Annals of Internal Medicine REVIEW

Pharmacologic Therapies in Patients With Exacerbation of Chronic Obstructive Pulmonary Disease

A Systematic Review With Meta-analysis

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Background: Chronic obstructive pulmonary disease (COPD) is characterized by frequent exacerbations.

Purpose: To evaluate the comparative effectiveness and adverse events (AEs) of pharmacologic interventions for adults with exacerbation of COPD.

Data Sources: English-language searches of several bibliographic sources from database inception to 2 January 2019.

Study Selection: 68 randomized controlled trials that enrolled adults with exacerbation of COPD treated in out- or inpatient settings other than intensive care and compared pharmacologic therapies with placebo, "usual care," or other pharmacologic interventions.

Data Extraction: Two reviewers independently extracted data and rated study quality and strength of evidence (SOE).

Data Synthesis: Compared with placebo or management without antibiotics, antibiotics given for 3 to 14 days were associated with increased exacerbation resolution at the end of the intervention (odds ratio [OR], 2.03 [95% CI, 1.47 to 2.80]; moderate SOE) and less treatment failure at the end of the intervention (OR, 0.54 [CI, 0.34 to 0.86]; moderate SOE), independent of severity of exacerbations in out- and inpatients. Compared with placebo in out- and inpatients, systemic corticosteroids given for 9 to 56 days were associated with less treatment failure at the end of the intervention (OR, 0.01 [CI, 0.00 to 0.13]; low SOE) but also with a higher number of total and endocrine-related AEs. Compared with placebo or usual care in inpatients, other pharmacologic interventions (aminophyllines, magnesium sulfate, anti-inflammatory agents, inhaled corticosteroids, and short-acting bronchodilators) had insufficient evidence, showing either no or inconclusive effects (with the exception of the mucolytic erdosteine) or improvement only in lung function.

Limitation: Scant evidence for many interventions; several studies had unclear or high risk of bias and inadequate reporting of AEs.

Conclusion: Antibiotics and systemic corticosteroids reduce treatment failure in adults with mild to severe exacerbation of COPD.

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Antibiotics, systemic corticosteroids, and short-acting bronchodilators are treatment mainstays of exacerbation of chronic obstructive pulmonary disease (COPD) (1). Whether all patients, especially those with mild exacerbations treated as outpatients, benefit from treatment with antibiotics and systemic corticosteroids is uncertain (2).

Bronchodilators, including short-acting β-adrenergic agonists (SABAs) and short-acting muscarinic antagonists (SAMAs), are used to relieve dyspnea and improve airflow obstruction during an exacerbation. Whether combining SABAs and SAMAs is superior to using a SABA or SAMA alone is unclear (3). Long-acting bronchodilators and inhaled corticosteroids (ICSs), which are used in stable COPD, may also have a role in the treatment of exacerbations. Increased doses of ICSs and long-acting β-agonists early in the exacerbation in cases of mild to moderate worsening of dyspnea may decrease the need for systemic corticosteroids in a large proportion of patients (4).

The benefits of several other interventions, such as aminophyllines, magnesium sulfate, and mucolytics, are unclear. In addition, anti-inflammatory treatments—for example, 5-lipoxygenase inhibitors and statins—are possible treatments for exacerbations.

We conducted a systematic review to evaluate the effect of pharmacologic interventions on health outcomes and adverse events (AEs) in adults with exacerbation of COPD. Specifically, we aimed to evaluate systemic antibiotics and corticosteroids compared with placebo or management without intervention in mild, moderate, and severe exacerbations of COPD; the comparative effectiveness of antibiotics and systemic corticosteroids on the basis of agent type, dosage, application route, and duration of treatments; pharmacologic interventions other than systemic antibiotics and corticosteroids compared with placebo or management without intervention; and the comparative effectiveness of inhalation treatments, including (combinations of) short-acting bronchodilators and ICSs.

See also:

Web-Only
Supplement
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METHODS

We report part of a larger systematic review on pharmacologic and nonpharmacologic therapies in adults with exacerbation of COPD (5). The full report contains additional details on methods and other results. With input from clinical and methodological experts and professional organizations, we developed a protocol for the review that was posted on 10 October 2018 at https://effectivehealthcare.ahrq.gov/products/copd/protocol and registered on PROSPERO (CRD42018111609) on 25 October 2018.

Date Sources and Searches

We searched EMBASE; epub ahead of print, in-process, and other nonindexed citations; MEDLINE Daily; MEDLINE; Cochrane Central Register of Controlled Trials; Ovid Cochrane Database of Systematic Reviews; and Scopus for English-language publications from database inception to 2 January 2019. We also searched ClinicalTrials.gov on 2 January 2019 and gray literature and conducted reference mining (**Supplement Table 1**, available at Annals.org).

Study Selection

We included studies if they were randomized controlled trials (RCTs) published in English; enrolled patients aged 18 years or older who had exacerbation of COPD; were done in out- or inpatient settings; compared a pharmacologic intervention with placebo or management without intervention ("usual care"), another pharmacologic intervention, or a different agent type, dosage, application route, or duration of treatment (for antibiotics and systemic corticosteroids only); and reported outcomes of interest. We excluded studies done in intensive care or chronic ventilator units and those in which patients received invasive or noninvasive mechanical ventilation at the beginning of the intervention.

Pairs of 2 independent reviewers (C.C.D., A.S.M., B.B., M.H.F., A.M.M., B.H., M.O.S., L.D., Z.W.) screened the titles and abstracts of all citations. Studies included by either reviewer were retrieved for full-text screening. Independent reviewers (C.C.D., A.S.M., B.B., M.H.F., A.M.M., M.E.W., B.H., M.O.S., Z.W.), again working in pairs, screened the full-text version of eligible references. Disagreements between the reviewers were resolved by a third reviewer.

Outcome Measures

Our main outcomes of interest were clinical resolution, treatment failure, repeated exacerbations, death, quality of life, hospital admission (readmissions in hospitalized patients and new admissions in outpatients), intensive care unit admission, and need for intubation. We also examined functional capacity (timed walking tests and endurance tests), symptoms, lung function (FEV_1), AEs, and number of participants who withdrew because of AEs or any reason. **Supplement Tables 2** and **3** (available at Annals.org) list our definitions of exacerbation resolution, treatment failure, repeated exacerbation, and dyspnea as well as categorizations of AEs. For severe AEs, we used the definitions in the original studies.

Data Extraction and Quality Assessment

Using a standardized form, which we piloted with 5 studies, 2 reviewers independently extracted information about study and patient characteristics, interventions, comparisons, outcomes at different time points, and related items for assessing study quality. Using the Cochrane Risk of Bias Tool (6), 2 reviewers independently assessed the risk of bias of studies at the study and intervention and outcome levels. Conflicts about extractions and risk-of-bias assessments were resolved through discussion and consensus.

Data Synthesis and Analysis

We categorized data by intervention type and comparator and followed the intention-to-treat principle for analysis of outcome data. We extracted or calculated the odds ratio (OR) for binary outcomes and the rate ratio for incidence of events (for example, AEs and number of hospital admissions). For continuous outcomes, we used the weighted mean difference when the same outcome measure was used. We calculated the standardized mean difference when different measures for the same outcome were reported (for example, different quality-of-life measurement tools) and standardized the direction of the measures, with higher scores representing better outcomes.

We used the DerSimonian–Laird random-effects method to combine direct comparisons between treatments if the number of studies included in the analysis was larger than 3 (7). The DerSimonian–Laird method with the modified Hartung–Knapp–Sidik–Jonkman variance correction was used as a sensitivity analysis of the DerSimonian–Laird random-effects method (8, 9). We used the fixed-effects method based on the Mantel–Haenszel method because of instability of between-study variance, when the number of studies in a meta-analysis was 3 or fewer and when there was little visual evidence of heterogeneity (10). We conducted predefined subgroup analyses on exacerbation severity for the comparisons between systemic antibiotics and corticosteroids and placebo and management without intervention. The severity of COPD exacerbations was classified on the basis of either the system used by the authors of the original studies or, if this information was missing, criteria mainly associated with location of treatment (hospital, emergency department, or outpatient setting). We did not include data from crossover trials in any of the meta-analyses because these studies had several reporting and methodological problems. We were unable to statistically evaluate publication bias because of the small number of studies included in each meta-analysis (11). All statistical analyses were done using Stata SE, version 15.1 (StataCorp).

Grading the Strength of Evidence

We followed the procedures outlined in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews to assess the applicability of the findings and the Strength of Evidence (SOE) for main outcomes (12). Two reviewers independently rated SOE for each of the main outcomes as high, moderate,

low, or insufficient to estimate an effect (Supplement Table 4, available at Annals.org) and then reached agreement or ratings by consensus.

Role of the Funding Source

This review was funded by the AHRQ. The AHRQ had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the article; or the decision to submit the article for publication.

RESULTS

Of 8952 citations (including systematic reviews and registered trials on ClinicalTrials.gov), 68 RCTs involving 10 758 participants met inclusion criteria (Supplement Figure, available at Annals.org). Trials involved patients treated in the outpatient setting (n = 19), emergency department (n = 10), hospital (n = 31), and mixed outpatient and hospital setting (n = 1). Treatment setting was unclear in 6 trials. Intervention length ranged from 4 to 56 days; follow-up ranged from 1 to 12 days.

Figure 1 shows the overall risk-of-bias assessment, by outcome. Details of studies and risk-of-bias assessments are shown in Supplement Tables 5 to 7 (available at Annals.org). The results for the effectiveness outcomes, including sensitivity analyses, AEs, and withdrawals, are shown in Supplement Tables 7 to 13 (available at Annals.org). Figure 2 displays the overall evidence map of interventions and effectiveness outcomes. Only 44 of the 68 trials (65%) reported AEs; none found that interventions were associated with statistically significant increases in serious AEs.

Antibiotics Versus Placebo or Management Without Antibiotics

Seven studies (13–19) evaluated the effectiveness of systemic antibiotics versus placebo or management without systemic antibiotics (given for 7 to 10 days) in outpatients (14, 16–19) or inpatients (13, 15). Two studies were done in patients with mild exacerbations of COPD (14, 17), 3 in patients with mild to moderate exacerbations (16, 18, 19), and 2 in patients with moderate to severe exacerbations (13, 15). Independent of exacerbation severity and study setting, antibiotics were associated with increased exacerbation resolution at the end of the intervention (n = 3; OR, 2.03 [95% CI, 1.47 to 2.80]; moderate SOE) (Figure 3) (15, 16, 19). At the longest follow-up, antibiotics were associated with increased exacerbation resolution, although the sensitivity analysis with the modified Hartung–Knapp–Sidik–Jonkman variance correction showed that the difference was not statistically significant (OR, 1.50 [CI, 0.77 to 2.92]) (Supplement Table 13) (13, 15, 16, 19). Studies that assessed treatment failure were conducted in outpatients with mild exacerbations of COPD. There was less treatment failure at the end of interventions that lasted 7 to 10 days (n = 2; OR, 0.54 [CI, 0.34 to 0.86]; moderate SOE) (Figure 3) (14, 17), but not at the longest follow-up at 1 month (n = 2; OR, 0.82 [CI, 0.58 to 1.14]; low SOE) (14, 15). Antibiotics given for 7 to 10 days were associated with reduced dyspnea (measured with a numerical scale, low SOE), cough, and other symptoms at the end of the intervention in mild to moderate (16) and moderate to severe (13, 15) exacerbation in inpatients (13, 15) and outpatients (16). There

Figure 1. Risk of bias, by outcome.

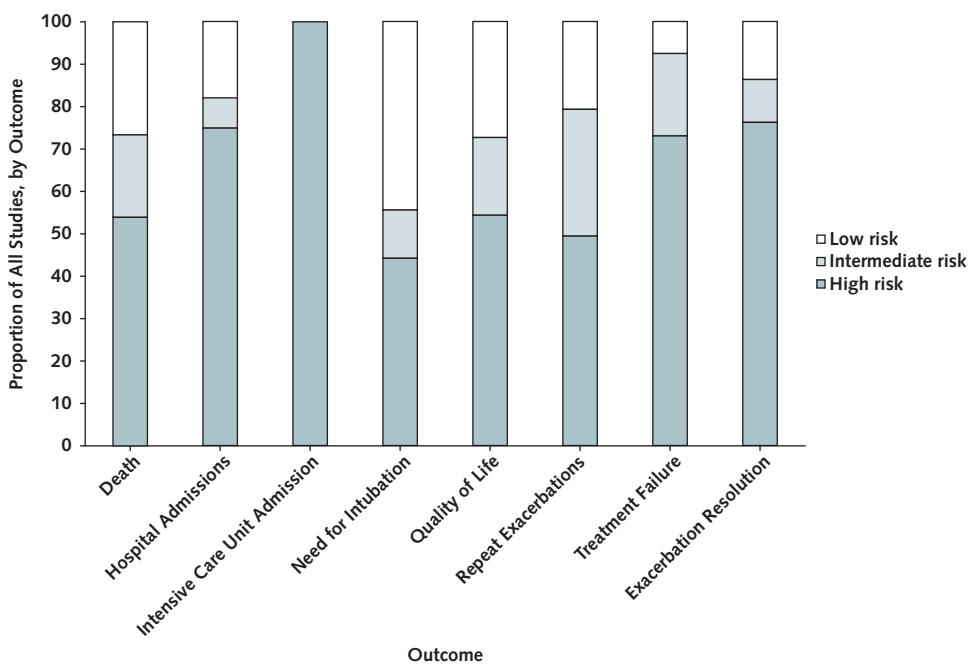


Figure 2. Evidence map of select interventions and outcomes for all severities of COPD exacerbation.

Interventions	Mortality	Dyspnea	QoL	FEV_1 (absolute or % predicted)	Need for Intubation	Repeat Exacerbation	Hospital Admissions	ECOPD Resolution	Treatment Failure
Systemic antibiotics vs. placebo or management without systemic antibiotics	3 RCTs	2 RCTs	1 RCT	4 RCTs	1 RCT	2 RCTs	1 RCT	5 RCTs	3 RCTs
Systemic corticosteroids vs. management without systemic corticosteroids	6 RCTs	2 RCTs		6 RCTs	2 RCTs	3 RCTs	2 RCTs		3 RCTs
IV aminophyllines vs. placebo	2 RCTs	2 RCTs		3 RCTs	1 RCT				
IV magnesium sulfate vs. placebo		1 RCT		2 RCTs					
Nebulized magnesium sulfate vs. placebo				1 RCT					
Oral mucolytics vs. placebo or management without oral mucolytics		2 RCTs		5 RCTs		1 RCT			
ICS vs. placebo		1 RCT		1 RCT	1 RCT		1 RCT		
ICS+SABA vs. placebo				2 RCTs					
ICS+LABA vs. placebo				1 RCT					1 RCT
Inhaled antibiotics vs. placebo				1 RCT					
5-lipoxygenase inhibitor vs. placebo	1 RCT			1 RCT	1 RCT		1 RCT		1 RCT
Statin vs. management without statin				1 RCT					
ICS+SABA vs. SABA				1 RCT				1 RCT	1 RCT
Amoxicillin + clavulanic acid for 3 d vs. 10 d	1 RCT					1 RCT	1 RCT	1 RCT	1 RCT
IV methylprednisolone vs. IV deflazacort hemisuccinate	1 RCT			1 RCT					
IV methylprednisolone, followed by oral methylprednisone vs. IV hydrocortisone, followed by oral prednisolone	1 RCT	1 RCT		1 RCT	1 RCT				1 RCT
Oral prednisolone vs. nebulized budesonide	1 RCT	1 RCT		1 RCT					
Subcutaneous prednisolone vs. nebulized budesonide				1 RCT		1 RCT	1 RCT		
Oral prednisolone (+inhaled formoterol) vs. inhaled budesonide (+inhaled formoterol)			1 RCT	1 RCT		1 RCT			1 RCT
Intravenous methylprednisolone vs. inhaled budesonide		1 RCT	1 RCT	2 RCTs		1 RCT			
Oral prednisolone vs. IV prednisolone	1 RCT		1 RCT	1 RCT			1 RCT		1 RCT
IV methylprednisolone vs. oral methylprednisolone	1 RCT	1 RCT	1 RCT	1 RCT			1 RCT		
Systemic corticosteroids for 8 wk vs. 2 wk	1 RCT				1 RCT		1 RCT		1 RCT
Systemic corticosteroids for 5 d vs. 14 d	1 RCT	1 RCT	1 RCT	1 RCT	1 RCT	1 RCT			
IV methylprednisolone for 3 d vs. 10 d		1 RCT		1 RCT		1 RCT			

Light green indicates no statistically significant difference in effectiveness between intervention and control at the end of the intervention and at the longest follow-up. Dark green indicates that the intervention was associated with a statistically significant benefit compared with the control at the end of the intervention and/or at the longest follow-up. Gray indicates that the control was associated with a statistically significant benefit compared with the intervention at the end of the intervention and/or at the longest follow-up. COPD = chronic obstructive pulmonary disease; ECOPD = exacerbation of COPD; ICS = inhaled corticosteroid; IV = intravenous; LABA = long-acting β-agonists; QoL = quality of life; RCT = randomized controlled trial; SABA = short-acting β-adrenergic agonists.

were no statistically significant differences in other outcomes (death, quality of life, hospital admissions, repeated exacerbations, need for intubations, and FEV_1) or in withdrawals (4 studies), withdrawals due to AEs (3 studies), total number of AEs (4 studies), or severe AEs (2 studies).

Systemic Corticosteroids Versus Placebo or Management Without Systemic Corticosteroids

Nine trials conducted in inpatients (20–24), outpatients (25, 26), and the emergency department (27, 28) compared the effectiveness of systemic corticosteroids versus placebo or management without systemic corticosteroids given for 1 to 56 days (20–28). Two studies were done in patients with mild exacerbation (25, 26), 5 in patients with moderate or severe exacerbation (21–24, 28), 1 in patients with severe exacerbation (20), and 1 in patients with exacerbations ranging from mild to severe (27). Independent of exacerbation severity and study setting, systemic corticosteroids were associated with less treatment failure at the end of the intervention at 9 to 56 days (n = 2; OR, 0.01 [CI, 0.00 to 0.13]; low SOE) (Figure 4) (24, 26). Systemic corticosteroids were also associated with reduced dyspnea (measured with a numerical scale, low SOE) at the end of the intervention at 7 to 9 days in outpatients with mild (26) and inpatients with moderate to severe (23) exacerbation. Increased absolute FEV_1 (21, 25, 26) was found in the systemic corticosteroid group at the end of the intervention (in all pooled studies and the subgroup of studies of mild exacerbation of COPD).

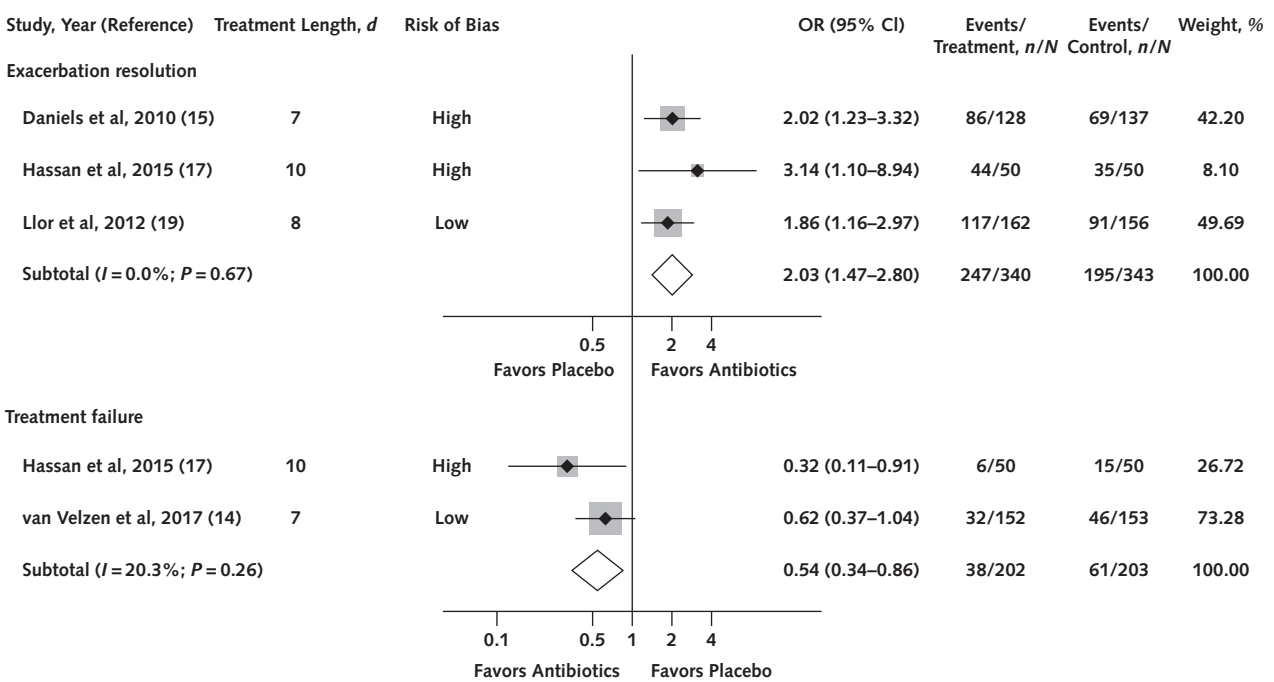
There were no statistically significant differences in death, hospital admission, repeated exacerbation, or intubation. Systemic corticosteroids were associated with a statistically significant higher number of total AEs and endocrine-related AEs.

Comparative Effectiveness of Antibiotics and Systemic Corticosteroids, by Agent Type or Dosage, Delivery Method, or Treatment Duration

Thirty-four RCTs involving 7311 patients evaluated the comparative effectiveness of antibiotics and systemic corticosteroids on the basis of agent type, delivery method, and treatment duration (22–24, 29–59). None of these studies evaluated comparative effectiveness of different application routes for antibiotics. Compared with prulifloxacin, levofloxacin reduced repeated exacerbations at 3-month follow-up (n = 1; OR, 0.44 [CI, 0.22 to 0.87]; low SOE; severity of exacerbation and study setting not specified) (35). Amoxicillin plus clavulanic acid given for 5 days was associated with more AEs than telithromycin in outpatients with mild exacerbation (48), whereas imipenem plus cilastatin given for 9 days was associated with more AEs than meropenem in inpatients with moderate to severe exacerbation (55). Inhaled budesonide during an exacerbation was associated with fewer endocrine-related AEs than intravenous methylprednisolone without any statistically significant difference in effectiveness outcomes in inpatients with moderate to severe exacerbation (59).

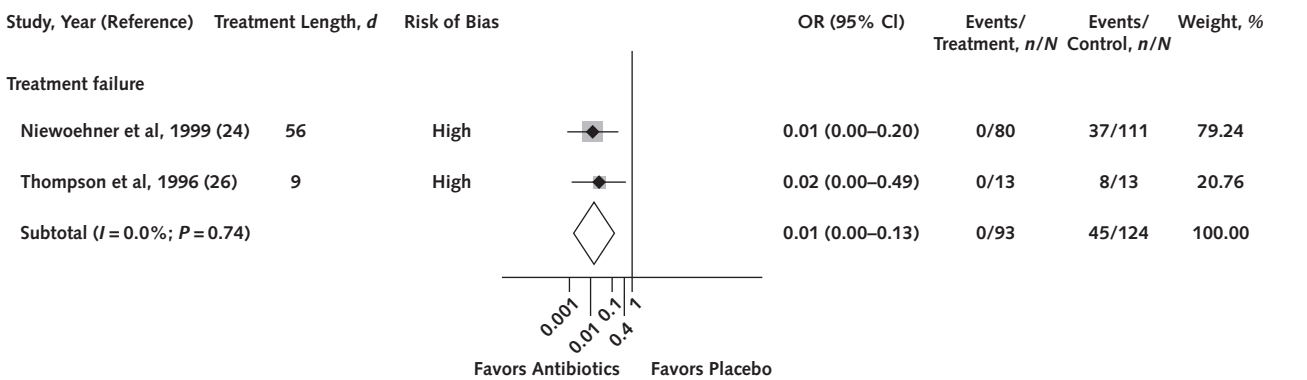
Three trials compared durations of systemic corticosteroid treatment (3 vs. 10 days [49], 5 vs. 14 days [58], and 2 vs. 8 weeks [24]) in inpatients with moderate to severe exacerbation. The only statistically significant difference in effectiveness outcomes and AEs was a

Figure 3. Effect of antibiotics versus placebo on exacerbation resolution and treatment failure at the end of intervention.



OR = odds ratio.

Figure 4. Effect of systemic corticosteroids versus placebo on treatment failure at the end of intervention.



OR = odds ratio.

lower absolute FEV_1 at the end of the intervention in the group treated for 3 days compared with the group treated for 10 days. Of note, 5 days of treatment with systemic corticosteroids was not inferior to 14 days of treatment (low SOE).

Aminophyllines Versus Placebo

Three RCTs (60–62) that evaluated intravenous aminophyllines compared with placebo given for 1 to 5 days found no statistically significant association with any effectiveness outcome. Higher total numbers of AEs and gastrointestinal AEs were reported in the aminophyllines group. Two studies were conducted in inpatients and patients in the emergency department with moderate to severe exacerbation (60, 61). In 1 study, the setting and severity of exacerbations were unclear (62).

Magnesium Sulfate Versus Placebo

Four RCTs evaluated the effectiveness of intravenous magnesium sulfate for 1 to 4 days in inpatients with moderate to severe exacerbation (63–66), and 1 study (67) evaluated the effectiveness of nebulized magnesium sulfate for 1 day in inpatients with moderate to severe exacerbation. Intravenous magnesium sulfate for 1 to 4 days in inpatients with moderate to severe exacerbation was associated with an increased absolute FEV_1 (64) but not FEV_1 percentage predicted (63) at follow-up (time not specified). No AEs were reported in the magnesium group (65).

Mucolytics Versus Placebo or Management Without Mucolytics

Four studies evaluated the effectiveness of the oral mucolytic *N*-acetylcysteine given for 7 to 30 days (68–71); 3 compared with placebo (68–70) and 1 compared with management without *N*-acetylcysteine (71). Three of these studies (69–71) were conducted in hospitalized patients with moderate to severe exacerbation and 1 in outpatients with mild exacerbation (68). The effectiveness of the oral mucolytic erdosteine given for 10 days compared with management without erdosteine was evaluated in 1 study of hospitalized patients with moderate to severe exacerbation (72). Erdosteine was associated with reduced repeated exacerbations at 2-month follow-up (but not at 1-month follow-up) and reduced symptoms (on the basis of the Breathlessness, Cough and Sputum Scale) as well as a higher FEV_1 percentage predicted at the end of the intervention (but not at the longest follow-up at 2 months) (72). *N*-acetylcysteine given for 7 to 30 days was not associated with any effectiveness outcomes in outpatients with mild (68) or in inpatients with moderate to severe exacerbation (69–71). No AEs were reported for any group in the erdosteine trial (72), and there was no statistically significant difference in AEs between groups in the *N*-acetylcysteine trials (68–71).

Anti-inflammatory Medications Versus Placebo or Management Without Anti-inflammatory Medications

Simvastatin given for 14 days was associated with an increased FEV_1 percentage predicted (n = 1; weighted mean difference, 0.68 [CI, 0.38 to 0.98]) at the end of the intervention compared with management without a statin (73). Another study (74) found an association between oral zileuton, a 5-lipoxygenase inhibitor, and increased absolute FEV_1 (but not FEV_1 percentage predicted) at the end of the intervention and at the longest follow-up at 1 month compared with placebo in inpatients with moderate to severe exacerbation. There was no statistically significant difference in total number of AEs, severe AEs, or withdrawals.

ICSs With or Without Inhaled Short- and Long-Acting Bronchodilators (SABAs and SAMAs) Versus Placebo

Four RCTs (22, 23, 25, 75) evaluated the effectiveness of inhaler treatments, including ICS versus placebo given for 7 to 14 days, of which 3 were conducted in inpatients with moderate to severe exacerbation (22, 23, 75) and 1 in outpatients with mild exacerbation (25). Inhaled corticosteroids were associated with a higher FEV_1 percentage predicted at the end of the intervention in inpatients with moderate to severe exacerbation (22). A combination of ICS plus SABA (budesonide plus terbutaline) was associated with a higher FEV_1 percent-

age predicted and absolute FEV_1 at the end of the intervention in inpatients with moderate to severe exacerbation (75). There was no statistically significant difference in total number of AEs, severe AEs, withdrawals, or withdrawals due to AEs.

Long-Acting Muscarinic Antagonists Versus Placebo

A crossover RCT (76) was done in patients with exacerbation of COPD and ischemic heart disease or cardiac arrhythmia. It found an association between the long-acting muscarinic antagonist oxitropium given for 2 days and absolute FEV_1 compared with placebo at the end of the intervention in outpatients with mild exacerbation.

Comparative Effectiveness of Inhalation Treatments Including (Combinations of) Short-Acting Bronchodilators and ICSs

Three RCTs (77–79) assessed the comparative effectiveness of inhalation treatments given for 1 to 28 days in inpatients with moderate to severe exacerbation. No final health outcomes were reported, and no statistically significant differences in FEV_1 or AEs were found for the comparisons of a SAMA versus a SABA (ipratropium vs. salbutamol) (78), a SAMA plus a SABA (ipratropium plus salbutamol) versus a SABA alone (salbutamol) (77, 78), or ICSs plus a SABA versus a SABA alone (beclomethasone plus salbutamol vs. fenoterol) (79).

DISCUSSION

This systematic review provides an overview of pharmacologic interventions for exacerbation of COPD. Compared with placebo or management without intervention, both antibiotics and systemic corticosteroids were associated with lower rates of treatment failure (independent of the exacerbation severity) and improved dyspnea at the end of the intervention. We found insufficient or no evidence supporting the use of pharmacologic treatments other than antibiotics and systemic corticosteroids. There was also insufficient or no evidence informing the optimal choice of antibiotic or corticosteroid treatment regimens (agent type, dosage, application route, or duration of treatment). Magnesium sulfate, erdosteine, simvastatin, zileuton, ICS, and ICS plus SABA were associated with improvement in FEV_1 (absolute or percentage predicted) compared with placebo or usual care. Aminophyllines were not associated with improved effectiveness outcomes but had more gastrointestinal AEs. Inhaled budesonide had fewer AEs than intravenous methylprednisolone, without any important difference in effectiveness outcomes.

Our results support the findings of previous systematic reviews (including a systematic review done for the European Respiratory Society and American Thoracic Society guidelines on management of COPD exacerbations published in 2017) that antibiotics are beneficial to the treatment of exacerbation of COPD (80–82). Our review included 3 additional trials (14, 16, 17) in outpatients with mild to moderate exacerbation of COPD compared with the guidelines review and confirmed a reduced risk for treatment failure with antibiotics. Our results also support the findings from previous systematic reviews that systemic corticosteroids reduce treatment failure (82–84). The inclusion of new studies on mild exacerbations treated in an outpatient setting in our review lends further support to the practice of treating even mild exacerbations with antibiotics and corticosteroids. Our systematic review significantly extends the 2017 European Respiratory Society and American Thoracic Society guideline on managing COPD exacerbations by examining pharmacologic interventions other than antibiotics and corticosteroids.

We found 3 studies that indicated that different durations of systemic corticosteroid treatment (3 vs. 10 days; 5 vs. 14 days; 2 vs. 8 weeks) did not alter effectiveness outcomes or AEs. The results are similar to those of previous systematic reviews (85, 86) and support the use of shorter regimens of systemic corticosteroids. The finding that ICSs were noninferior to systemic corticosteroids for clinically important outcomes strengthens the evidence from a previous systematic review that found no statistically significant difference in surrogate outcomes (87). Given that ICSs were associated with reduced AEs compared with systemic corticosteroids in our review, it is worth further investigating their effectiveness in large, well-conducted RCTs.

We did not find any improvements in effectiveness outcomes but did find increased gastrointestinal AEs with the use of aminophyllines. These updated findings support the results of a Cochrane systematic review published in 2003 (88). Magnesium sulfate, erdosteine, simvastatin, and zileuton, which showed improved FEV_1, need to be assessed in large, high-quality RCTs with clinical outcomes.

For most interventions, only 1 or 2 trials report our main outcomes of interest, which limits inference from the quantitative synthesis. We did not include trials published in languages other than English and, therefore, may have missed some relevant studies. Only 65% of the trials reported AEs, and the true rate of (serious) AEs associated with interventions may have been underestimated. Most studies were conducted in hospitalized patients with moderate to severe exacerbations; results of these studies may not be applicable to patients with milder forms of exacerbation treated in an outpatient setting. Because we excluded studies done in intensive care settings, some of our findings may not be extrapolated to the sickest patients.

Ongoing or upcoming relevant RCTs registered on ClinicalTrials.gov that are worth mentioning are a study comparing low- with high-dose corticosteroids (NCT02294734, recruiting), a study comparing 3 versus 5 days of oral corticosteroids (NCT04075331, recruiting), and studies comparing biological therapies with placebo or usual care (NCT04098718 and NCT04075331, not yet recruiting).

Our review found a lack of good-quality, reliable evidence to answer many of the important clinical questions surrounding treatment of patients with exacerbation of COPD. Future studies should focus on high-

quality study design and patient-centered outcomes—particularly clinical resolution of exacerbation and risk for repeated exacerbation, rather than lung function measurements. Studies on systemic corticosteroids should assess the treatment effect stratified by eosinophil count to determine whether the benefits of systemic corticosteroids are limited to patients with high eosinophil counts.

The results of this systematic review support use of antibiotics and systemic corticosteroids in COPD exacerbations, independent of severity. Because other pharmacologic interventions have insufficient evidence, have been found not to be effective (with the exception of erdosteine), or have only been associated with improvement in the surrogate outcome FEV_1, we do not recommend them for treatment of exacerbations.

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Reproducible Research Statement: *Study protocol:* Available at https://effectivehealthcare.ahrq.gov/products/copd/protocol and registered on PROSPERO (CRD42018111609). *Statistical code and data set:* Available from Dr. Wang (e-mail, Wang.Zhen@mayo.edu).

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