Evidence-based approach to acute exacerbations of COPD
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Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the United States, and it accounts for approximately 500,000 hospitalizations for exacerbations each year. New definitions of acute COPD exacerbation have been suggested, but the one used by Anthonisen et al. is still widely accepted. It requires the presence of one or more of the following findings: increase in sputum purulence, increase in sputum volume, and worsening of dyspnea. Patients with COPD typically present with acute decompensation of their disease one to three times a year, and 3% to 16% of these will require hospital admission. Hospital mortality of these admissions ranges from 3% to 10% in severe COPD patients, and it is much higher for patients requiring ICU admission. The etiology of the exacerbations is mainly infectious (up to 80%). Other conditions such as heart failure, pulmonary embolism, nonpulmonary infections, and pneumothorax can mimic an acute exacerbation or possibly act as “triggers.” Baseline chest radiography and arterial blood gas analysis during an exacerbation are recommended. Oxygen administration through a venturi mask seems to be appropriate and safe, and the oxygen saturation should be kept just above 90%. Either a short acting β2-agonist or an anticholinergic is the preferred bronchodilator agent. The choice between the two depends largely on potential undesirable side effects and the patient’s coexistent conditions. Adding a second bronchodilator to the first one does not seem to offer much benefit. The evidence suggests similar benefit of MDIs when compared with nebulized treatment for bronchodilator delivery. If MDIs are to be used, spacer devices are recommended. Steroids do improve several outcomes during an acute COPD exacerbation, and a 10- to 14-day course seems appropriate. Antibiotic use has been shown to be beneficial, especially for patients with severe exacerbation. Changes in bacteria strains have been documented during exacerbations, and newer generations of antibiotics might offer a better response rate. There is no role for mucolytic agents or chest physiotherapy in the acute exacerbation setting. Noninvasive positive pressure ventilation might benefit a group of patients with rapid decline in respiratory function and gas exchange. It has the potential to decrease the need for intubation and invasive mechanical ventilation and possibly decrease in-hospital mortality. Current Opinion in Pulmonary Medicine 2003, 9:117–124

Chronic obstructive pulmonary disease (COPD) is not only the fourth leading cause of death in the United States, but is also a disease of high morbidity [1]. Each year, it accounts for an estimated 14-million office visits and approximately 500,000 hospitalizations for exacerbations of COPD [2]. The annual hospitalization rate for COPD in the United States has increased from 9.7 to 24.5 per 10,000 population between 1988 and 1998 [3].

Definition of acute COPD exacerbation
Even though other conditions such as asthma and bronchiectasis are included in some definitions of COPD, this review deals with COPD due to chronic bronchitis and emphysema. Acute COPD exacerbation is variously defined in the medical literature, and an exact definition is still a matter of debate. After the 1999 Aspen Lung Conference dedicated to COPD, a common operational definition of acute COPD exacerbation emerged from a group of respiratory physicians from the United States and Europe. COPD was defined as “a sustained worsening of the patient’s condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD [4].” Based on healthcare utilization, an exacerbation can be further classified as: mild, when the patient has an increased need for medication, which he/she can manage in his/her own normal environment; moderate, when the patient has an increased need for medication and feels the need to seek additional medical assistance; or severe, when the patient/caregiver recognizes obvious and/or rapid deterioration in condition, requiring hospitalization. However, most of the studies published in the medical literature during the last decade, have followed the earlier definition used by Anthonisen et al. [5]. It requires the presence of one or more of the following findings: increase in sputum purulence, increase in sputum volume,
and worsening of dyspnea. Type I (severe) has all of the three symptoms, type II (moderate) has two, and type III (mild) has one symptom plus at least one of the following: upper respiratory infection in the past 5 days, fever without another apparent cause, increased wheezing, increased cough, or increase in respiratory rate or heart rate by 20% above baseline. This definition based on symptoms and findings can be linked to therapeutic decisions that are elaborated later.

**Implications of acute COPD exacerbations**

Patients with COPD typically present with acute decompensation of their disease one to three times a year [6,7]. However, 50% of the exacerbations are not reported to physicians [6,8]. Of the reported exacerbations, 3% to 16% will require hospital admission [8,9]. Hospital mortality of these admissions ranges from 3% to 10% in severe COPD patients [10,11]. The 180-day, 1-year, and 2-year mortality after a hospital admission is 13.4%, 22%, and 35.6%, respectively [12]. The hospital mortality rate after an ICU admission is 15% to 24% and goes up to 30% in patients more than 65 years old [13,14]. After an acute exacerbation, a temporary decrement in functional status and quality of life is expected [8]. One study showed that the peak flow had returned to normal in only 75% of patients 35 days after exacerbation, and 7% of patients still had not returned to their baseline levels of lung function 91 days after exacerbation [6]. Half of the patients who are hospitalized required readmission at least once in the following 6 months [11].

**Etiology of acute COPD exacerbations**

Respiratory infections are the most common causes of COPD exacerbations. However, other conditions such as air pollutants, heart failure, pulmonary embolism (PE), nonpulmonary infections, and pneumothorax can mimic an acute exacerbation or possibly act as “triggers” of an exacerbation [11]. The available evidence suggests that at least 80% of the acute COPD exacerbations are infectious in origin. Of these infections, 40 to 50% are caused by bacteria, 30% by viruses, and 5 to 10% by atypical bacteria (Table 1). Concomitant infections by more than one infectious pathogen appear to occur in 10 to 20% of patients [15-16,25]. Although there is epidemiological data suggesting that increased pollutants are associated with mild increase in COPD exacerbations and hospital admissions, the mechanisms involved are largely unknown. In an European study, increases of 50 µg/m³ in the daily level of pollutants were shown to increase the relative risk of hospital admissions for COPD for SO2 (RR 1.02), NO2 (RR 1.02), and ozone (RR 1.04) [26]. PE can also cause an acute COPD exacerbation, and, in one recent study, PE was present in 8.9% of the patients hospitalized with a COPD exacerbation [27].

**Evidence based data for individual interventions in acute COPD exacerbations**

**Diagnostic testing**

**Chest roentgenography**

Use of routine thoracic diagnostic imaging (Chest x-ray) has been found to be helpful in the initial assessment of patients with acute COPD exacerbation. Data from observational studies show that in 16% to 21% of the chest radiographs of patients with acute COPD exacerbation, there were abnormalities significant enough to justify changes in the management of those patients [28–30].

**Arterial blood gases sampling**

Arterial blood gas analysis is helpful in assessing the severity of an exacerbation. It properly assesses the degree of hypoxemia (as compared with indirect measurement by pulse oximetry) and hypercarbia, and adds valuable information to identify patients that are likely to require additional mechanical ventilatory support [31].

**Spirometric testing**

Available evidence does not support the routine measurement of lung function tests (either spirometry or peak flow) in patients with acute COPD exacerbations, since it does not seem to affect the therapeutic approach [31].

**Therapeutic interventions**

**Oxygen**

Based on previous data, it appears that patients with simultaneous hypercarbia and hypoxemia are at greatest risk of worsening respiratory failure during an acute COPD exacerbation [32]. The administration of oxygen has potential therapeutic benefits, which include relief of pulmonary vasoconstriction, decrease on right heart strain, and decrease in myocardial ischemia (if present), and it has become part of the “standard-of-care” during 32.

**Table 1. Infectious causes of acute COPD exacerbations**

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Virus</th>
<th>Atypical bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nontypeable haemophilus influenzae</td>
<td></td>
<td>Chlamydia pneumoniae</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>Rhinovirus (common cold)</td>
<td>Mycoplasma pneumoniae (rare)</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Influenza</td>
<td>Legionella</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Parainfluenza</td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>Coronavirus</td>
<td></td>
</tr>
<tr>
<td>Haemophilus parainfluenzae</td>
<td>Adenovirus</td>
<td>Respiratory syncytial virus</td>
</tr>
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Data from Sethi [15], Wedzicha [16], Sethi and Murphy [17,20], Miravitlles et al. [18], Sethi et al. [19], Lieberman et al. [21–23], Greenberg et al. [24], and Seemungal et al. [25].
an acute decompensation. However, many clinicians are concerned about worsening of hypercarbia and respiratory failure, when oxygen is administered to this group of patients. Several observational studies have shown consistent increase in arterial PaCO₂ during administration of oxygen to patients with acute COPD exacerbation. However, two recent small studies (n = 34 and n = 18) have shown more reassuring results about the safety of administering oxygen. The first study did not find major complications rates (i.e., severe symptomatic acidosis, hypotension, symptomatic cardiac arrhythmia) secondary to significant hypercarbia in either of the groups who received oxygen titrated to keep a PaO₂ greater than 60 mm Hg or 70 mm Hg [33••]. The second study compared two groups, assigned to get oxygen through a venturi mask or nasal prongs for 24 hours, with a therapeutic goal of keeping the O₂ saturation above 90% [34]. After 24 hours, the patients were crossed over to the other oxygen delivery system. It was observed that oxygen administered through both delivery systems improved arterial oxygen tension to the same extent (P = NS), without any significant effect upon arterial carbon dioxide tension or pH. Additional analysis suggested that the venturi mask system kept the oxygen saturation above 90% for more hours than the nasal prongs (P < 0.05). Based on these data and the previous literature, one can conclude that the risk of worsening hypercarbia and respiratory acidosis should not deter one from using controlled oxygen treatment in patients with simultaneous hypercarbia and hypoxemia during an acute COPD exacerbation. Keeping the O₂ saturation just above 90% (or PaO₂ > 60 mm Hg) is recommended, and administration of oxygen through a venturi mask may be safer and more effective than through nasal prongs.

**Bronchodilating agents**

A recent systematic review of the literature found very few controlled trial data on the use of inhaled short-acting β2-agonist agents in acute exacerbations of COPD, and none that compared these agents with placebo [31••,35]. Overall, the available data show similar FEV₁ improvement during an acute exacerbation, when short acting β2-agonists were compared with anticholinergic-type bronchodilators. Both agents also did better when compared with all parenterally administered bronchodilators (i.e., parenteral methylxanthines and sympathomimetics). Anticholinergic agents have a safer and more tolerable side effect profile (tremors, dry mouth, and urinary retention) when compared with β2-agonists (tremors, headache, nausea, vomiting, palpitations, heart rate, and blood pressure variations). This may be an important point to consider, when deciding which bronchodilator agent to use during an acute exacerbation. A recent position paper on acute COPD exacerbations suggests a benefit of adding a second inhaled bronchodilating agent (i.e., anticholinergic or short acting β2-agonist agent) once the maximal dose of the initial agent is reached [36]. However, systematic reviews have not found strong evidence to confirm this recommendation [35]. The use of a methylxanthine drug, such as aminophylline as an additional bronchodilator agent during an acute exacerbation, is not well supported by evidence. One study did show a decrease in hospitalization rate in the aminophylline group compared with the control group but this was not statistically significant [37]. A recent systematic review on use of methylxanthines in acute COPD exacerbation did not find any evidence to support its routine use [38]. Methylxanthines do not appreciably improve FEV₁ during COPD exacerbations and cause important adverse effects (including nausea, vomiting, headache, arrhythmias, and seizures). Furthermore, another systematic review found that the use of intravenous aminophylline in acute asthma did not result in any additional bronchodilation when compared with standard care with β-agonists [39].

There is very limited data describing use of long-acting β2-agonists (formoterol and salmeterol). Two recent small studies suggest similar effects of a short acting agent vs the long acting agents on FEV₁ measurements, when either agent was given during a mild acute COPD exacerbation [40,41]. Additional evidence is needed before these agents are recommended as first line therapy in exacerbations.

Regarding the choice of delivery systems, a recent meta-analysis found that bronchodilator delivery by means of a metered-dose inhaler (MDI) or wet nebulizer is equivalent in the acute treatment of adults with airflow obstruction [42]. Spacer devices were used for bronchodilator delivery with an MDI in most studies and are recommended for the treatment of acute airflow obstruction. The decision of what method to use will depend on the need for expedient treatment, availability of staff, and consideration of costs.

**Steroids**

Appraisal of the current literature on glucocorticosteroids for acute COPD exacerbation show that a short course of systemic corticosteroid therapy improves spirometry and decreases the relapse rate [31••]. A systematic review of this topic also concluded that treatment with oral or parenteral corticosteroids increases the rate of lung function improvement over the first 72 hours of a COPD exacerbation; however, the benefit was not maintained after 72 hours [43••]. The largest trial on use of corticosteroids for acute exacerbation included 271 patients, randomized to receive placebo or 3 days of IV methylprednisolone [44]. The latter group included patients who completed a 2-week regimen of oral prednisone after the initial 3-day IV dose (with progressive tapering of the oral prednisone) or an 8-week regimen of oral prednisone. The corticosteroid group showed a significant reduction in the rate of first treatment failure when com-
pared with the placebo group at 30 days (23% vs 33%, \( P = 0.04 \)) and at 90 days (37% vs 48%, \( P = 0.04 \)). Treatment-failure rates did not differ significantly at 6 months. Also, the duration of glucocorticoid therapy (2-week vs 8-week regimen) had no significant effect on the rate of treatment failure at any time. The difference in improvement of FEV\(_1\) was evident by the first day of therapy, but this difference was no longer significant between the steroid and placebo groups by the end of 2 weeks. Hyperglycemia was the most common side effect in the intervention group. Another recent study compared the impact on PaO\(_2\) and FEV\(_1\) levels between two groups of patients assigned to receive glucocorticoids for 3 days (IV methylprednisolone, 0.5 mg/Kg IV q6h) vs 10 days (first 3 days of same IV methylprednisolone dose and dose tapering over the next 7 days according to protocol) during an acute COPD exacerbation [45]. Both groups showed improvement in outcomes, but the 10-day regimen group did better with significantly higher levels of PaO\(_2\) and FEV\(_1\), improved FVC, and decreased dyspnea on exertion.

Most studies using steroids for exacerbations have been done on patients requiring hospitalization, and only few have described the role of steroids in the outpatient setting. A randomized controlled trial studied 27 patients with acute COPD exacerbations not requiring hospitalization [47]. Patients were assigned to receive a 9-day tapering dose of oral prednisone or placebo (in addition to continuing their baseline medications and increasing their \( \beta_2 \)-agonist use). The prednisone group showed a more rapid improvement in PaO\(_2\), FEV\(_1\), and peak expiratory flow (PEF), all of which were statistically significant results. This therapy also resulted in fewer treatment failures (\( P = 0.002 \)) and a trend toward more rapid improvement in dyspnea scale scores compared with the placebo groups.

Are inhaled corticosteroids in lieu of systemic steroids effective in treating acute exacerbations of COPD? A randomized control trial was carried out in 199 patients with acute COPD exacerbations requiring hospitalization, and they were assigned to receive nebulized budesonide, oral prednisolone, or placebo [46]. By 3 days after treatment, the steroid groups (inhaled and oral) showed a significant improvement in FEV\(_1\) (0.10–0.16 L) when compared with the placebo group. The difference between the two steroid groups was not statistically significant. The limited data on this issue (inhaled steroids for acute COPD exacerbations) makes it difficult to make a recommendation at this point. However, if future research on this area confirms this finding, inhaled steroids would be a safer therapeutic option.

**Antibiotics**

As infectious etiologies account for approximately 80% of the acute COPD exacerbations, it is reasonable to expect that the outcome of such exacerbations would be improved with antibiotic therapy. Anthonisen et al. [5] demonstrated a significant benefit of antibiotic treatment in acute COPD exacerbations, with a success rate of 68% for the antibiotic group vs 55% for the placebo group. This study also established useful clinical criteria to determine the severity of an exacerbation, depending on how many symptoms and signs are present (ie, increased dyspnea, sputum production, and sputum purulence). Patients in whom these three findings are present during an exacerbation exhibit a greater benefit from the antibiotic administration compared with those who have only one or two of the clinical findings. Subsequent meta-analysis and literature appraisal of this topic have found that antibiotics are beneficial in the treatment of patients with acute exacerbations of COPD [31••,48] and that patients with more severe exacerbations are more likely to benefit than those who are less ill. Analysis of the randomized controlled trials (RCTs) found that the peak expiratory flow rate (PEFR) was the most consistently measured end point, and it improved a mean of 10.75 L/min more in patients treated with antibiotics than in patients treated with placebo [48].

Many initial studies on antibiotics and COPD exacerbation were conducted in a very mild antibiotic resistance era. Controversy exists regarding the need to use newer and more broad-spectrum (and more expensive) antibiotics vs the more older and traditional antibiotics (ie, co-trimoxazole, doxycycline, and erythromycin). This issue has not been resolved yet, but some light has been shed by more careful documentation of the infectious agents associated with exacerbations [15••,16–25]. Organisms, such as *Pseudomonas aeruginosa* and nontypeable *Haemophilus influenzae*, have been recovered especially from patients who have more severe underlying lung disease established by an FEV\(_1\) < 50% [18]. Also, active tobacco smoking was associated with a high risk of *H. influenzae* isolation [18]. The presence of purulent sputum as subjectively described by the patients (and objectively confirmed by the investigators allocating a sputum number by reference through a standard color chart) was described in another study as highly predictive of the presence of active infection [49•]. In this study, a positive bacterial culture was obtained from 84% of patients’ sputum, when it was purulent on presentation, compared with only 38%, when it was mucoid (\( P < 0.0001 \)). This difference was also correlated by statistically significantly elevated levels of C-reactive protein measured during the acute exacerbation episode. In the stable clinical state, the incidence of a positive bacterial culture from sputum was similar for both groups. In essence, the presence of green (purulent) sputum was 94.4% sensitive and 77% specific for the yield of a high bacterial load. This subset of patient episodes identified at presentation is likely to benefit most from antibiotic therapy.
Two recent trials found significantly lower failure rates (defined as return visits within 14 days of the initial presentation with the patient having persistent or worsening symptoms) in patients who were treated with antibiotics [50,51]. They also concluded that the type of antibiotic used made a difference in the failure rates. In the first trial, significant amounts of bacteria were found in about 50% of the patients [50]. The most common bacteria isolated from 362 patient visits were Haemophilus species, Moraxella catarrhalis, and Streptococcus pneumoniae. There were no significant differences in other therapies prescribed to treat the acute exacerbation (i.e., bronchodilators and corticosteroids) in patients who did and did not relapse. Interestingly, patients who were treated with amoxicillin had a higher relapse rate than those who did not receive antibiotics ($P = 0.006$). The second trial studied 224 episodes of acute COPD exacerbation [51]. Patients receiving first-line agents (amoxicillin, cotrimoxazole, tetracyclines, and erythromycin) failed more frequently than third-line agents (co-amoxiclav, azithromycin, and ciprofloxacin): 19% vs 7% ($P < 0.05$). Also, patients who were prescribed first-line agents were hospitalized more often within 2 weeks of outpatient treatment when compared with patients who were prescribed third-line agents (18% vs 5.3% third-line agents; $P < 0.02$). As a counterpoint, a recent study tried to identify factors associated with poor treatment outcome of 232 exacerbations over a 2-year period [52]. In this study, use of home oxygen and frequency of exacerbation correctly classified failures in 83.3% of the patients, but the choice of an antibiotic did not affect the treatment outcome. Regimens that are administered once a day for 3–5 days might offer better compliance rates when compared with 7- to 10-day regimens (BID or TID).

Mucolytic agents

Five RCTs comparing different mucolytic agents in acute exacerbations of COPD were reviewed in a recent analysis [31••]. There was no evidence of shortening in the duration of the exacerbations or improvement of the FEV$_1$ values. The analysis did suggest that mucolytics might improve symptoms compared with controls [53,54]. In the nonacute COPD setting, systematic reviews have found a reduction in the number of acute exacerbations and days of illness when mucolytics were routinely used [55,56].

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Chest physiotherapy

When used during acute COPD exacerbations, mechanical percussion of the chest as applied by physical/respiratory therapists is ineffective in improving symptoms or lung function. Furthermore, there might even be a transient decrease in FEV$_1$ after chest percussion [31••].

Noninvasive positive pressure ventilation

Mechanical ventilation through an endotracheal tube adds morbidity and mortality risks to patients with acute COPD exacerbation. Noninvasive mechanical ventilation has become an acceptable option for ventilatory support of COPD patients with exacerbation. During the last decade, several studies have consistently shown that noninvasive positive-pressure ventilation (NIPPV) decreases the likelihood of requiring invasive mechanical ventilation and possibly increases survival time [57–59]. A meta-analysis found that patients randomized to receive NIPPV had a statistically significant decrease in the need for invasive mechanical ventilation and in the risk of death [60]. These findings have been replicated [61]. Patients hospitalized for exacerbations of COPD with rapid clinical deterioration should be considered candidates for NIPPV, according to a recent international consensus conference in intensive care medicine [62•]. The use of NIPPV in this setting should prevent further deterioration in gas exchange, respiratory workload, and the need for endotracheal intubation. However, it should be noted that there are no standardized criteria to predict which patients will benefit from this therapy and which may deteriorate. Contraindications for this type of therapy are summarized in Table 2.

**Heliox**

Helium is an inert gas that in combination with oxygen (heliox) has been used as an additive treatment in upper airway obstructions and other causes of respiratory failure. The rationale for its use is to diminish respiratory effort, peak pressure, and intrinsic positive end-expiratory pressure. A recent meta-analysis evaluated the limited literature on the use of heliox in acute COPD exacerbations (ventilated or nonventilated patients) and concluded that there is insufficient data to support its use [63]. One of the randomized trials included in the meta-analysis evaluated the administration of heliox as a driving gas for the updraft nebulization of bronchodila-

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Table 2. Patient contraindications for noninvasive positive pressure ventilation trial

<table>
<thead>
<tr>
<th>Respiratory</th>
<th>Nonrespiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory arrest</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>Upper airway obstruction</td>
<td>Mental status changes (i.e., obtundation)</td>
</tr>
<tr>
<td>Unable to protect the airway</td>
<td>Active upper gastrointestinal bleeding</td>
</tr>
<tr>
<td>Unable to clear respiratory secretions</td>
<td>Facial surgery or trauma</td>
</tr>
<tr>
<td>High risk for aspiration</td>
<td>Facial deformity</td>
</tr>
<tr>
<td></td>
<td>Nonfitting mask (i.e., significant air leaks)</td>
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</tbody>
</table>
tors during the first 2 hours of treatment of an acute COPD exacerbation. The use of heliox in this trial failed to improve FEV1 faster than the use of air [64]. A recent retrospective study evaluated acute COPD exacerbations initially treated in the emergency department (39 patients on heliox vs 42 patients without it). The authors found a statistically significant decrease in intubation and mortality rates in the heliox group [65]. This study is limited by its retrospective design, but offers intriguing findings that will likely prompt larger RCTs.

**Summary and recommendations**

**Definition of acute COPD exacerbation**

Even though new operational definitions have been described, the definition and types of exacerbation suggested by Anthonisen et al. [5] has been used extensively in the current literature and should be followed for now to maintain a more consistent terminology.

**Predictors of poor outcome in acute COPD exacerbations**

This issue has been addressed by several studies, but there seems to be significant differences in the findings by different authors [31••]. Use of home oxygen and frequency of exacerbations predicted treatment failures in 83% of acute COPD exacerbations in the outpatient setting in one study [52]. Treatment failure has been defined as a return visit for persistent respiratory symptoms that required a change of an antibiotic in < 4 weeks. Use of antibiotics has been suggested to decrease the failure rate. However, antibiotic selection might also be important, since use of amoxicillin had higher failure rates in one study [50]. This increased risk of failure rate because of “proper” antibiotic selection has not been confirmed in all studies [52]. Treatment failure is seen in 12–14% of the outpatient treatments. More than half of these failures will require hospitalization.

**Table 3. Indications for hospitalization of patients with acute chronic obstructive pulmonary disease exacerbation**

| 1. Presence of acute exacerbation characterized by dyspnea plus one or more of the following: |
| Inadequate response of symptoms to outpatient management |
| Inability to walk between rooms (patient previously mobile) |
| Inability to eat or sleep because of dyspnea |
| Conclusion by family and/or physician that patient cannot manage at home, with supplementary home care resources not immediately available |
| High risk comorbid condition, pulmonary (eg, pneumonia) or nonpulmonary |
| Prolonged, progressive symptoms before emergency visit |
| Altered mentation |
| Worsening hypercapnia |
| New or worsening hypercapnia |
| 2. Patient has new or worsening cor pulmonale unresponsive to outpatient management |
| 3. Planned invasive surgical or diagnostic procedure requires analgesics or sedatives that may worsen pulmonary function |
| 4. Comorbid condition, eg, severe steroid myopathy or acute vertebral compression fractures, has worsened pulmonary function |

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**Diagnostic testing**

Current literature suggests a benefit in ordering chest radiograph and arterial blood gas analysis in patients admitted with an acute COPD exacerbation.

**Need for hospitalization and ICU admission**

Tables 3 and 4 provide general guidelines to decide when to admit a patient to the hospital or to the ICU [66]. Individual patient factors may affect these decisions.

**Therapy**

**Oxygen**

Patients should receive the necessary amount of oxygen to maintain an oxygen saturation just above 90%. There seems to be benefit of delivering the oxygen through a venturi mask but nasal prongs can also be used. It is important to remember that PaCO2 may increase secondary to oxygen use, but the available evidence shows that this effect might not be as severe as previously thought.

**Bronchodilator agents**

Short acting β2-agonists or anticholinergic agents seem to be the preferred bronchodilators to be used. The choice between the two might depend on potential undesirable side effects based on the comorbidity of the patient. Adding a second bronchodilator to the first one does not seem to add much benefit. Methylxanthines do not offer additional improvement, and they might add significant and serious side effects. The mode of delivery for the bronchodilators might depend on several issues (ie, staff availability and costs) but the evidence suggests similar benefit of MDIs when compared with nebulized treatment. If MDIs are to be used, spacer devices are recommended.

**Steroids**

Steroids do seem to improve several outcomes during an acute COPD exacerbation. Even though the optimal dose and duration of therapy has not been established, a 10- to 14-day course of steroid treatment would be appropriate. Different tapering methods have been used, but some studies have shown that it is safe to stop steroids without dose tapering at the end of the 10- to 14-day period (provided the patient was not on chronic steroid therapy before the exacerbation). Parenteral ad-
ministration of high doses of methylprednisolone was used during the first few days of therapy in most of the trials, and this might be the recommended option during the initial treatment.

Antibiotics

Use of antibiotics seems to benefit patients with acute COPD exacerbation (especially those with severe exacerbations) and improve several outcomes (i.e., lung function and decrease in treatment failure rates). Patients with documented purulent sputum might benefit the most from antibiotic treatment compared with patients with clear sputum. Severe COPD patients with very low FEV₁ (< 35% predicted) may be at an increased risk of infection by Pseudomonas aeruginosa or Haemophilus influenzae. The latter seems to be increased in active smokers also. While several studies still recommend the use of the traditional antibiotics (i.e., amoxicillin and co-trimoxazole) for treatment of an exacerbation, recent evidence suggests that new bacteria strains are important [19–[•]]. These new strains can include antibiotic-resistant bacteria, and they might require newer and more potent antibiotics (i.e., newer generation of macrolides and fluoroquinolones) for an effective treatment. Our recommendation is to try to establish a narrow spectrum coverage, while keeping in mind the need for treatment of more resistant bacteria. This purpose might be better served by newer generations of antibiotics but we agree that additional evidence is needed to confirm this recommendation [67•].

Mucolytic agents and chest physiotherapy

The current evidence does not suggest a role for these interventions in the acute setting, and they should not be instituted in patients with acute COPD exacerbations.

NIPPV

This intervention does seem to benefit a group of patients with rapid decline in respiratory function and gas exchange. It has the potential to decrease the need for intubation and invasive mechanical ventilation, and it might even decrease mortality. The physician should be aware of the contraindications for this intervention and especially recognize the features that suggest when the patient might need invasive mechanical ventilation (Table 4).

Heliox

No clear-cut benefit has been demonstrated through prospective investigation, even though some retrospective data seemed promising. For now, it should not be part of the evidence-based approach to treatment of an acute COPD exacerbation.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• Of special interest

•• Of outstanding interest


Obliterative, occupational, and environmental diseases


This trial identifies the frequency and association of pulmonary embolism to acute COPD exacerbations.


Excellent evidence-based review of the available literature in acute COPD exacerbations.


This study provides reassurance about safety of oxygen use during acute COPD exacerbations.


This paper nicely suggests a higher benefit of antibiotic use in the presence of a purulent looking sputum.


Consensus statement of indications and benefit of NIPPV during COPD exacerbations.


