

Managing Acute Respiratory Failure During Exacerbation of Chronic Obstructive Pulmonary Disease

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Summary

Exacerbations of chronic obstructive pulmonary disease (COPD) are a major health problem, causing more than half a million hospital admissions per year in the United States. Although overall mortality is low, it is substantially higher with severe exacerbations that require intensive care and mechanical ventilation. The majority of COPD exacerbations result from infection, with typical bacterial organisms most commonly identified. Numerous randomized controlled trials and meta-analyses have documented the benefits of antibiotics, low-flow oxygen, and systemic corticosteroids, and the therapeutic equivalency of the major classes of bronchodilators (short-acting β -agonist and anticholinergics). Randomized controlled trials also demonstrate that noninvasive ventilation can decrease the incidence of intubation, shorten stay, reduce infectious complications, and improve survival. Although patients who require intubation have the worst prognosis, the vast majority of them can be successfully liberated from mechanical ventilation. For invasively ventilated patients the clinical emphasis should be on improving patient-ventilator interaction and avoiding dynamic hyperinflation (intrinsic positive end-expiratory pressure). *Key words: chronic obstructive pulmonary disease, COPD, respiratory failure, bronchodilator, corticosteroid, oxygen therapy, mechanical ventilation, evidence-based medicine.* [Respir Care 2004;49(7):766–782. © 2004 Daedalus Enterprises]

Introduction

Chronic obstructive pulmonary disease (COPD) affects more than 5% of the adult population and is a major cause

of morbidity and mortality in the United States and worldwide.¹ Approximately 16 million United States adults have

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COPD, and it is the 4th leading cause of death and 12th leading cause of disability.^{2,3} Annually COPD causes an estimated 600,000 hospitalizations and over 13 million out-patient visits in the United States alone. The direct costs due to COPD are approximately \$15 billion.

Definitions of COPD exacerbation differ but typically include a combination of increased sputum volume, sputum purulence, and increasing dyspnea.^{4,5} Having all 3 of those symptoms is a Type I COPD exacerbation; having 2 of the symptoms is a Type II exacerbation; having just 1 of the symptoms is a Type III exacerbation. The Aspen Lung Conference in 2000 developed a working definition of COPD exacerbation as a "sustained worsening of the patient's condition from the stable state and beyond normal day-to-day variation [and] necessitating a change in medication."⁶ Fever, wheezing, increased cough, and tachypnea are also sometimes used as exacerbation indicators.

On average, COPD patients experience 2–3 exacerbations per year, and the exacerbation risk is highest among active smokers. Indeed, smoking cessation can decrease exacerbation frequency by nearly one third.⁷ Patients who suffer frequent COPD exacerbations have significantly more rapid decline in forced expiratory volume in the first second (FEV₁).⁸ Donaldson et al⁸ followed 109 patients who had moderate-to-severe COPD (mean FEV₁ approximately 1.0 L) for 4 years and identified 757 COPD exacerbations. Patients who suffered more frequent COPD exacerbation ($\geq 2.9/y$) had more rapid decline in both FEV₁ (40 vs 32 mL/y) and peak expiratory flow (PEF) (2.9 vs 0.7 L/min/y).⁸ Patients who suffered frequent exacerbations ($> 3/y$) also have worse quality of life.⁹ Exacerbations are associated with increased peripheral muscle weakness (measured by quadriceps torque), which is negatively correlated with systemic interleukin 8 levels.¹⁰

There are no adequately validated variables to determine which COPD-exacerbation patients will require hospital admission. The Global Initiative for Chronic Obstructive Lung Disease (www.goldcopd.com)¹¹ suggests the following criteria for hospital admission:

- Marked increase in symptom intensity (eg, sudden onset of resting dyspnea)
- New physical findings (eg, cyanosis, peripheral edema)
- Severe underlying COPD
- Presence of important comorbidities (eg, cardiac disease)
- New arrhythmias
- Older age
- Failure to respond to initial medical treatment
- Diagnostic uncertainty
- Insufficient home support

Unlike asthma exacerbations, which may be rapidly reversible, the median time to recovery from a COPD exacerbation is 7 days.¹² Thirty-five days after COPD exacerbation only 75% of patients have returned to their baseline PEF. Recovery time is longer with severe exacerbation, and severe exacerbation can cause acute respiratory failure (ARF). Mortality associated with hospitalization for COPD exacerbation can be considerable. One cross-sectional study of a 1996 nationwide in-patient sample (20% of non-federal hospitals in the United States), which included 71,130 patients over the age of 40 years who had a discharge diagnosis of COPD exacerbation, found an in-hospital mortality of 2.5%.¹³ And in-hospital mortality is $> 20%$ among patients who require intensive care unit (ICU) admission.^{14,15} Factors associated with higher hospital mortality include older age, higher Acute Physiology and Chronic Health Evaluation (APACHE III) score, lower pre-admission functional status, lower ratio of P_{aO₂} to fraction of inspired oxygen (P_{aO₂}/F_{IO₂}), hypercapnia, lower serum albumin, lower body mass index, and the presence of cor pulmonale.^{3,14}

A study conducted in England and Wales found higher mortality in hospitals that had fewer physicians and fewer patients under the care of a specialist.¹⁶ ICU admission portends poor long-term prognosis, with reported 1-year and 3-year mortality as high as 48% and 64%, respectively.¹⁷ Approximately half of patients admitted with a COPD exacerbation are readmitted to a hospital within the subsequent 6 months, and 70% are readmitted within 1 year of discharge.^{14,18} Patients admitted with COPD exacerbation have a moderate to high prevalence of potentially modifiable risk factors (eg, have not had vaccination for influenza, underutilization of pulmonary rehabilitation, under-treatment of chronic hypoxemia, ongoing smoking, or second-hand smoke exposure).¹⁹

Etiology of COPD Exacerbations

Exacerbations are most commonly caused by infection (either bacterial or viral), air pollution, or gastroesophageal reflux (or aspiration), but in up to one third of cases the causes are not evident. Traditionally, acute tracheobronchial bacterial infection was thought to be the major cause of COPD exacerbation, with *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* being frequently isolated.^{20,21} A recent prospective study in the Netherlands found that 50% of COPD-exacerbation patients had sputum cultures positive for bacteria, with *H. influenzae*, *Streptococcus*, and *Pseudomonas* being the most common isolates.²² Patients with lower FEV₁ had a higher incidence of bacterial infection. Those researchers found no correlation between the organism isolated and the clinical characteristics of the case. The presence of green/purulent sputum identifies high bacterial load with

good sensitivity (99%) and specificity (77%).²³ Severe exacerbation (eg, that requires mechanical ventilation) is more likely to involve Gram-negative infection, especially with *Pseudomonas*.²¹ COPD-exacerbation patients have increased sputum immunoglobulin A against *Fusobacterium nucleatum* and *Prevotella intermedium* (oral anaerobes), which suggests that tracheal aspiration may play a role.²⁴ Resistant pathogens are more likely in the setting of recent antibiotic use or in chronically institutionalized (eg, nursing home) individuals. Atypical bacterial pathogens and viruses (such as rhinovirus) can also cause exacerbations.^{25,26} *Chlamydia pneumoniae* in particular may be an important pathogen or co-pathogen in COPD exacerbations.^{27,28} Indeed, viral pathogens are thought to cause as many as one third of exacerbations and can be isolated in $\geq 50\%$ of cases.^{26,29} As an example, Rohde et al noted that 56% of 85 hospitalized COPD-exacerbation patients had a respiratory virus isolated, whereas only 19% of stable COPD patients had a respiratory virus isolated, with picornavirus, influenza, and respiratory syncytial virus being most frequently detected.²⁹ Viral infection may also promote or predispose to secondary bacterial infection.³⁰ As an example, the relative risk for isolating pneumococcus and *H. influenzae* after influenza infection is increased by more than 2-fold.

Evaluation for a bacterial etiology for COPD exacerbation is complicated by the airway colonization frequently detected in patients with stable chronic bronchitis. How often these colonizing bacteria precipitate an exacerbation is unknown. Nevertheless, airway colonization is important because organisms thought to be colonizers can evolve into new strains that increase the risk of exacerbations.³¹ Sethi et al followed 81 out-patients for 56 months, performing at each visit a sputum assessment with molecular typing of bacteria isolated. One third of patients who had a new bacteria strain isolated experienced COPD exacerbation, compared to 15% of patients who did not have a new strain.³¹ Another study noted elevated serum and sputum antibodies to *M. catarrhalis* among COPD-exacerbation patients.³²

Environmental factors and air pollution are thought to be the second most common exacerbation precipitant. Hospital admission rates for COPD exacerbation in the United States and Europe rise when ozone and the number of small, respirable particles ($< 10 \mu\text{m}$) increase.^{33–35} Pollutants such as sulfur dioxide and nitrogen dioxide have been implicated as contributors to COPD exacerbation.⁵ Dysphagia and swallowing dysfunction (imaged via videofluoroscopy) are common in COPD, though their role in COPD exacerbation has not been determined.³⁶

In approximately one third of COPD exacerbations no clearly identifiable precipitant is present. During COPD exacerbation ARF may be attributable to cardiac ischemia, congestive heart failure, pulmonary embolism, pneumo-

nia, pneumothorax, lobar atelectasis, or lung cancer.¹⁴ Pulmonary emboli are found in up to 30% of autopsy series that include COPD-exacerbation patients.³⁷ One study of 56 hospitalized COPD-exacerbation patients found that 6 patients had positive lower-extremity Doppler studies for deep venous thrombosis and 5 had ventilation-perfusion (\dot{V}/\dot{Q}) scans that indicated intermediate or high probability of pulmonary embolism.³⁸ A prospective investigation of 196 patients found ultrasound evidence of deep venous thrombosis in 21 patients (10.7%), 18 of whom were asymptomatic.³⁹ Clinical variables could not separate patients who had deep venous thrombosis from COPD patients who did not have deep venous thrombosis. Differentiating acute pulmonary embolus from an exacerbation can be particularly difficult because \dot{V}/\dot{Q} scanning is more often nondiagnostic in COPD. As an example, Hartmann et al compared 91 COPD patients with suspected pulmonary embolism to a large cohort without COPD.⁴⁰ There was no difference in pulmonary embolism prevalence (29 vs 31%). COPD patients were more likely to have nondiagnostic \dot{V}/\dot{Q} scans (46 vs 21%), including a 2-fold higher likelihood of having a false positive high probability scan (21 vs 10%). In contrast to \dot{V}/\dot{Q} scanning, the accurate diagnostic tools with COPD patients are D-dimer levels, pulmonary arteriography, and spiral computed tomography. It is crucial to have a high index of suspicion, as mortality rates for pulmonary embolism are higher among COPD patients,⁴¹ which may result from either the greater difficulty in recognizing the presence of thromboembolism in COPD patients or their reduced cardiopulmonary reserve.

Cardiac ischemia (with or without cardiogenic pulmonary edema) may be confused with COPD exacerbation or may accompany it, perhaps as a consequence of the increased work of breathing (WOB). In one study troponin I measured at admission or 24 h later was positive in 18% of 71 patients admitted with COPD exacerbation.⁴² The diagnosis of congestive heart failure in the setting of COPD exacerbation can be aided by chest radiography and measurement of plasma brain natriuretic peptide. As an example, COPD patients presenting to an emergency room with dyspnea attributable to congestive heart failure had higher brain natriuretic peptide levels than those without congestive heart failure (731 ± 764 vs 47 ± 23 pg/mL).⁴³ Similarly, brain natriuretic peptide levels were higher in a small cohort with diastolic cardiac dysfunction than in COPD patients (224 ± 240 vs 14 ± 12 pg/mL, $p < 0,0001$).⁴⁴ Although plasma brain natriuretic peptide levels were significantly elevated in patients with chronic respiratory failure complicated by cor pulmonale, the values were still well below those seen with congestive heart failure (81.5 ± 13.1 pg/mL).⁴⁵ PEF may also help differentiate COPD exacerbation from cardiogenic pulmonary edema. McNamara and Cionni found higher PEF among

18 congestive heart failure patients (224 ± 82 L/min) than among 23 COPD patients (108 ± 49 L/min).⁴⁶

Initial Assessment

The following physical signs may indicate a severe COPD exacerbation:

- Thoracoabdominal paradox
- Use of accessory respiratory muscles
- Depressed mental status
- Hypotension
- Signs of right-sided heart failure

A severe exacerbation is often associated with an FEV₁ of < 1 L (or PEF < 100 L/min), but such values may also be seen in stable severe COPD. Therefore, PEF and FEV₁ (on admission and in response to therapy) have much less utility in COPD assessment than in asthma assessment. Nevertheless, in one study an FEV₁ < 40% of predicted was associated with hospitalization and higher risk of relapse.⁴⁷ FEV₁ correlates with serum pH and correlates inversely with P_{aCO₂}, and hypercapnia is unlikely when the FEV₁ is > 35% of predicted.⁴⁸ Furthermore, FEV₁ may help predict the need for intensive care.⁴⁹

Arterial blood gas analysis is crucial in assessing the severity of disease and the need for oxygen therapy and mechanical ventilation. At presentation 20–47% of COPD-exacerbation patients have hypercapnia.^{18,50} For example, a pH < 7.30–7.35 or P_{O₂} < 50 mm Hg suggests that ICU admission is required and that noninvasive or invasive ventilatory support may be necessary.⁵¹ In contrast, noninvasive positive-pressure ventilation (NPPV) does not improve outcome when pH is > 7.35, probably because prognosis is good with such a mild exacerbation.⁵² On the other hand, patients with the most severe respiratory acidosis are more likely to fail NPPV and require invasive ventilation.⁵³

Chest radiograph discloses important abnormalities in approximately one fifth of patients presenting with symptoms of COPD exacerbation. In a study of 685 emergency department visits, there were radiographic abnormalities in 16% of patients who presented with COPD exacerbation.⁵⁴ In a study of 107 patients with COPD exacerbation, 16% had radiographic abnormalities and approximately half of those abnormalities were thought to be clinically important (eg, congestive heart failure or pulmonary infiltrates).⁵⁵ Another prospective investigation found that chest radiograph findings changed short-term management in 21% of cases with patients who had asthma or COPD.⁵⁶ Important radiographic findings that indicate alternative diagnoses include pneumothorax, subcutaneous air, pneumonia, lo-

bar atelectasis, or a pattern consistent with pulmonary edema.

With more severe COPD exacerbations the clinician should consider admitting the patient directly to an intensive care unit. The Global Initiative for Chronic Obstructive Pulmonary Disease¹¹ suggests the following indications for ICU admission:

- Severe dyspnea that does not adequately respond to initial treatment
- Confusion, lethargy, coma
- Persistent or worsening hypoxemia (P_{aO₂} < 50 mm Hg) despite supplemental oxygen
- Severe/worsening hypercapnia (P_{aCO₂} > 70 mm Hg) despite NPPV
- Severe/worsening respiratory acidosis (pH < 7.30) despite NPPV

Oxygen Therapy

The majority of patients hospitalized for COPD exacerbation have substantial hypoxemia, the primary cause of which is worsening \dot{V}/\dot{Q} mismatch, a condition that typically responds to treatment with low-flow oxygen (≤ 4 L/min via nasal cannula). A requirement for high-flow oxygen suggests alternative diagnoses such as pulmonary thromboembolism, pneumonia, or cardiogenic pulmonary edema. The physiologic benefits of supplemental oxygen include decreased hypoxic pulmonary vasoconstriction, decreased pulmonary artery pressure, decreased right heart strain, improved mucociliary clearance, and improvement in cardiac ischemia, if present.

Supplemental oxygen can worsen hypercapnia, and 3 mechanisms have been proposed to explain this phenomenon:

- Increased dead-space due to \dot{V}/\dot{Q} changes resulting from the release of hypoxic vasoconstriction
- Loss of hypoxic respiratory drive
- Haldane effect: carbon dioxide binding capacity decreases as hemoglobin oxygen saturation increases.

Some investigators have suggested that increased dead-space ventilation plays a predominant role in oxygen-induced worsening hypercapnia.^{57–60} As an example, COPD-exacerbation patients given 100% oxygen demonstrated a 23% increase in P_{aCO₂}, which could not be explained by a small (7%) decrease in minute ventilation (\dot{V}_E).⁵⁷ In contrast, in a study of oxygen-induced hypercapnia among COPD-exacerbation patients, those who retained carbon dioxide suffered a significant decrease in ventilation when

breathing 100% oxygen (as measured with the multiple inert-gas elimination technique), compared to those who did not retain carbon dioxide.⁶¹ Notably, both groups demonstrated increased perfusion to lung units that had low \dot{V}/\dot{Q} , indicating a release of hypoxic vasoconstriction. These mechanisms may not be operative during mechanical ventilation, as increasing the F_{IO_2} from 0.3–0.4 to 0.7 did not significantly increase P_{aCO_2} or respiratory rate, or decrease respiratory drive (as measured by airway occlusion pressure at 0.1 s).⁶²

There is controversy about how to identifying the patients who are at greatest risk for oxygen-induced hypercapnia. Bone et al found that “dangerous” respiratory acidosis was unlikely to develop when the measured pH was greater than the pH calculated from the formula $pH = 7.66 - 0.0675 \times P_{aO_2}$ (kPa),* determined on an F_{IO_2} of 24%.⁶³ In contrast, a study of 24 patients noted that risk was greatest among patients who had the most severe hypercapnia at presentation.⁶⁴

During COPD exacerbation oxygen therapy should balance the avoidance of severe hypercapnia with the maintenance of adequate oxygen delivery. A recent study compared oxygen therapy titrated to keep $P_{aO_2} > 50$ mm Hg versus > 70 mm Hg. Although there was no difference in outcome, the number of patients studied was small and the findings were confounded by the concomitant use of the respiratory stimulant doxapram.⁶⁵ Given the configuration of the hemoglobin oxygen saturation curve, targeting an oximetry-measured saturation of 90% or a P_{aO_2} of 60 mm Hg may be the optimal strategy. Low-flow oxygen via nasal cannula or controlled therapy with air-entrainment mask (F_{IO_2} 24–40%) is associated with only a small risk of significantly worsening hypercapnia.⁶⁴ One investigation directly compared air-entrainment mask to nasal cannula and found air-entrainment mask superior in minimizing the duration of hypoxemia, and both strategies avoided clinically important hypercapnia.⁶⁶ With high-flow oxygen the risk of hypercapnia is substantial, so arterial blood gas should be measured again within 30–60 min. In a large audit of patients treated for COPD exacerbation, Roberts et al found that only 34% of patients underwent repeat arterial blood gas analysis.¹⁶ NPPV should be considered when higher arterial oxygen carrying capacity is mandated (eg, in the presence of nonpulmonary organ failure) or if substantial hypercapnia persists despite low-flow oxygen.

Helium-Oxygen Mixture

Helium-oxygen mixture (heliox) is a low-density gas that can decrease airflow turbulence and thereby decrease WOB and improve gas exchange in COPD patients.^{67,68} A

retrospective study by Gerbeaux et al found a lower intubation rate and better survival with heliox.⁶⁹ However, a prospective, randomized trial with COPD patients in an ICU who were treated with NPPV found that heliox (vs oxygen) provided no statistically significant benefit in ICU stay, mortality, or intubation rate, though there was a trend toward lower intubation rate with heliox. Overall hospital stay and costs were lower in the heliox group.⁷⁰

Heliox can improve the administration of bronchodilators. With an *in vitro* mechanical ventilation model, Goode et al found that heliox increased delivery of both metered-dose inhaler (MDI) and nebulizer aerosol.⁷¹ In contrast, an emergency-department study of COPD-exacerbation patients found that using heliox as a driving gas for bronchodilator nebulization did not improve FEV_1 .⁷² In a randomized controlled cross-over trial Diehl et al studied 13 intubated COPD-exacerbation patients who were thought to be capable of spontaneous breathing and, therefore, extubation.⁷³ Heliox provided significantly lower WOB than did air/oxygen, mainly by reducing resistance.

Bronchodilators

Short-acting bronchodilators (β agonists, anticholinergics, or a combination of those) are a crucial component of therapy for COPD exacerbation. In a European study COPD-exacerbation patients received β agonists (78%), anticholinergics (56%) and methylxanthines (31%).⁷⁴ In an audit of 1,400 patients admitted to 38 United Kingdom hospitals, Roberts et al found that 91% of COPD-exacerbation patients received nebulized β agonists, 77% received a combination of β agonists and anticholinergics, and only 2% received anticholinergics only.¹⁶ Among COPD patients (age > 55 y) treated in 29 emergency departments in 15 states in the United States and 3 Canadian provinces, 91% received short-acting inhaled β agonists, 77% received inhaled anticholinergics, and just 0.3% received methylxanthines.⁷⁵ In a systematic review of 14 randomized controlled trials, Bach et al found no significant efficacy difference between β agonists and anticholinergics.³ Combination therapy is feasible and safe, but there are no convincing data that demonstrate superiority to either agent alone.⁷⁶ In a meta-analysis of 12 randomized controlled trials, Turner et al found no difference between bronchodilators administered via nebulizer versus via MDI with spacer.⁷⁷ One approach is to begin with nebulizer therapy and switch to MDI after the patient's condition improves. There is no evidence supporting the use of continuously nebulized bronchodilators in COPD exacerbation.

Theophylline has several favorable effects, including bronchodilation, respiratory stimulation, respiratory-muscle-function enhancement, and anti-inflammatory action. Nevertheless, a meta-analysis of 4 randomized, controlled

* 1 kPa = 7.5 mm Hg.

trials ($n = 169$ patients) found that theophylline did not benefit spirometry values, clinical variables, or symptom scores, and theophylline was associated with more nausea, vomiting, hand tremor, palpitations, and arrhythmias.⁷⁸ Based on that analysis, theophylline should not be routinely used for COPD exacerbation.

One concern about β agonists for COPD exacerbation is the potential adverse cardiac effects. β agonists increase tachycardia, though the clinical importance of that adverse effect is unclear. A study of 14 patients who had both COPD and ischemic heart disease compared β agonists to inhaled anticholinergics and found no difference in heart rate or premature ventricular contractions.⁷⁹ A recent analysis of 7 randomized controlled trials (n of approximately 3,000 patients) compared a long-acting β agonist (salmeterol) to placebo and found no increase in adverse cardiovascular effects among stable-COPD patients.⁸⁰ The R-isomer of albuterol (levalbuterol) (1.25 mg) does not appear to induce less tachycardia, hand tremor, or hypokalemia than does racemic albuterol (2.5 mg) at comparable therapeutic doses needed to treat acute bronchospasm in stable COPD or asthma.^{81–83}

Administering bronchodilator to invasively ventilated patients presents special challenges. Nosocomial outbreaks of ventilator-associated pneumonia have been associated with contaminated multi-dose vials of bronchodilator solution.⁸⁴ Airflow through ventilator tubing and the hygroscopic effects of fluid in the tubing can impact the delivery of aerosols. Earlier studies found that minimal drug reached the airways when the MDI device was actuated directly into the ventilator tubing,⁸⁵ whereas using a spacer device with the MDI dramatically enhances drug delivery to the airways. In a physiologic study of ventilated patients with COPD exacerbation, Dhand et al found the best reduction in airway resistance with 4 puffs of albuterol delivered via spacer.⁸⁶ Higher doses (8 and 16 puffs) did not further reduce airway resistance but significantly increased heart rate. In a bench study Fink et al found that aerosol delivery was greatest with dry (nonhumidified) gas, with spontaneous breathing (compared to assist-control or pressure-support ventilation), with an inspiratory pause, and with a longer duty cycle.⁸⁷ In contrast, in a series of studies with COPD-exacerbation patients Mouloudi et al found no better bronchodilator effect with an inspiratory pause (5 s), higher tidal volume, slower inspiratory flow, or a square-wave (vs decelerating) flow pattern.^{88–91} For patients undergoing NPPV, bronchodilators can be delivered via MDI with spacer.⁹²

Corticosteroids

Airway inflammation is a component of the pathophysiology of COPD exacerbations. COPD-exacerbation patients have elevated neutrophil, tumor necrosis factor al-

pha, and interleukin 8 levels.^{93,94} Systemic steroids are thought to reduce that inflammatory component of COPD exacerbation and there may be other benefits as well. For example, 90 min after an infusion of methylprednisolone (0.8 mg/kg), inspiratory resistance and intrinsic positive end-expiratory pressure (PEEPi) were significantly decreased in ventilated COPD patients.⁹⁵

There have been 7 randomized, placebo-controlled studies of steroid therapy for COPD exacerbation (Table 1).^{48,96–102} The studies used different steroid doses and duration of therapy, and assessed different end points. However, some general conclusions can be made. Six of the 7 studies found benefit from steroids. Only 1 study showed placebo to be superior to steroid.¹⁰² However, that study used only a single dose of intravenous steroid, given in the emergency department. The studies that used a longer course of steroids all showed some benefit. The largest study, the Systemic Corticosteroids in COPD Exacerbations (SCCOPE) trial, included 271 patients and compared 2 steroid regimens to placebo.¹⁰⁰ All steroid patients received 125 mg intravenous methylprednisolone every 6 hours for the first 3 days. They were then switched to prednisone 60 mg/d and tapered over either 2 or 8 weeks. Patients in the steroid groups had faster improvement in FEV₁, shorter hospital stay, and fewer treatment failures. There was no benefit from the longer steroid taper; in fact there was a nonsignificant trend toward higher infection rate in the 8-week-taper group. Steroids were relatively well tolerated, with hyperglycemia being the most common adverse effect. Shorter courses of systemic steroids are probably ineffective: a small, prospective, randomized trial found that a 10-day course of methylprednisolone gave greater improvement in dyspnea and lung function than did a 3-day course.¹⁰³ A recent study of out-patients treated and discharged from an emergency department indicated that prednisone 40 mg/d for 10 days was efficacious.⁹⁶

To investigate the effect of different steroid preparations, Li et al randomized 142 COPD-exacerbation patients to either methylprednisolone or dexamethasone.¹⁰⁴ Tapering doses were given over 7–14 days, followed by 2–3 weeks of prednisone. All patients received oxygen, antibiotics, and bronchodilators. Greater maximum benefit was seen with methylprednisolone: percent-of-predicted FEV₁ increased from 47 to 68%.

Maltais et al randomized 199 patients with nonsevere COPD exacerbation to 72 hours of treatment with either oral prednisolone (30 mg twice daily), nebulized budesonide (2 mg 4 times daily), or placebo.¹⁰⁵ Patients were excluded if they were mechanically ventilated or admitted to ICU, or if pH was < 7.3 , P_{aCO₂} was > 70 mm Hg, or P_{aO₂} was < 50 mm Hg despite supplemental oxygen therapy. Both prednisolone and budesonide improved airflow better than did placebo, and there was no difference between oral and inhaled therapy. In stable hypercapnic, ventilated patients a randomized controlled trial found that 5

MANAGING ACUTE RESPIRATORY FAILURE DURING COPD EXACERBATION

Table 1. Randomized Controlled Trials of Corticosteroids for COPD Exacerbation

First Author (Year)	<i>n</i>	Setting	Steroid Regimen	Benefits of Steroid
Albert ⁹⁷ (1980)	44	In-patient facility	Methylprednisolone 0.5 mg/kg every 6 h for 3 d	Greater improvement in FEV ₁
Emerman ¹⁰² (1989)	96	Emergency department	Methylprednisolone 100 mg intravenously, once	No benefit identified
Bullard ⁹⁸ (1996)	113	Emergency department	1. Hydrocortisone 100 mg intravenously every 4 h for 4 d 2. If discharged from hospital prior to day 4, prednisone 40 mg for 4 d total treatment	Greater improvement in FEV ₁
Thompson ¹⁰¹ (1996)	27	Out-patients	Prednisone taper 60 mg × 3 d, then 40 mg × 3 d, then 20 mg × 3 d	Greater improvement in FEV ₁ Greater improvement in Pao ₂ Improved dyspnea scores
Niewoehner ¹⁰⁰ (1999)	271	In-patient facility	Methylprednisolone 125 mg every 6 h for 3 d, then prednisone taper for either 2 or 8 wk	Greater improvement in FEV ₁ Shorter hospital stay Fewer treatment failures No added benefit from longer steroid taper
Davies ⁹⁹ (1999)	56	In-patient facility	Prednisone 30 mg × 14 d	Greater improvement in FEV ₁ Shorter hospital stay
Aaron ⁹⁶ (2003)	147	Emergency department/out-patients	Prednisone 40 mg × 10 d	Greater improvement in FEV ₁ Lower relapse rate Improved dyspnea scores

COPD = chronic obstructive pulmonary disease
FEV₁ = forced expiratory volume in the first second

days of fluticasone (via MDI, 2,000 μ g) significantly reduced airway resistance and PEEPi.¹⁰⁶

Mucolytic Agents and Mucokinetic Techniques

A meta-analysis of 5 randomized controlled trials using different mucolytic agents (domiodol, bromhexine, ambroxol, S-carboxymethylcysteine, potassium iodide) showed no convincing evidence for benefit to lung function.^{3,107–109} Two of 5 individual studies reported improvement in subjectively determined symptom score. Of the 3 randomized, controlled trials examining mechanical percussion of the chest (applied by respiratory or physical therapists), none reported benefit for FEV₁, forced vital capacity, or symptoms.^{110–112} In fact, chest percussion can transiently decrease lung function.^{110,112} Based on those studies there appears to be no role for the routine application of mucolytic agents or mucokinetic respiratory therapy techniques.

Antibiotics

Numerous randomized, placebo-controlled trials support the use of antibiotics for COPD exacerbation, and the patients most likely to benefit are those with COPD exacer-

beration Types I and II. The majority of the available evidence comes from studies performed more than 15 years ago, when bacterial resistance to commonly used antimicrobials was less prevalent. For example, the classic study by Anthonisen et al demonstrated that (compared to placebo) antibiotics (amoxicillin, tetracycline, trimethoprim-sulfamethoxazole) decreased the duration of exacerbation, increased PEF recovery rate, and were associated with greater overall treatment success (defined as symptom resolution within 21 d) in 237 out-patients experiencing 362 exacerbations.⁴ A 1995 meta-analysis concluded that antibiotics provide a small but statistically significant improvement in clinical and physiologic outcome, particularly with the most severe exacerbations.¹¹³ Two more recent meta-analyses (which included 11 randomized controlled trials) also found benefit from antibiotic therapy for patients with COPD exacerbation and purulent sputum.^{9,114} Whether newer antibacterial agents are superior to older (more extensively studied) antibiotics is unclear. A retrospective cohort study that compared azithromycin to trimethoprim-sulfamethoxazole or amoxicillin in COPD-exacerbation out-patients found no difference in failure rates, need for hospitalization, or time to subsequent exacerbation.¹¹⁵ However, an investigation that compared telithromycin (a new

Table 2. Randomized Controlled Trials of Noninvasive Positive-Pressure Ventilation for COPD Exacerbation

Study	n	NPPV Mode	Benefits of NPPV
Bott ¹²⁴ (1993)	60	Volume-controlled, via nasal mask	Greater improvement in pH, P _{CO} ₂ Trend toward lower mortality
Brochard ¹²³ (1995)	85	Pressure-support, via face mask	Lower intubation rate Lower mortality Shorter hospital stay Fewer complications
Kramer ¹²⁵ (1995)	23	BiPAP, via nasal mask	Lower intubation rate
Barbe ⁵² (1996)	24	BiPAP, via nasal mask	No benefits identified
Celikel ¹²⁷ (1998)	30	Pressure-support, via face mask	Better pH, P _{CO} ₂ , PO ₂ , respiratory rate Shorter hospital stay
Plant ¹²⁶ (2000)	236	BiPAP, via nasal or face mask	Lower intubation rate Lower mortality Better pH and respiratory rate

NPPV = noninvasive positive-pressure ventilation
BiPAP = bilevel positive airway pressure

ketolide antibiotic) to amoxicillin and potassium clavulanate (Augmentin) found better outcomes with telithromycin.¹¹⁶

Bronchoscopic studies that used a protected-specimen-brush technique and quantitative cultures indicate that typical organisms (pneumococcus, *H. influenzae*, and *M. catarrhalis*) are most likely in COPD-exacerbation outpatients.²⁰ Although studies performed in ventilated COPD-exacerbation patients also find typical bacterial organisms most prevalent, a large minority of patients have Gram-negative bacilli, *Staphylococcus aureus*, and atypical organisms isolated.^{21,117} Those observations influence the selection of antimicrobial therapy in more severely ill patients. Indeed, a randomized, placebo-controlled trial with 93 ventilated COPD-exacerbation patients showed that 10 days of fluoroquinolone (ofloxacin) found lower mortality (4 vs 22%), shorter duration of mechanical ventilation, and shorter hospital stay.¹¹⁸

The ideal duration of antibiotic treatment has not been rigorously determined. Recommendations generally advocate 5–10 days of therapy.⁷ A recent study of 235 COPD-exacerbation outpatients found 5 days of azithromycin or 7 days of levofloxacin to be equivalent and highly successful (favorable clinical outcomes in 89 vs 92%).¹¹⁹

Ventilatory Support

Noninvasive Ventilation

Approximately half of patients suffering hypercapnic respiratory failure (COPD exacerbation) respond favorably to medical therapy, half of those within the first 24 hours and 92% within 72 hours.¹²⁰ Therefore, half of pa-

tients require some type of ventilatory support. When properly applied, NPPV provides the same physiologic benefits (improved gas exchange and reduced WOB) as does invasive ventilation.¹²¹ NPPV has been increasingly utilized for COPD exacerbations and may be indicated for a substantial minority of COPD-exacerbation patients.¹²² In a study in the United Kingdom 16% of COPD exacerbation cases were deemed appropriate candidates for NPPV.⁵⁰ And a number of randomized controlled trials have demonstrated the effectiveness of NPPV for COPD exacerbation, with approximately 70–80% of such patients avoiding intubation (Table 2).^{52,123–127} In those studies NPPV was applied using various ventilators (ICU ventilators and small portable ventilators), ventilation modes (volume-cycled and pressure-cycled), and interfaces (nasal mask or full face mask). Two recent systematic reviews both concluded that NPPV benefits selected patients suffering respiratory failure due to COPD exacerbation.^{128,129} Specifically, NPPV was associated with lower mortality, less need for intubation, shorter stay, and greater improvement in pH, P_{CO}₂, and respiratory rate. The analysis by Keenan et al found a 28% risk reduction for intubation, 10% risk reduction for mortality, and a 4.6-day shorter hospital stay.¹²⁹ Those benefits are principally observed with severe COPD exacerbations. One of the few reported negative studies was notable for a having less-sick patient population: none of the control patients required intubation.⁵²

The superiority of NPPV appears to be from the fact that it has a lower infection risk than invasive ventilation. A case-control study of 100 patients with either COPD exacerbation or congestive heart failure found NPPV to be associated with lower risk of nosocomial pneumonia.¹³⁰ In

a larger, prospective study Nouridine et al found NPPV associated not only with fewer cases of ventilator-associated pneumonia but also with fewer urinary tract infections, fewer catheter-related infections, and less bacteremia.¹³¹

Factors associated with a higher NPPV success rate include a less severely ill patient (lower APACHE II score), younger age, ability to cooperate, minimal leak, intact dentition, hypercapnia ($P_{aCO_2} > 45$ mm Hg), acidemia (pH < 7.35), and evidence of improvement within the first few hours of NPPV application.^{53,132,133} In contrast, NPPV is contraindicated in the presence of hemodynamic instability, substantial craniofacial abnormalities, facial burns, significantly impaired consciousness, or high aspiration risk. Patients with the most severe exacerbations (eg, pH < 7.10 , $P_{aCO_2} > 90$ mm Hg) are more likely to fail NPPV.^{134,135} That said, one group analyzed their experience with NPPV for COPD exacerbation over an 8-year period¹³⁶ and found that, despite worsening severity of illness over the course of the study period (defined by lower pH and higher P_{aCO_2} and APACHE II scores), NPPV continued to be applied with equal success.

Patients who do not show rapid improvement in respiratory rate, sensation of dyspnea, use of accessory respiratory muscle, and P_{aCO_2} within the initial 1–4 h are at higher risk for NPPV failure.¹³⁷ And late application of NPPV may not provide the same benefits as early NPPV application. Conti et al randomized 49 patients who failed standard therapy in the emergency room to either intubation or NPPV.¹³⁸ Fifty-two percent of NPPV patients required intubation, but overall there were no differences in ICU stay, days of mechanical ventilation, complications, or ICU or hospital mortality. As in other investigations, 1 year after discharge the NPPV group had experienced fewer hospital readmissions for COPD exacerbation.¹³⁹

The routine use of NPPV for stable COPD remains controversial,^{140,141} but in a study of highly selected patients who had recurrent hospital admissions for COPD exacerbation, domiciliary NPPV appeared to be effective in decreasing the subsequent admissions and reducing exacerbations.¹⁴²

One key to successful application of NPPV is choosing an effective interface. A study with stable hypercapnic COPD patients compared nasal plugs, nasal mask, and full face mask.¹⁴³ The nasal mask was best tolerated but was less effective than full face mask in lowering P_{aCO_2} . In a randomized controlled trial with 70 ARF patients (one third of whom had COPD exacerbation), Kwok et al found more mask intolerance and a trend toward a lower success rate with nasal mask than with full face mask.¹⁴⁴ Antonelli et al recently compared 33 historical control COPD-exacerbation patients who had been treated with NPPV via face mask to 33 patients who received NPPV via a novel helmet interface.¹⁴⁵ Both groups had improved P_{aCO_2} and pH,

but the standard face mask was somewhat more effective. There were no differences in intubation rate, duration of stay, or mortality. In some centers with particular expertise, negative-pressure ventilators (“iron lungs”) provided benefits similar to those of NPPV for COPD exacerbation.¹⁴⁶

Invasive Ventilation

As discussed above, invasive ventilation is required for patients in respiratory failure who do not improve with NPPV, are hemodynamically unstable, have cardiopulmonary arrest, or are not NPPV candidates. In a retrospective study 54% of 138 patients with hypercapnic COPD exacerbation required intubation, on average within 8 hours of presentation.¹²⁰ Contrary to common expectations, the mortality in patients intubated for COPD is not greater than that in patients with other causes of ARF. A recent international study of over 5,000 patients mechanically ventilated for ARF found that those patients intubated for COPD exacerbation had a mortality of 22%, versus an overall mortality of 31%. Even when adjusted for severity of illness, the mortality in the COPD group was no worse than other groups.¹⁴⁷ A smaller study of 300 patients mechanically ventilated for ARF found no difference between COPD patients and the other patients, despite the fact that COPD patients had a higher reintubation rate.¹⁴⁸ A study of 166 hospitalized COPD patients found an overall in-hospital mortality of 28%. However, in the subgroup of patients intubated exclusively for COPD exacerbation, mortality was 15%. Surviving a prior episode of mechanical ventilation predicted better survival, whereas the need for ventilation for > 72 hours predicted higher mortality.¹⁴⁹

Few robust comparative data exist to identify the best mode of invasive mechanical ventilation for COPD-exacerbation patients. COPD-exacerbation patients are particularly prone to poor patient-ventilator interaction because of high respiratory drive, expiratory flow limitation, increased resistive and elastic WOB, and reduced respiratory muscle function. Respiratory drive is markedly elevated in ARF patients, so high inspiratory flow is required,¹⁵⁰ and reducing inspiratory flow increases WOB and respiratory effort.¹⁵¹ Using flow-triggering rather than pressure-triggering also reduces WOB with ventilated COPD patients.¹⁵² A high level of pressure-support can cause poor patient-ventilator interaction. Jubran et al found that pressure-support ventilation (PSV) effectively decreased inspiratory WOB (inspiratory pressure-time product), but it increased expiratory WOB.¹⁵³ With pressure-support of 20 cm H₂O the onset of expiratory effort preceded the cessation of inspiratory flow in 5 of 12 patients, perhaps a result of the flow-cycling criteria used to trigger machine expiration. That adverse interaction may be overcome by using ventilators that can adjust the expiratory flow-cycling

criteria or change to time-cycled ventilation modes (eg, volume control or pressure control).

Invasive mechanical ventilation can be associated with considerable risks with COPD patients—a fact that may explain the very high mortality rate reported in some early studies. Life-threatening hypotension occurs in 25% of cases of emergency intubation of COPD patients, particularly among those with hypercapnia.¹⁵⁴ In one survey of patients with pulseless electrical activity of unknown etiology, 74% had COPD.¹⁵⁵ Application of high \dot{V}_E or tidal volume can cause dynamic hyperinflation, severe PEEPi (and consequent hypotension), worsening oxygenation and gas exchange, and barotrauma. Barotrauma occurred in 19% of mechanically ventilated COPD patients treated with high tidal volumes (average of 13.6 mL/kg),¹⁵⁶ and in patients with chronic hypercapnia excessive \dot{V}_E can abruptly lower P_{aCO_2} and cause severe alkalemia.

The presence of PEEPi can be detected by physical examination¹⁵⁷ or by examination of expiratory flow curves, but obtaining a quantitative PEEPi measurement¹⁵⁸ requires the end-expiratory occlusion technique (static PEEPi) or, with spontaneously breathing patients, determining the decrease in esophageal pressure between the onset of inspiratory effort and the initiation of inspiratory flow (dynamic PEEPi).¹⁵⁸ Those techniques are confounded by active expiratory muscle contraction and the heterogeneity of the COPD lung. Strategies for reducing PEEPi include decreasing the expiratory flow limitation (with bronchodilators or steroids) and reducing \dot{V}_E . Increasing the inspiratory flow decreases the inspiratory time and increases the expiratory time. Concern has been raised about this approach, because normal subjects demonstrate increased respiratory rate and reduced expiratory time in response to increased inspiratory flow.¹⁵⁹ To further address this issue Laghi et al conducted a study with 10 stable-COPD patients, using a mouthpiece and assist-control ventilation.¹⁶⁰ Increasing inspiratory flow from 30 to 90 L/min reduced inspiratory time but increased respiratory rate from 16 to 21 breaths/min. Despite that increase, expiratory time increased (from 2.1 to 2.3 s) and PEEPi decreased (from 7 to 6.4 cm H₂O).

Applied PEEP (at approximately 80% of PEEPi) can reduce inspiratory work by decreasing the relative drop in airway pressure required to trigger the ventilator.^{161–163} In fact that strategy may increase patient tolerance for spontaneous breathing trials (SBTs).¹⁶⁴

Weaning and Extubation

Although the majority of mechanically ventilated patients are easily liberated from the ventilator, for the remaining patients the time consumed in weaning can be substantial. Two studies found that 60% of total ventilator time for COPD patients was spent trying to wean.^{149,165}

Numerous studies have focused on identifying readiness for SBT, the best method for conducting SBT, and the optimal approach to progressive withdrawal of mechanical ventilation (weaning).^{166–170} Many COPD patients were included in those investigations, but the number studied and the subgroup analyses are not adequate for making disease-specific recommendations. However, assuming that the findings of those studies can be generalized to COPD patients, we recommend:

1. A COPD patient should undergo SBT when there is evidence of clinical improvement, the patient is hemodynamically stable, and P_{aO_2}/F_{IO_2} is > 150 mm Hg (or > 120 mm Hg in the setting of chronic hypoxemia).¹⁷¹
2. The use of objective physiologic measurements as predictors of weaning success is controversial. A recent systematic review found the known predictors to be, at best, only moderately helpful in predicting weaning success or failure.¹⁷² Therefore an evidence-based weaning consensus group recommended that such predictors not be used routinely in weaning decision-making.¹⁷¹
3. SBTs can be conducted with either T-piece, continuous positive airway pressure, or a low level of inspiratory pressure support.
4. Patients who fail SBT may require a slower method of progressive withdrawal, by daily T-piece SBTs of increasing duration or daily reductions in PSV or PSV/SIMV. The SIMV mode alone should not be used for weaning.
5. An organized approach using a weaning protocol directed by ICU nurses and respiratory therapists improves outcomes.¹⁷¹

Investigations of patients intolerant of SBT indicate that failed weaning is associated with increasing total WOB (including resistive, elastic, and PEEPi components).¹⁷³ Another study found that weaning failure was associated with elevated inspiratory tension-time index, which is an indicator of the imbalance/balance between respiratory load and respiratory muscle capacity.¹⁷⁴

COPD patients often have risk factors for coronary artery disease, so cardiac ischemia and congestive heart failure may also limit efforts to liberate patients from mechanical ventilation.^{175,176} Lemaire et al found that the change from positive pressure to spontaneous breathing through an endotracheal tube (negative pressure) immediately and significantly increased pulmonary artery occlusion pressure in COPD patients.¹⁷⁷ Ischemia can be detected by electrocardiography or nuclear imaging, though chest pain may be absent.^{175,176,178,179} Even in the absence of coronary artery disease, the large negative swings in intrathoracic pressure with spontaneous breathing can increase left ventricular afterload and reduce ejection fraction.¹⁸⁰ When cardiac ischemia is suspected, cardioelec-

tive β blockade is indicated to decrease myocardial work. Salpeter et al analyzed 19 single-dose and 10 continued-dose studies of cardioselective β blockers administered to patients who had asthma or COPD.¹⁸¹ Cardioselective β blockade reduced FEV₁ by 7%, but subsequent “rescue” therapy with inhaled β agonist resulted in an overall FEV₁ increase of 5%. Therefore, use of cardioselective β blockade appears to be safe for COPD.

Using NPPV to Facilitate Weaning and Prevent Extubation Failure

Some COPD-exacerbation patients are difficult to wean and NPPV may assist in weaning. In a 2-year survey of a 22-bed medical ICU, 143 of 604 patients who required mechanical ventilation received NPPV, and 30% of those NPPV applications were to facilitate weaning or prevent extubation failure.¹⁸² Older uncontrolled studies suggested that NPPV could facilitate weaning.^{183,184} NPPV can correct or counterbalance some of the causes of weaning failure. NPPV can reverse rapid shallow breathing, increase alveolar ventilation, reduce WOB, counterbalance PEEPi, and improve gas exchange.¹²¹ Nava et al studied 50 patients intubated for COPD exacerbation (average P_{aCO₂} 90 mm Hg) who had failed a T-piece SBT after approximately 48 hours of mechanical ventilation.¹⁸⁵ Patients were randomized to either invasive pressure-support weaning or extubation to NPPV (pressure-support mode with a standard ICU ventilator) with full face mask. The NPPV group had an average of 7 days less mechanical ventilation, 9 days shorter ICU stay, and better weaning success and survival at 60 days. As with other NPPV studies, the NPPV advantages may have resulted from a lower rate of nosocomial pneumonia (0 vs 25%). A subsequent study by Girault et al showed that NPPV reduced the duration of invasive mechanical ventilation, though there were no differences in ICU stay, hospital stay, need for reintubation, or 3-month survival.¹⁸⁶ Most recently Ferrer et al randomized 43 patients (77% with chronic lung disease) who had failed 3 consecutive T-piece SBTs to either NPPV (minimum of 24 h) or conventional weaning.¹⁸⁷ NPPV weaning was associated with shorter duration of invasive ventilation (9.5 vs 20.1 d), shorter ICU stay (14 vs 25 d), shorter hospital stay (28 vs 49 d), fewer tracheotomies (5 vs 59%), better ICU survival (90 vs 59%), better 90-day survival, fewer reintubations (14 vs 27%), and a lower incidence of nosocomial pneumonia and septic shock. Based on those 3 randomized controlled trials, it is reasonable to consider NPPV weaning for selected COPD patients suffering acute-on-chronic respiratory failure. Patients must satisfy readiness criteria for spontaneous breathing, criteria for extubation (ability to protect the airway), and otherwise be good candidates for NPPV. The patient must be capable of sustaining spontaneous breathing for a minimum of 5–10

min, as that time is necessary to apply the NPPV interface and adjust the NPPV settings.

Observational studies indicate that NPPV can be used with patients who tolerate SBT but then demonstrate evidence of respiratory failure shortly after extubation.^{182,188} In a case-control study Hilbert et al observed that NPPV (in PSV mode) was effective with 30 COPD patients who had suffered post-extubation respiratory failure.¹⁸⁹ Compared to historical controls, NPPV reduced the need for intubation (30 vs 67%) and shortened ICU stay (8 vs 14 d). Hilbert et al also demonstrated that measurement of airway occlusion pressure during routine face-mask NPPV after extubation can help identify patients destined to develop post-extubation respiratory failure.¹⁹⁰ In a randomized controlled trial with 81 patients ventilated for > 48 h, Keenan et al found that NPPV did not improve outcomes of post-extubation respiratory failure.¹⁹¹ After the first year of the study COPD patients were excluded. More recently, Esteban et al randomized 221 patients who had signs of early respiratory failure within 48 h of extubation to either standard care or NPPV.¹⁹² The study design provided for a separate randomization for COPD patients. NPPV did not decrease the need for reintubation. Indeed, ICU mortality was higher among patients randomized to NPPV (12 h vs 2 h among the controls), perhaps reflecting the delayed reintubation among those patients. In a post hoc analysis of the COPD patients (*n* = 23), a nonsignificant NPPV benefit was observed: reintubation was avoided in 7 NPPV COPD patients (50%) versus 3 (33%) in the conventional treatment group.

Summary

There is now a substantial and robust evidence base to guide effective therapy for COPD exacerbation. These advances in therapy derive directly from increased understanding of the causes and pathophysiologic basis of COPD exacerbation. Pharmacologic therapy centers on inhaled bronchodilators, low-flow supplemental oxygen, antibiotics, and systemic corticosteroids. For severe exacerbations characterized by respiratory acidosis and hypercapnia, NPPV decreases the need for intubation, reduces infectious complications, and increases survival. For intubated patients there are effective strategies to improve patient-ventilator interaction and reduce the adverse consequences of PEEPi. Although intubated patients have the worst prognosis, the vast majority of them can be successfully liberated from mechanical ventilation.

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