGRQ scores normally indicate more physical limitations; however, the authors reported improvement in some domains.

Evidence Profile #4

Comparison: Usual care plus non-invasive mechanical ventilation vs. usual care alone for COPD exacerbations.

Bibliography: **39)** Andeev S, Tretyakov A, Grigoryants R, Kutsenko M, Chuchalin A. Noninvasive positive airway pressure ventilation: role in treating acute respiratory failure caused by chronic obstructive pulmonary disease. Anesteziologita Reanimatologia 1998;3:45-51. **40)** Barbe R, Togores B, Rubi M, Pons S, Maimo A, Agusti A. Noninvasive ventilatory support does not facilitate recovery from acute respiratory failure caused by chronic obstrucive pulmonary disease. Eur Respir J 1996;9:1240-5. **41)** Bott J, Carroll M, Conway J, Keilty S, Ward E, Brown A et al. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. Lancet 1993;341(8860):1555-7. **42)** Brochard L, Mancebo J, Wysocki M, Lofaso F, Conti G, Rauss A et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. New Engl J Med 1995;333(13):817-22. **43)** Celikel T, Sungur M, Ceyhan B, Karakurt S. 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Int J Clinical Pract 2002;56(2):85-8. **47)** Khilnani GC, Saikia N, Banga A, Sharma SK. Non-invasive ventilation for acute exacerbation of COPD with very high PaCO(2): A randomized controlled trial. Lung India 2010 July;27(3):125-30. **48)** Kramer N, Meyer T, Meharg J, Cece R, Hill N. Randomised prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. Am J Resp Crit Care Med 1995;151(6):1799-806. **49)** Plant P, Owen J, Elliott M. Early use of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicenter, randomised, controlled trial. Lancet 2000;355(9219):1931-5. **50)** Servillo G, Ughi L, Rossano F, Leone D. Nonionvasive mask pressure support ventilation in COPD patients. Intensive Care Medicine 1994;20:S54. **51)** Thys F, Roeseler J, Reynaert M, Liistro G, Rodenstein D. 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Non-invasive ventilation in chronic hypercapnic COPD patients with exacerbation and a pH of 7.35 or higher. European Journal of Internal Medicine 2007; 18(7):524-530; **56)** Schmidbauer W, Ahlers O, Spies C, Dreyer A, Mager G, and Kerner T. Early prehospital use of non-invasive ventilation improves acute respiratory failure in acute exacerbation of chronic obstructive pulmonary disease. Emergency Medicine Journal 2011; 28(7):626-627. **57)** Vargas F, Bui HN, Boyer A, Salmi LR, Gbikpi-Benissan G, Guenard H, Gruson D, and Hilbert G. Intrapulmonary percussive ventilation in acute exacerbations of COPD patients with mild respiratory acidosis: a randomized controlled trial. Critical Care 2005; 9(4):R382-R389. **58)** Wang C. Collaborative Research Group of Noninvasive Mechanical Ventilation for Chronic Obstructive Pulmonary Disease. 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Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NIV**	**Usual Care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (%)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NIV**	**Usual Care**	**Relative (95% CI)**	**Absolute (95% CI)**		
17	randomised trials	serious[1]	not serious	not serious	not serious	none	41/575 (7.1%)	81/581 (13.9%)	**RR 0.54** (0.38 to 0.76)	50 fewer per 1000 (from 20 fewer to 80 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Intubation rate (%)												
21	randomised trials	serious[2]	not serious	not serious	not serious	none	80/664 (12.0%)	205/670 (30.6%)	**RR 0.43** (0.35 to 0.53)	190 fewer per 1000 (from 120 fewer to 270 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Length of hospital stay (days)												
15	randomised trials	serious[3]	serious[4]	not serious	not serious	none	577	582	-	**MD 2.88 days fewer** (4.59 fewer to 1.17 fewer)[5]	⊕⊕◯◯ LOW	CRITICAL
Length of ICU stay (days)												
3	randomised trials	serious[6]	not serious	not serious	serious[7]	none	35	26	-	**MD 4.99 fewer** (9.99 fewer to 0)	⊕⊕◯◯ LOW	CRITICAL
Complications of treatment (%)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NIV**	**Usual Care**	**Relative (95% CI)**	**Absolute (95% CI)**		
5	randomised trials	serious[8]	not serious	not serious	not serious	none	22/140 (15.7%)	60/143 (42.0%)	**RR 0.39** (0.26 to 0.59)	256 fewer per 1000 (from 172 fewer to 310 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
pH one hour post-intervention												
13	randomised trials	serious[9]	serious[10]	not serious	serious[7]	none	521	522	-	**MD 0.02 higher** (0.01 lower to 0.06 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
Nosocomial pneumonia (%)												
NR	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

Abbreviations: NIV= non-invasive mechanical ventilation; CI= confidence intervals; RR= relative risk; MD= mean difference; ICU= intensive care unit.

[1] 7 out of 17 trials had unclear allocation concealment; none of the 17 trials was blinded.
[2] 9 out of 21 trials had unclear concealment of allocation; only one out of 21 trials was blinded.

[3] 5 out of 15 trials had unclear allocation concealment; only one of the 15 trials was blinded.

[4] There was significant heterogeneity, I^2=82%. In addition, one patient in Keenan et al. was an outlier; however sensitivity analysis excluding the outlier did not significantly change the result or the heterogeneity level.

[5] The values reported for Carrera et al. were assumed to be mean and standard deviation.

[6] 1 out of 3 trials had unclear concealment of allocation; 2 out of 3 studies were no blinded.

[7] Wide confidence intervals; the ends of the confidence interval would lead to different clinical decisions.
[8] 1 out of 5 studies had unclear concealment of allocation; none of the studies were blinded.
[9] 5 out of13 studies had unclear concealment of allocation; none of the studies were blinded.
[10] There was significant heterogeneity, I^2=93%.

Evidence Profile #5

Comparison: Hospital-at-home vs. hospital admission for acute exacerbations of COPD.

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Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Hospital at home**	**Hospital admission**	**Relative (95% CI)**	**Absolute**		
Hospital readmission (%)												
All trials												
9[1]	randomised trials	not serious	not serious[2]	not serious	serious[3]	none	153/571 (26.8%)	150/438 (34.2%)	**RR 0.78** (0.62 to 0.99)	80 fewer per 1000 (from 0 fewer to 130 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Trials that discharged patients from the emergency department to a hospital-at-home												
5[4]	randomised trials	not serious	serious[5]	not serious	serious[3]	none	93/316 (29.4%)	92/245 (37.6%)	**RR 0.81** (0.54 to 1.20)	71 fewer per 1000 (from 173 fewer to 75 more)	——	——
Trials that discharged patients to a hospital-at-home following a brief hospitalization												

3[6]	randomised trials	not serious	not serious	not serious	serious[3]	none	56/233 (24.0%)	50/171 (29.2%)	**RR 0.82** (0.59 to 1.13)	53 fewer per 1000 (from 120 fewer to 38 more)	——	——
Mortality (%)												
All trials												
8[7]	randomised trials	not serious	not serious	not serious	serious[3]	none	31/558 (5.6%)	36/426 (8.5%)	**RR 0.66** (0.41 to 1.05)	30 fewer per 1000 (from 50 fewer to 5 more)	⊕⊕⊕O MODERATE	CRITICAL
Trials that discharged patients from the emergency department to a hospital-at-home												
4[8]	randomised trials	not serious	not serious	not serious	serious[3]	none	24/303 (7.9%)	26/233 (11.1%)	**RR 0.74** (0.43 to 1.27)	29 fewer per 1000 (from 64 fewer to 30 more)	——	——
Trials that discharged patients to a hospital-at-home following a brief hospitalization												
3[6]	randomised trials	not serious	not serious	not serious	serious[3]	none	6/233 (2.6%)	10/171 (5.8%)	**RR 0.37** (0.14 to 1.00)	37 fewer per 1000 (from 50 fewer to 0 fewer)	——	——
Time to first readmission (days)												
1	randomised trials	not serious	not serious	not serious	serious[3]	none	70	69	-	**MD 8 higher** (3.7 lower to 19.7 higher)	⊕⊕⊕O MODERATE	CRITICAL
Hospital acquired infections (%)												
NR	-	-	-	-	-	-	-	-	-	-	_	IMPORTANT
Quality of Life (SGRQ) (Better indicated by lower values)												

NR[9]	-	-	-	-	-	-	-	-	-	-	–	IMPORTANT

Abbreviations: CI= confidence intervals; RR= relative risk; FEV1= forced expiratory volume in one second; MD= mean difference; SMD= standard mean difference; QoL= quality of life; SGRQ= St. George's Respiratory Questionnaire; NR= not reported.

[1] Davies 2000; Hernandez 2003; Ojoo 2002; Ricauda 2008; Nicholson 2001; Cotton 2000; Skwarska 2000; Nissen 2007; and, Utens 2012.
[2] Some heterogeneity was detected, i^2=30%; however, the panel elected to not downgrade the quality of evidence because it was judged too mild to reduce their confidence in the estimated effects.
[3] Wide confidence intervals; the ends of the confidence interval would lead to different clinical decisions.
[4] Davies 2000; Hernandez 2003; Nicholson 2001; Ojoo 2002; and, Ricauda 2008.
[5] Inconsistency: I^2=56%. P(het)=0.06.
[6] Cotton 2000; Skwarska 2000; and, Utens 2012.
[7] Davies 2000; Hernandez 2003; Ojoo 2002; Ricauda 2008; Cotton 2000; Skwarska 2000; Nissen 2007; and, Utens 2012.
[8] Davies 2000; Hernandez 2003; Ojoo 2002; and, Ricauda 2008.
[9] Not reported in a useful manner. Among the three trials that reported the outcome, one did not provide standard deviations, another only provided SGRQ scores for a subgroup of the participants, and the third measured generic HRQoL using the EuroQoL-5D. The analyses were not considered by the panel.

Evidence Profile #6

Comparison: Early pulmonary rehabilitation vs. usual care (i.e., late pulmonary rehabilitation or no pulmonary rehabilitation) for COPD exacerbations

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Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Early rehabilitation versus control**	**Control**	**Relative (95% CI)**	**Absolute**		
Hospital readmission												
All trials												
7[1]	randomised trials	serious[2]	serious[3]	not serious	serious[4]	none	156/350 (44.6%)	179/349 (51.3%)	**RR 0.56** (0.33 to 0.93)	210 fewer per 1000 (from 40 fewer to 380 fewer)	⊕⊕⊕O VERY LOW	CRITICAL
Pulmonary rehabilitation initiated during hospitalization												
3[5]	randomised trials	serious[2]	serious[6]	not serious	serious[4]	none	136/257 (52.9%)	135/255 (52.9%)	**RR 0.74** (0.39 to	140 fewer per 1000 (from 390 fewer to 120 more)	––	––

									1.40)			
Pulmonary rehabilitation initiated following discharge from the hospital												
4[7]	randomised trials	serious[2]	serious[8]	not serious	serious[4]	none	20/93 (21.5%)	44/94 (46.8%)	**RR 0.37** (0.14 to 0.97)	270 fewer per 1000 (from 120 fewer to 420 fewer)	––	––
Mortality												
All trials												
4[9]	randomised trials	serious[2]	not serious	not serious	serious[4]	none	51/260 (19.6%)	36/256 (14.1%)	**RR 1.44** (0.97 to 2.13)	0 more per 1000 (from 100 fewer to 100 more)	⊕⊕OO LOW	CRITICAL
Pulmonary rehabilitation initiated during hospitalization												
2[10]	randomised trials	serious[2]	not serious	not serious	serious[4]	none	50/210 (23.8%)	32/205 (15.6%)	**RR 1.54** (1.03 to 2.29)	80 more per 1000 (from 0 more to 150 more)	––	––
Pulmonary rehabilitation initiated following discharge from the hospital												
2[11]	randomised trials	serious[2]	not serious	not serious	serious[4]	none	1/50 (2.0%)	4/51 (7.8%)	**RR 0.37** (0.06 to 2.29)	60 fewer per 1000 (from 150 fewer to 30 more)	––	––
Quality of Life- St. George's Respiratory Questionnaire score (Better indicated by lower values)												
All trials												
5[12]	randomised trials	serious[2]	serious[13]	not serious	serious[4]	none	112	113	-	**MD** 11.75 lower (19.76 to 3.75 lower)	⊕⊕⊕O VERY LOW	CRITICAL
Pulmonary rehabilitation initiated during hospitalization												
0	––	––	––	––	––	––	––	––	––	––	––	––

Pulmonary rehabilitation initiated following discharge from the hospital												
5[12]	randomised trials	serious[2]	serious[13]	not serious	serious[4]	none	112	113	-	**MD** 11.75 lower (19.76 to 3.75 lower)	––	––
6 minute walking test (Better indicated by higher values)												
All trials												
8[14]	randomised trials	serious[2]	serious[15]	not serious	not serious	none	239	183	-	**MD** +88.89 m (+26.67 m to +151.11 m)	⊕⊕OO LOW	IMPORTANT
Pulmonary rehabilitation initiated during hospitalization												
5[16]	randomised trials	serious[2]	serious[15]	not serious	not serious	none	156	111	-	**MD** +107.92 m (+17.57 m to +198.27 m)	––	––
Pulmonary rehabilitation initiated following discharge from the hospital												
3[17]	randomised trials	serious[2]	serious[18]	not serious	not serious	none	83	72	-	**MD** +57.47 m (+20.04 m to +94.89 m)	––	––

[1] Behnke 2000; Eaton 2009; Greening 2014; Ko 2011; Man 2004; Murphy 2005; and Seymour 2010.
[2] None of the trials was blinded. Many of the trials had unclear concealment of allocation and either unclear or no adherence to intention-to-treat principle.
[3] Inconsistency: I^2=73%, P(het)=0.001.
[4] Wide confidence intervals: the ends of the confidence interval would lead to different clinical decisions.
[5] Behnke 2000; Eaton 2009; and Greening 2014.
[6] Inconsistency: I^2=71%, P(het)=0.03.
[7] Ko 2011; Man 2004; Murphy 2005; and Seymour 2010.
[8] Inconsistency: I^2=65%, P(het)=0.03.
[9] Behnke 2000; Greening 2014; Ko 2011; and, Man 2004. The five trials did not include Nava S, et al, which we excluded because it counted patients dying while they were still admitted to ICU. A sensitivity analysis demonstrated that exclusion of the trial had little effect on the results
[10] Behnke 2000 and Greening 2014.
[11] Ko 2011 and Man 2004.
[12] Deepak 2014; Ko 2011; Man 2004; Murphy 2005; and Seymour 2010.
[13] Inconsistency: I^2=70%, P(het)=0.009.
[14] Behnke 2000; Deepak 2014; Eaton 2009; Ghanem 2010; Kirsten 1998; Ko 2011; Nava 1998; and, Troosters 2010.
[15] Inconsistency: I^2=97%, P(het)=0.00001.
[16] Behnke 2000; Eaton 2009; Kirsten 1998; Nava 1998; and, Troosters 2010.
[17] Deepak 2014; Ghanem 2010; and, Ko 2011.
[15] Inconsistency: I^2=70%, P(het)=0.04.