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Contemporary Management of Acute Exacerbations of COPD*

A Systematic Review and Metaanalysis

Bradley S. Quon, MD; Wen Qi Gan, MD; and Don D. Sin, MD, FCCP

Background: Systemic corticosteroids, antibiotics, and noninvasive positive pressure ventilation (NPPV) are recommended for patients with acute exacerbation of COPD. However, their clinical benefits in various settings are uncertain. We undertook a systematic review and metaanalysis to systematically evaluate the effectiveness of these therapies.

Methods: MEDLINE and EMBASE were searched to identify relevant randomized controlled clinical trials published from January 1968 to November 2006. We identified additional studies by searching bibliographies of retrieved articles.

Results: Compared with placebo, systemic corticosteroids reduced treatment failure by 46% (95% confidence interval [CI], 0.41 to 0.71), length of hospital stay by 1.4 days (95% CI, 0.7 to 2.2), and improved FEV₁ by 0.13 L after 3 days of therapy (95% CI, 0.04 to 0.21). Meanwhile, the risk of hyperglycemia significantly increased (relative risk, 5.88; 95% CI, 2.40 to 14.41). Compared with placebo, antibiotics reduced treatment failure by 46% (95% CI, 0.32 to 0.92) and in-hospital mortality by 78% (95% CI, 0.08 to 0.62). Compared with standard therapy, NPPV reduced the risk of intubation by 65% (95% CI, 0.26 to 0.47), in-hospital mortality by 55% (95% CI, 0.30 to 0.66), and the length of hospitalization by 1.9 days (95% CI, 0.0 to 3.9).

Conclusions: For acute COPD exacerbations, systemic corticosteroids are effective in reducing treatment failures, while antibiotics reduce mortality and treatment failures in those requiring hospitalization and NPPV reduces the risk of intubation and in-hospital mortality, especially in those who demonstrate respiratory acidosis. (CHEST 2008; 133:756–766)

Key words: controlled clinical trial; COPD; exacerbation; metaanalysis

Abbreviations: BPAP = bilevel positive airway pressure; CI = confidence interval; GOLD = Global Initiative for Chronic Obstructive Lung Disease; LOS = length of hospital stay; NPPV = noninvasive positive pressure ventilation; RR = relative risk

Acute exacerbations of COPD are associated with significant morbidity, mortality, and health-care expenditures. The in-hospital mortality rate for acute COPD exacerbations is approximately 10%,¹ and approximately 25% for those requiring admission to an ICU.² Hospitalizations for COPD exacerbations have increased significantly over the past 10 years. For instance, the number of hospitalizations for COPD exacerbations in the United States was 463,000 in 1990; whereas by 2000, it was 726,000, representing a 57% increase in just 10 years.³ The total economic costs of COPD in the United States were estimated at \$32 billion in 2002, with \$18 billion representing direct medical expenditures related largely to in-hospital care.⁴ The Global Initia-

tive for Chronic Obstructive Lung Disease (GOLD) committee⁵ defines COPD exacerbation as a change in a patient's "baseline dyspnea, cough, and/or sputum that is beyond day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD." Lung inflammation and infection appear to play prominent roles in the pathogenesis of COPD exacerbations, leading to worsening of symptoms and health status and a decline in lung function.⁶ The most common putative precipitants of exacerbations are bacterial or viral infections, and environmental pollution, although in many cases a clear precipitant is not apparent.^{7,8} As patients frequently experience worsening of lung function and health status, most clini-

Table 1—Search Strategy and Terms

Intervention To Be Studied	Search Terms	Hits
Systemic corticosteroids	(Antiinflammatory agents OR corticosteroids OR steroids OR prednisone OR methylprednisolone OR prednisolone)	365
Antibiotics	(Antimicrobial* OR antibiotic* OR penicillin OR ampicillin OR amoxicillin OR fluoroquinolone* OR *floxacin OR cephalosporin* OR cefalosporin* OR cefaclor OR cefalexine OR cephalotin OR cefazolin OR cefixime OR cefotaxime OR cefpodoxime OR cephadrine OR ceftizoxime OR ceftriaxone OR cefuroxime OR tetracyclin* OR demeclocycline OR doxycycline OR minocycline OR oxytetracycline OR *cycline OR macrolide* OR *thromycin OR azithromycin OR clarithromycin OR dirithromycin OR erythromycin OR roxythromycin OR telithromycin OR troleandomycin OR fluoroquinolone* OR ciprofloxacin OR gatifloxacin OR gemfloxacin OR grepafloxacin OR levofloxacin OR lomefloxacin OR moxifloxacin OR ofloxacin OR sparfloxacin OR trovafloxacin OR *floxacin OR chloramphenicol OR clindamycin OR trimethoprim/sulfa* OR cotrimoxazole OR carbapenem* OR imipenem OR meropenem)	423
NPPV	(NIPPV OR NPPV OR NIMV OR NIV OR BIPAP OR bi-level ventilat* OR noninvasive ventilat* OR noninvasive ventilat* OR positive-pressure ventilat* OR positive-pressure ventilat*)	316

cal guidelines recommend the use of bronchodilators (short-acting β_2 -agonists and anticholinergics) to reduce dynamic hyperinflation, systemic corticosteroids to reduce lung inflammation, antibiotics to treat potential bacterial pathogens, and occasionally noninvasive positive pressure ventilation (NPPV) in select cases to reduce the work of breathing. Despite these widely promulgated recommendations, very few studies have systematically evaluated the clinical benefits of these interventions in comparison with placebo or standard therapy. The objective of this study was to systematically review and quantitatively synthesize the impact of systemic corticosteroids, antibiotics, and NPPV on treatment failure, need for intubation, in-hospital mortality, and LOS during COPD exacerbations.

METHODS AND MATERIALS

We decided *a priori* to examine the published evidence for systemic corticosteroids, antibiotics, and NPPV in the treatment of acute COPD exacerbations. For each of these therapies, we conducted a literature search by using MEDLINE and EMBASE. We limited the search to English-language articles

published from January 1968 to November 2006, conducted in adults (> 19 years of age) using a randomized, controlled trial design. To limit the studies to COPD, we used the following terms: *chronic obstructive lung disease, chronic obstructive airway disease, COPD, emphysema, chronic bronchitis, or chronic airflow obstruction*. Detailed search terms for each of the therapies and search results are available in Table 1. To supplement this search, we examined the Cochrane Database of Systematic Reviews as well as bibliographies of retrieved articles.

We included only studies that were conducted during acute COPD exacerbations, as defined by worsening cough or dyspnea or increased sputum production. Studies were excluded when there was clearly an alternative primary diagnosis such as asthma, pneumonia, or cardiogenic pulmonary edema. Most of the included studies had criteria excluding patients with an alternative primary diagnosis based on clinical examination. In all included studies, the treatment group was compared with placebo or with standard medical therapy. Standard medical therapy included supplemental oxygen (if the patients were hypoxemic), bronchodilators, antibiotics, corticosteroids, and diuretics but could not include the treatment being studied. We used the Jadad scale, which is composed of 5 questions about study design, to adjudicate the methodologic quality of the studies (the higher the score, the better the quality of trial design).⁹ For systemic corticosteroids and antibiotics, we restricted the analysis to randomized clinical trials that had a Jadad score ≥ 3 . For NPPV, we accepted studies with a score ≥ 2 because study blinding was not possible for practical reasons. All included studies had complete or near-complete follow-up data, and baseline characteristics that were well balanced between the treatment and control groups. Studies in abstract form were included if the methods and results could be adequately analyzed to minimize publication bias.

Data were abstracted from each trial by two authors (B.S.Q., W.Q.G.) independently using a prestandardized data abstraction form. Any discrepancies were resolved by iteration and consensus. Results were analyzed by intention to treat whenever possible. Treatment failures following treatment of COPD exacerbations were defined variably between studies. In most cases, treatment failures were defined as unchanged or deteriorated symptoms requiring additional treatment during the follow-up period. When possible, for each outcome we combined the results from individual studies to produce summary effect estimates. For dichotomous outcomes, relative risks (RRs) and 95% confidence intervals (CIs) were calculated. For continuous variables, weighted mean differences (and 95% CIs) were used to

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Table 2—Summary of Clinical Trials for Systemic Corticosteroids Compared With Placebo*

Source	No.	Drug	Route	Dose, mg	Frequency	Full Dose Days, No.	Taper Duration, d	Age, yr	FEV ₁ , L	RR of Treatment Failure (CI)	LOS, d	Change in Day 3 FEV ₁ (CI), L	Change in Day 10 to 14 FEV ₁ (CI), L
Albert et al, 1980 ¹¹	44	MP	IV	0.5/kg	q6h	3	NA	62	0.72	NR	NR	0.22 (0.05, 0.39)	NR
Emerman et al, 1989 ¹⁴	96	MP	IV	100	q24h	1	NA	64	NR	NR [§]	NR	NR	NR
Rostom et al, 1994 ¹⁷	30	MP	IV	40	q6h	3	16	NR	NR	NR	NR	NR	NR
Bullard et al, 1996 ¹²	113	HC	IV	100	q4h	4	4	66	0.55	0.32 (0.12, 0.82)	NR	NR	NR
Thompson et al, 1996 ¹⁸	27	Pred	PO	60	q24h	3	6	68	0.90	0.13 (0.02, 0.93)	NR	0.19 (0.00, 0.38)	0.37 (0.11, 0.63)
Wood-Baker et al, 1998 ¹⁹	47†	Pred	PO	0.6/kg, 2.5/kg	q24h, q24h	3, 7	NA, 7	NR	0.60	NR	0.50 (-2.30, 3.30)	NR	NR
Davies et al, 1999 ¹³	56	MP	PO	30	q24h	14	NA	67	NR	0.19 (0.02, 1.49)	-2.00 (-3.77, -0.23)	NR	NR
Niewoehner et al, 1999 ¹⁶	271‡	MP	IV	125, 125	q6h, q6h	3, 3	12, 54	68	0.75	0.69 (0.47, 1.02)	-1.20 (-2.28, -0.12)	0.06 (-0.05, 0.17)	0.02 (-0.11, 0.15)
Maltais et al, 2002 ¹⁵	128	MP	PO	30	q12h	3	7	70	0.86	0.40 (0.11, 1.44)	-2.00 (-3.55, -0.45)	NR	NR
Aaron et al, 2003 ¹⁰	147	HC	PO	40	q24h	10	NA	69	1.00	0.62 (0.39, 1.00)	NR	NR	0.19 (0.07, 0.31)
Pooled summary Heterogeneity	959									0.54 (0.41, 0.71) p = 0.27	-1.42 (-2.18, -0.65) p = 0.40	0.13 (0.04, 0.21) p = 0.23	0.16 (0.00, 0.33) p = 0.03

*MP = methylprednisolone; HC = hydrocortisone; Pred = prednisone; NR = not reported/could not be ascertained; NA = not available; PO = parenteral.

†High-dose short duration and moderate-dose long duration prednisolone treatment groups combined.

‡Two-week and 8-week glucocorticoid treatment groups combined.

§Not included in summary estimate because limited follow-up period.

pool the data. Heterogeneity of results across individual studies was examined using the χ^2 test. If significant heterogeneity was observed ($p \leq 0.10$), the DerSimonian and Laird random-effects model was used to pool the results together. In the absence of significant heterogeneity ($p > 0.10$), a fixed-effects model was used. All analyses were conducted using statistical software (RevMan version 4.2; Cochrane Collaboration; Oxford, England).

RESULTS

Systemic Corticosteroids

A total of 10 studies^{10–19} involving 959 patients (Table 2) were identified that examined the effects of systemic corticosteroids during acute COPD exacerbations. The mean age of patients of these studies was 67 years. The patients at the time of presentation to the hospital demonstrated an average arterial pH of 7.40 and Paco_2 of 42 mm Hg. Most of the patients were active smokers with a mean smoking history of 63 pack-years. The treatment was initiated in hospital in eight of the studies,^{11–17,19} while in two studies^{10,18} systemic corticosteroids were administered in an outpatient setting. In half of the studies,^{11,12,14,16,17} investigators used parenteral methylprednisolone or hydrocortisone, while in the other half of the studies,^{10,13,15,18,19} oral prednisone or prednisolone was used.

Six of the 10 studies^{10,12,13,15,16,18} (involving 742 patients) examined the effects of systemic corticosteroids on treatment failure defined as either clinical deterioration, withdrawal from the study due to unsatisfactory clinical improvement, or relapse of exacerbation symptoms during the follow-up period. The follow-up period varied from 10 to 30 days. Overall, the treatment failure rate was reduced by 46% with the use of systemic corticosteroids compared with placebo during acute exacerbations (RR, 0.54; 95% CI, 0.41 to 0.71; $p = 0.27$ for heterogeneity) [Fig 1]. The study by Emerman et al¹⁴ was excluded from the analysis because patients were administered just one dose of IV methylprednisolone and were followed up for just 48 h. The method of administration (oral or parenteral) did not modify the beneficial effects of systemic corticosteroids on treatment failures.

Systemic corticosteroids also had beneficial effects in reducing the length of hospitalization. Mean LOS was reduced by a weighted mean of 1.42 days with systemic corticosteroids (95% CI, 0.65 to 2.18; $p = 0.40$ for heterogeneity) [Fig 2].

Information on adverse drug effects including heartburn, GI bleeding, hyperglycemia, infection, psychomotor disturbance, and weight gain was variably (and scarcely) reported. The only potential adverse effect that was consistently reported in most of the

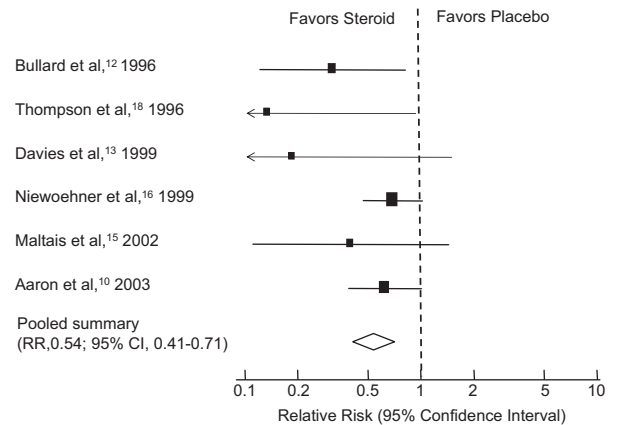


FIGURE 1. Effects of systemic corticosteroid therapy on the risk of treatment failure.

studies was hyperglycemia. The risk of hyperglycemia was significantly increased with corticosteroid treatment (RR, 5.88; 95% CI, 2.40 to 14.41).^{13,15,16} There was insufficient information on the effect of corticosteroids on mortality.

Antibiotics

There have been several placebo-controlled studies^{20–30} that have examined the impact of antibiotics on clinically important outcomes during COPD exacerbations (Table 3). Of the 11 eligible studies, only 3 placebo-controlled studies^{23,24,27} have been performed since 1987, likely reflecting the acceptance of antibiotics as standard of care in the management of COPD exacerbations over the past 2 decades. Three of the studies^{20,22,24} were conducted in outpatients, seven studies^{21,23,25,26,28–30} were conducted in patients in medical wards, and one study²⁷ was conducted in a medical ICU. The mean age of the patients in these studies was 63 years. Minimum and mean durations of treatment were 7 days and 8.9

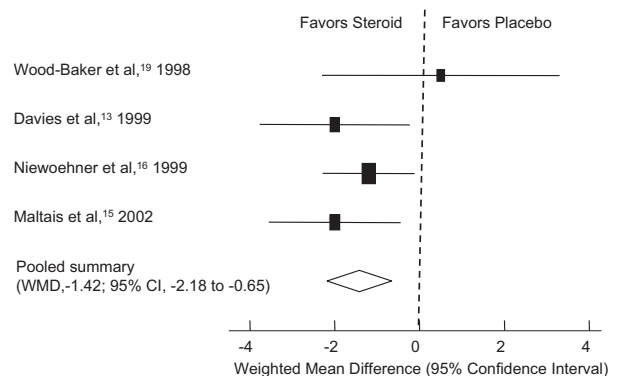


FIGURE 2. Effects of systemic corticosteroid therapy on LOS. WMD = weighted mean difference.

Table 3—Summary of Clinical Trials for Antibiotics Compared With Placebo*

Source	No.	Inpatient or Outpatient	Drug	Dose, mg	Frequency	Duration, d	Age, yr	PEFR, L/min	RR (95% CI) of Treatment Failure	RR (95% CI) of In-hospital Mortality
Fear and Edwards, 1962 ²²	62†	Out	Oxytetracycline	500	q12h	7	NR	NR	NR	NR
Elmes et al, 1965 ²¹	58	In	Ampicillin	1,000	q6h	7‡	63	79	0.36 (0.15, 0.86)	0.20 (0.02, 1.61)
Petersen et al, 1967 ²⁸	43	In	Chloramphenicol	500	q6h	10	62	NR	NR	NR
Pines et al, 1968 ³⁰	30	In	Penicillin/streptomycin	3 MU/500	q12h	14/7	67	87	0.42 (0.20, 0.89)	0.33 (0.04, 2.85)
Pines et al, 1972 ²⁹	259‡	In	Tetracycline, chloramphenicol	500, 500	q6h, q6h	12, 12	NR	146	NR	NR
Nicotra et al, 1982 ²⁶	40	In	Tetracycline	500	q6h	7	56	160	NR	NR
Anthomisen et al, 1987 ²⁰	116§	Out	TMP-SMX, amoxicillin, doxycycline	160/800, 250, 200	q12h, q6h, q24h	10, 10, 10¶	67	228	0.69 (0.48, 1.00)	NR
Manresa et al, 1987 ²⁵	19	In	Cefaclor	500	q8h	8	67	173	NR	NR
Hansen et al, 1990 ²³	40	In	Amoxicillin	750	q12h	7	NR	NR	NR	NR
Jorgensen et al, 1992 ²⁴	260	Out	Amoxicillin	750	q12h	7	59	295	1.10 (0.80, 1.50)	NR
Nouira et al, 2001 ²⁷	93	In	Ofloxacin	400	q24h	10	66	NR	0.18 (0.06, 0.59)	0.22 (0.08, 0.62)
Pooled summary Heterogeneity	1,020								0.54 (0.32, 0.92) p = 0.92	0.22 (0.08, 0.62) p = 0.002

*PEFR = peak expiratory flow rate; MU = million units; TMP-SMX = trimethoprim-sulfamethoxazole; See Table 2 for expansion of abbreviations.

†Data obtained from stage II of the study (intermittent therapy).

‡Data from the two antibiotic treatment groups combined.

§Data from all three antibiotic treatment groups combined; data obtained from first exacerbation only.

¶1,000 mg for 3 d and then 500 mg for 4 d.

‡‡200 mg for 1 d and then 100 mg for 6 d.

days, respectively. The antibiotics most commonly used were oral β -lactams (43%) and tetracycline derivatives (29%).

Compared with placebo, antibiotic use during COPD exacerbations (five studies^{20,21,24,27,30} involving 557 patients) reduced treatment failures, defined as requiring additional antibiotics within the first 7 days or unchanged or deteriorated symptoms within 21 days, by 46% (RR, 0.54; 95% CI, 0.32 to 0.92) [Fig 3]. However, there was significant heterogeneity of findings across the studies ($p = 0.002$). Stratification of studies according to patient type (in-hospital vs an outpatient setting) attenuated the heterogeneity. Antibiotics significantly reduced treatment failures when they were administered to patients who were hospitalized (for three inpatient studies^{21,27,30}; RR, 0.34; 95% CI, 0.20 to 0.56; $p = 0.48$ for heterogeneity) but not when they were used in ambulatory patients (for two outpatient studies^{20,24}; RR, 0.88; 95% CI, 0.56 to 1.39; $p = 0.06$ for heterogeneity). Three clinical trials^{21,27,30} involving 181 patients demonstrated that in-hospital mortality can be reduced by 78% with the use of antibiotics during acute COPD hospitalizations (RR, 0.22; 95% CI, 0.08 to 0.62; $p = 0.92$ for heterogeneity). Some studies^{25,27} reported the effect of antibiotics on short-term lung function, blood gas measurements, or length of stay in hospital, but antibiotics did not materially affect these outcomes compared with placebo.

Noninvasive Positive Pressure Ventilation

Fourteen studies compared the use of NPPV to standard therapy in the management of acute COPD exacerbations (Table 4). All of the studies were performed since 1993.^{31–44} Mean age of the patients in these studies was 67 years. Arterial blood gas measurements on study entry for included patients

revealed a mean pH of 7.31 and $Paco_2$ of 68 mm Hg. In most cases, investigators used bilevel positive airway pressure (BPAP) administered through a ventilator via nasal or face mask. NPPV was initiated as early as possible following hospitalization on a general medical or respiratory ward, or an ICU. The mean duration of NPPV use was 8.5 h/d, with a range of 6 to 14 h/d for a mean duration of 4.3 days (range, 3 to 10 days). NPPV was continued as long as necessary to avoid endotracheal intubation. Most studies had prespecified clinical criteria for endotracheal intubation based on a set of clinical parameters and arterial blood gas measurements obtained serially during follow-up.

The totality of randomized controlled trials demonstrates that NPPV reduced the need for intubation, improved the risk of in-hospital mortality, and shortened hospital stays during acute COPD exacerbations. In the 12 controlled randomized trials (959 patients), NPPV reduced the need for intubation by 65% (RR, 0.35; 95% CI, 0.26 to 0.47; $p = 0.82$ for heterogeneity) [Fig 4].^{31,32,34–44} The benefits were modified by the average pH of the study participants. The beneficial effects of NPPV increased as the baseline pH decreased ($p = 0.047$) [Fig 5].

We found 11 studies^{31,32,34–36,38–44} involving 940 patients that evaluated the effects of NPPV on in-hospital mortality. Overall, compared with placebo, the in-hospital mortality rate was reduced by 55% (RR, 0.45; 95% CI, 0.30 to 0.66; $p = 0.99$ for heterogeneity) [Fig 6]. Although there was significant heterogeneity in the data ($p = 0.005$ for heterogeneity), the length of hospital stay was significantly shortened by a weighted mean of 1.94 days with the use of NPPV (95% CI, 0.01 to 3.87) [Fig 7].

DISCUSSION

Acute exacerbations of COPD are an increasing cause of morbidity, mortality, and economic burden in the United States and elsewhere. Despite the widespread promulgation of clinical guidelines by various expert committees and professional societies over the past decade, there continues to be considerable heterogeneity in the way in which acute exacerbations are managed between physicians.³¹ For instance, a large survey³¹ found that < 3% of patients with acute COPD exacerbations were treated with NPPV and < 85% were treated with antibiotics and systemic corticosteroids, which are thought to be cornerstones of inpatient management. The primary objective of this study³¹ was to determine the strength of clinical data that support the use of these therapies on clinically relevant health outcomes such as treatment failures, the need for

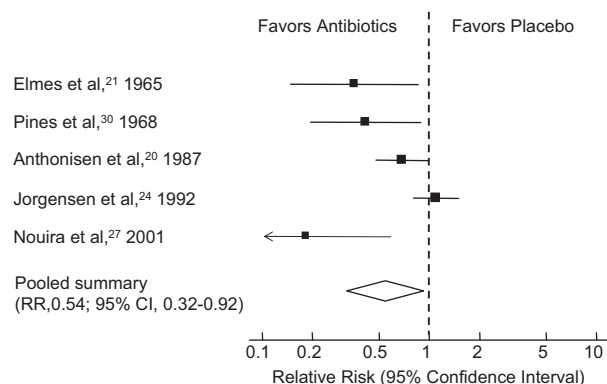


FIGURE 3. Effects of antibiotic therapy on the risk of treatment failure.

Table 4—Summary of Clinical Trials for NPPV Compared With Standard Therapy*

Source	No.	NPPV Mode	Interface	Mean Usage, h/d	Mean Duration, d	Age, yr	Arterial pH	PaCO ₂ , mm Hg	RR (95% CI) of Need for Intubation	RR (95% CI) of In-hospital Mortality	Mean Change (95% CI) in LOS, d
Bott et al, 1993 ^{43†}	60	VC	Nasal	7.6	6	NR	7.34	65	0.09 (0.01, 1.57)	0.33 (0.10, 1.11)	0.00 (− 8.63, 8.63)
Daskalopoulou et al, 1993 ⁴⁴	16	BPAP	Nasal	NR	NR	66	7.25	79	0.14 (0.01, 2.39)	NR	− 7.00 (− 15.76, 1.76)
Servillo et al, 1994 ⁴⁵	10	PSV	NR	NR	NR	NR	NR	NR	0.33 (0.05, 2.21)	1.00 (0.08, 11.93)	− 13.00 (− 38.55, 12.55)
Brochard et al, 1995 ⁴⁶	85	PSV	Face	NR	4	70	7.28	70	0.35 (0.20, 0.60)	0.33 (0.11, 0.93)	− 12.00 (− 23.21, − 0.79)
Kramer et al, 1995 ⁴⁷	23	BPAP	Nasal or ON	14.4‡	4	68	7.28	81	0.14 (0.02, 0.92)	0.55 (0.06, 5.21)	− 2.40 (− 11.12, 6.32)
Angus et al, 1996 ^{48†}	17	BPAP	Nasal	NR	NR	63	7.31	76	0.18 (0.03, 1.22)	0.13 (0.01, 2.16)	NR
Barbe et al, 1996 ⁴⁹	20	BPAP	Nasal	6	3	67	7.33	59	NR	NR	− 0.70 (− 3.80, 2.40)
Celik et al, 1998 ⁵⁰	30	PSV	Face	NR	NR	NR	7.28	69	0.17 (0.02, 1.22)	0.33 (0.01, 7.58)	− 2.90 (− 5.87, 0.07)
Martin et al, 2000 ⁵¹	23	BPAP	Nasal or ON or face	NR	3	61	7.28	79	0.55 (0.17, 1.78)	0.92 (0.06, 12.95)	NR
Plant et al, 2000 ⁵²	236	PSV	Nasal or face	NR	3	69	7.32	66	0.56 (0.34, 0.94)	0.50 (0.26, 0.95)	0.00 (− 7.63, 7.63)
Dikensoy et al, 2002 ⁵³	34	PSV	Face	NR	NR	65	7.29	78	0.29 (0.07, 1.18)	0.50 (0.05, 5.01)	− 4.30 (− 6.16, − 2.44)
CRC et al, 2005 ⁵⁴	342	BPAP	ON	11	10	69	7.35	66	0.31 (0.14, 0.66)	0.58 (0.24, 1.45)	2.00 (− 0.13, 4.13)
Dhamija et al, 2005 ⁵⁵	29	PSV	Nasal or face	6	3	NR	7.38	63	0.36 (0.02, 8.07)	0.36 (0.02, 8.07)	− 0.43 (− 3.77, 2.91)
Keenan et al, 2005 ⁵⁶	54	BPAP	Nasal or face	6	3	70	7.40	50	0.46 (0.10, 2.19)	0.58 (0.31, 0.67)	− 2.60 (− 6.05, 0.85)
Pooled summary	979								0.35 (0.26, 0.47)	0.45 (0.30, 0.66)	− 1.94 (− 3.87, − 0.01)

*VC = volume cycled; ON = oronasal; PSV = pressure support ventilation; see Table 2 for expansion of abbreviation.

†Doxapram was utilized in the standard therapy group.

‡Mean usage over the first 2 days.

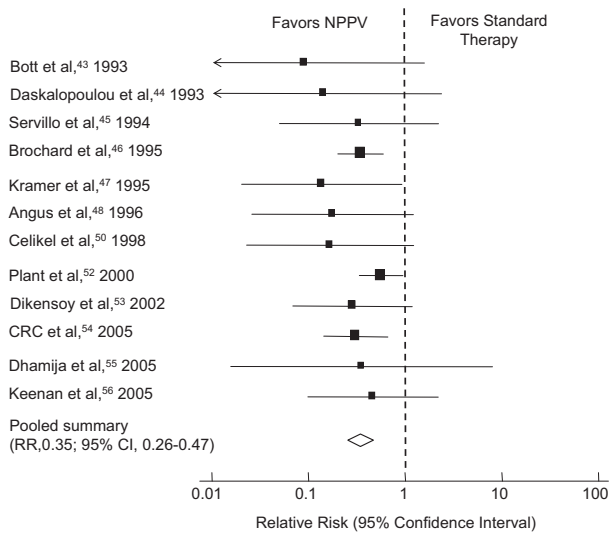


FIGURE 4. Effects of NPPV on the risk of intubation during COPD exacerbations. CRC = Collaborative Research Group of Noninvasive Mechanical Ventilation for Chronic Obstructive Pulmonary Disease.

intubation, in-hospital mortality, and LOS. The present study builds on previous systematic reviews and meta-analysis by adding data from most recently published trials by integrating the findings on these three therapies in one succinct report (as opposed to previous published analyses, which have evaluated these interventions separately, which we believe will enhance the translation of these findings into clinical practice),³² and by presenting “new” analyses to address clinical issues that have not been previously evaluated.

GOLD guidelines recommend systemic corticosteroids for in-hospital management of COPD exacerbations, while antibiotics are recommended for

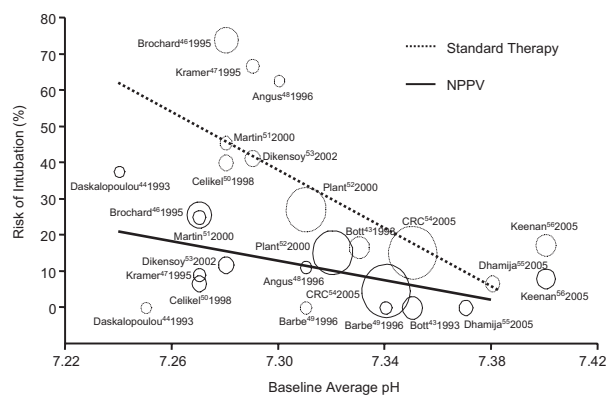


FIGURE 5. Relationship between arterial pH and the risk of intubation in patients treated and not treated with NPPV during COPD exacerbations. For standard therapy group, $R^2 = 0.53$, $p = 0.005$; for NPPV group, $R^2 = 0.36$, $p = 0.029$; $p = 0.047$ for the slope difference between two groups. See Figure 4 legend for expansion of abbreviation.

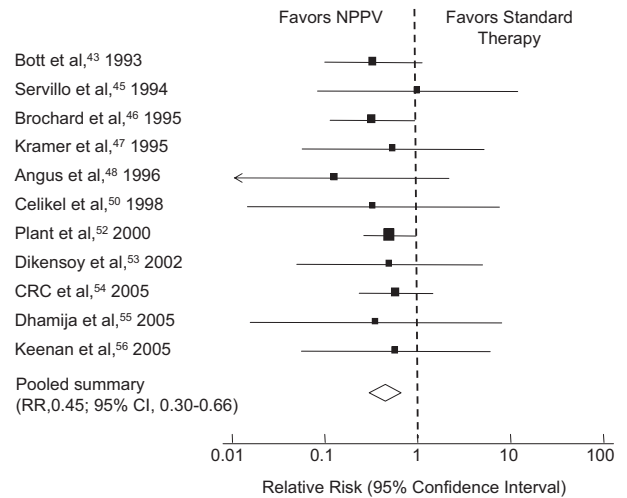


FIGURE 6. Effects of NPPV on the risk of in-hospital mortality during COPD exacerbations. See Figure 4 legend for expansion of abbreviation.

any exacerbations (regardless of severity) that lead to increased dyspnea, sputum volume, and sputum purulence. NPPV is believed to be beneficial only in exacerbations that are associated with moderate-to-severe respiratory acidosis.⁵ The findings of this review largely support these recommendations with some notable exceptions. Firstly, we found that systemic corticosteroids reduced treatment failure by 46% during both inpatient and outpatient management of COPD exacerbations, which are similar to the findings by Wood-Baker and colleagues.³³ Secondly, we found that antibiotics reduced treatment failures by 46% and improved survival of hospitalized patients. The survival effect was ob-

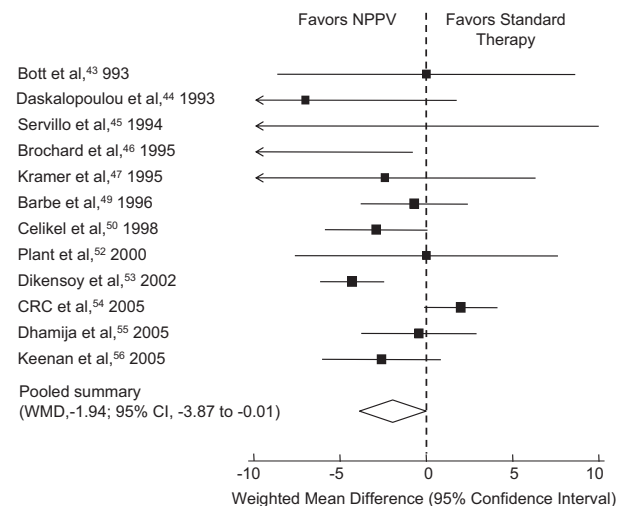


FIGURE 7. Effects of NPPV on LOS during COPD exacerbations. See Figure 2, 4 legends for expansion of abbreviations.

served only among hospitalized patients. It should be noted, however, that although the combined analysis showed a survival benefit, each individual study was relatively small in size and was underpowered to answer this critical question. Even in the treatment failure data, there was significant heterogeneity in the findings across the studies indicating lack of consistency and robustness in the results. In the future, large clinical trials are needed to clearly determine the role of antibiotics in the management of COPD exacerbations. Until then, the current evidence suggests that antibiotics might be a reasonable choice for severe exacerbations requiring hospitalization or exacerbations that fail to improve despite systemic corticosteroid therapy.³⁴ Thirdly, we found that NPPV reduced the need for endotracheal intubation in patients with severe exacerbations and demonstrated arterial (respiratory) acidosis. The beneficial effect of NPPV was modified by the arterial pH of the study patients. At pH of 7.26, for instance, the risk of intubation in the standard group was nearly 60%; whereas in the NPPV group, the risk was only 20%. At higher pH values, the risk differential was much smaller. Thus, our findings support the recommendations of the GOLD committee that NPPV may be used for severe exacerbations when the pH is < 7.35. Our findings are also consistent with three systematic reviews^{35–37} that evaluated the role of NPPV for acute exacerbations of COPD.

In view of the high mortality risk associated with COPD exacerbations, mortality reduction is one of the major aims of hospital-based management of acute COPD. We found that both antibiotics and NPPV reduced in-hospital mortality in a selected group of patients but the mechanisms responsible for their survival benefits were uncertain. It is likely that antibiotics reduced mortality by reducing treatment failure and by possibly preventing nosocomial infections during hospitalizations especially in patients who require endotracheal intubation. The risk of developing ventilator-associated pneumonia can be as high as 30%, and the case fatality rate associated with such infections can be > 50%.³⁸ A metaanalysis³⁹ involving 36 trials and 6,922 patients demonstrated a 22% reduction in mortality with the administration of antibiotic prophylaxis in patients receiving ventilation. The survival benefit from NPPV, however, may be related in part to a 65% reduction in the need for endotracheal intubation and invasive mechanical ventilation and its associated morbidity and mortality.⁴⁰ The impact of systemic corticosteroids on mortality is uncertain. Only four small studies^{10–13} (involving 360 patients) reported on mortality, and the event rates were too small (total of 10 deaths) to draw any meaningful conclusions.

Both systemic corticosteroids and NPPV can reduce LOS by a weighted mean of 1.42 days and 1.94

days, respectively. Only two studies^{25,27} analyzed the impact of antibiotics on LOS, and the results were conflicting. More studies on antibiotics are needed to determine their effect on LOS. Reducing LOS is an important goal of acute COPD management because hospital stays are associated with morbidity and with increased costs. An average hospital day costs the system approximately \$600.⁴¹ Although we found that antibiotics improved clinical outcomes in patients who require hospital-based care, we did not observe a significant difference in the clinical benefits among different classes of antibiotics. In the study by Anthonisen et al,²⁰ for instance, there were no material differences in clinical efficacy between trimethoprim-sulfamethoxazole, amoxicillin, or doxycycline. Several other studies⁴² comparing the various antibiotic agents head-to-head have also failed to demonstrate clear superiority of newer agents over older classes of respiratory antibiotics. Antibiotic selection should therefore be guided by recent history of antibiotic use and local microbial resistance patterns.

Another controversial area is the optimal dose and duration of systemic corticosteroid treatment. In the studies^{10,12,13,15,16,18} showing clinical benefits, the corticosteroid dose (expressed in oral prednisone equivalents) varied from 0.5 to 1.0 mg/kg/d, and the treatment duration varied from 8 to 15 days. Extending the duration of therapy beyond 2 weeks does not appear to confer additional benefits. Niewoehner et al,¹⁶ for instance, failed to demonstrate additional benefits from extending systemic corticosteroid therapy from 2 to 8 weeks. Despite the numerous adverse drug effects associated with corticosteroid use, the only short-term adverse effect reported from the included studies was a sixfold increase in the risk of hyperglycemia.

There were several important limitations to this systematic review. Firstly, the definition of an acute exacerbation was based on clinical criteria and not based on more objective measures such as lung function, which may have resulted in some diagnostic misclassification. This may have in certain circumstances (*eg*, misclassification with asthma) led to a slight overestimation of the benefit of systemic corticosteroids. Secondly, not all studies included in the analysis of NPPV had objective criteria for intubation. Since it was not possible to blind the treating physicians and other health-care professionals, patients in the standard medical therapy group may have been intubated sooner than the NPPV group, resulting in a higher “need for intubation” rate. However, the overall mortality benefit of NPPV would unlikely to have been influenced by this bias. Thirdly, although antibiotics resulted in a larger reduction in treatment failure rates among hospitalized compared with ambulatory patients, the exact

severity or clinical characteristics of patients who benefited from antibiotic therapy is uncertain since there was a scarcity of reported data on lung function and blood gases in these studies. Fourthly, although there were many short-term clinical benefits of systemic corticosteroids, antibiotics and NPPV, the long-term effects of these interventions remain uncertain. Fifthly, publication bias is of concern. To mitigate this bias, we carefully searched the bibliographies of salient articles and included studies that were published only in the abstract form. Finally, owing to a variety of methodologic and clinical issues including heterogeneity of trial design, definitions of exacerbations and underlying clinical characteristics of study patients, the risk estimates of the interventions are not directly comparable.

In summary, acute COPD exacerbations may be treated effectively with systemic corticosteroids, antibiotics, and NPPV. Systemic corticosteroids reduce treatment failures in both in-hospital and outpatient settings, while antibiotics appear more effective in patients requiring hospitalization. NPPV should be considered for carefully selected patients who demonstrate arterial respiratory acidosis.

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