Acute exacerbation of COPD

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ABSTRACT

The literature of acute exacerbation of chronic obstructive pulmonary disease (COPD) is fast expanding. This review focuses on several aspects of acute exacerbation of COPD (AECOPD) including epidemiology, diagnosis and management. COPD poses a major health and economic burden in the Asia-Pacific region, as it does worldwide. Triggering factors of AECOPD include infectious (bacteria and viruses) and environmental (air pollution and meteorological effect) factors. Disruption in the dynamic balance between the ‘pathogens’ (viral and bacterial) and the normal bacterial communities that constitute the lung microbiome likely contributes to the risk of exacerbations. The diagnostic approach to AECOPD varies based on the clinical setting and severity of the exacerbation. After history and examination, a number of investigations may be useful, including oximetry, sputum culture, chest X-ray and blood tests for inflammatory markers. Arterial blood gases should be considered in severe exacerbations, to characterize respiratory failure. Depending on the severity, the acute management of AECOPD involves use of bronchodilators, steroids, antibiotics, oxygen and noninvasive ventilation. Hospitalization may be required, for severe exacerbations. Nonpharmacological interventions including disease-specific self-management, pulmonary rehabilitation, early medical follow-up, home visits by respiratory health workers, integrated programmes and telehealth-assisted hospital at home have been studied during hospitalization and shortly after discharge in patients who have had a recent AECOPD. Pharmacological approaches to reducing risk of future exacerbations include long-acting bronchodilators, inhaled steroids, mucolytics, vaccinations and long-term macrolides. Further studies are needed to assess the cost-effectiveness of these interventions in preventing COPD exacerbations.

Key words: etiology, chronic obstructive pulmonary disease, diagnosis, exacerbation, intervention.

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BMI, body mass index; CF, cystic fibrosis; CO, carbon monoxide; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; FiO2, fraction of inspired oxygen; GOLD, Global Obstructive Lung Disease; ICU, intensive care units; JRS, Japanese Respiratory Society; MDI, metered dose inhalers; MTS, Malaysian Thoracic Society; ND, no data; NIV, noninvasive ventilation; NO2, nitrogen dioxide; O3, ozone; PaCO2, partial arterial carbon dioxide concentration; PCCP, Philippine College of Chest Physicians; PCR, polymerase chain reaction; PM, particulate matter; QOL, quality of life; RCT, randomized controlled trial; SO2, sulphur dioxide; TSANZ, Thoracic Society of Australia and New Zealand.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common disease worldwide1–3 with significant morbidity and mortality, and incurs intensive expenditure of healthcare resources. The literature of acute exacerbation of COPD (AECOPD) is fast expanding. This review focuses on several aspects of AECOPD including epidemiology in the Asia-Pacific region, diagnostic approach including investigations and acute management of exacerbations. The evidence for nonpharmacological interventions for patients who have had a recent exacerbation is reviewed, and treatments to reduce future risk of exacerbations are discussed.

Epidemiology and Economic Burden of COPD

The COPD poses a major health and economic burden in the Asia-Pacific region, as it does worldwide. In a recent population-based survey conducted in nine Asia-Pacific territories, the prevalence of COPD was estimated at 6.2%.4 Of patients with COPD, 46% had at least one exacerbation in the previous year, and 19% required hospitalization.4 A study from Hokkaido,
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Japan, reported an exacerbation frequency ranging from 0.06 to 0.78 events per person per year. Patients with exacerbations in the first year of the study had more frequent AECOPD during follow-up and worse quality of life (QOL). The COPD is one of the leading causes of mortality worldwide, and acute exacerbations contribute substantially to this. COPD was the fifth leading cause of death in 2002 and will rank third by 2030. In Hong Kong, COPD ranked as the third leading cause of respiratory death, after respiratory infection and cancer. A Japanese study of 177,207 patients admitted with COPD as the primary condition or comorbidity found a higher mortality in patients with older age, male gender, lower body mass index (BMI), more severe dyspnoea, lower level of consciousness and worse activities of life. A New Zealand study of patients with AECOPD requiring hospitalization found that the CURB65 score (0 to 1, 2 and 3 to 5) was associated with increasing 30-day mortality rate (2.0%, 6.7% and 21.3%, respectively). Impairment of working ability or early retirement in COPD patients due to physical disability contributes to a substantial socioeconomic loss and health expenditure. A survey in 2008 of 8217 COPD patients (48% male) performed in rural areas of Xuzhou, China, found that a high proportion of patients (36%) required hospitalization due to respiratory symptoms, with a total indirect economic loss estimated at 4,327,050 yuan ($US 678,000). These patients were found to have poor knowledge about COPD, and the treatment given during both the stable and acute exacerbation states did not match international standards, which could partly explain the high exacerbation rate.

AETIOLOGIES OF AECOPD

The triggering factors of AECOPD include infectious and noninfectious precipitants. However, up to 30% of AECOPD is of unknown aetiology.

Infections
Respiratory tract infections, either viral or bacterial, are major causes of AECOPD. The true prevalence depends on the definition of the individual study. A study in South Korea estimated that up to 83% of AECOPD cases had a precipitating respiratory tract infection, based on compatible infective symptoms and computed tomography findings. A prospective study from Australia estimated that 56% of the AECOPD was due to respiratory infection based on positive microbiological results, irrespective of radiological findings.

Viral infections
In a systematic review involving the Asia-Pacific countries, the weighted mean prevalence of respiratory viral infections in AECOPD was 34%. Significant geographical variation in viral prevalence was noted in this review, with influenza virus being the most common in Asia, while picornavirus was more common in Australia, Europe and North America. Other relatively common causative viruses included respiratory syncytial virus, coronaviruses, parainfluenza, adenovirus and human metapneumovirus. When compared with noninfective AECOPD, those with viral infection had a more severe clinical course, as reflected by longer length of hospital stay, deterioration of lung function and worse hypoxaemia. Multiple studies have also found that AECOPD due to viral infection is more common in the spring and winter seasons.

Bacterial infections
Bacterial infection is a major cause of infective AECOPD, with prevalence ranging from 26% to 81%. Pseudomonas aeruginosa, Klebsiella pneumoniae and Haemophilus influenzae were the three most common pathogens identified in mainland China and Taiwan. In Hong Kong and Australia, P. aeruginosa and Moraxella catarrhalis were the major pathogens. The most common causative microbes from a Korean study were Streptococcus pneumoniae, P. aeruginosa and K. pneumoniae. Although more than 80% of the Pseudomonas strains were susceptible to common antipseudomonal antibiotics in China, pseudomonal infection itself was associated with poor clinical outcome in a study in Taiwan.

A diverse range of bacterial pathogens is implicated in AECOPD, and hence, a wide variability of antibiotics resistance patterns has been observed in different countries in the Asia-Pacific region. Standard antibiotic therapy recommended by COPD guidelines in Western countries may not be directly applicable in the Asia-Pacific region. Continuous surveillance of the prevailing organisms and their antibiotic resistance pattern is warranted. Co-infection by virus and bacteria at the time of AECOPD is not uncommon, ranging from 9% to 19%. An Australian study found that AECOPD patients with co-infection had a lower forced expiratory volume in 1 s, a longer length of hospital stay and higher likelihood of hospital readmission.

Noninfectious causes
Noninfectious causes of AECOPD including air pollution, meteorological effect and comorbidities of the patients such as pulmonary embolism and heart failure always need to be considered.

Outdoor air pollution
In the Asia-Pacific region, outdoor air pollution is an important cause of AECOPD. The exact prevalence varies when different pollutants are taken into account. Although well accepted, the causal relationship between air pollution and AECOPD is difficult to establish, as most of the studies have focused on the temporal relationship between the two. These studies should be interpreted with caution due to variable definitions and study designs. An increase in air pollutants such as sulphur dioxide (SO₂), nitrogen dioxide (NO₂) and ozone (O₃)
small-diameter particulate matter (PM$_{2.5}$) increases the risk of AECOPD and/or hospitalizations, with either immediate harmful effects or a time lag of several days. Mortality rate increases from 4% to 38% with an increase in concentrations of PM$_{2.5}$, PM$_{10}$ and NO$_2$. In Hong Kong, with the introduction of restrictions on the sulphur content in fuel oil in July 1990, there was an immediate fall in ambient SO$_2$, leading to a significant decline in all-cause and respiratory disease mortality.

The relationship between carbon monoxide (CO) exposure and AECOPD is not straightforward. Recent data from Tian et al. from Hong Kong showed a reduction in hospitalization for COPD and respiratory tract infections after short-term exposure to ambient CO. The effect was robust even after the adjustment of other pollutants, weather variables and the lag days of CO exposure. The protective effect may be secondary to an acute protective effect from respiratory tract infection, a reduction in sputum eosinophils or improvement of bronchial responsiveness. However, the direct clinical effect of CO exposure on the rate of AECOPD remains to be confirmed.

**Indoor air pollution**

Second-hand smoking and exposure to biomass fuel combustion are major sources of indoor air pollution. Exposure to second-hand smoke was associated with increased risk of visits to emergency department by patients with COPD and a greater risk of hospitalization in a study from San Francisco, USA. However, similar studies are not available in the Asia-Pacific region. There is as yet little information on the effect of exposure to combustion of biomass fuels on symptoms or exacerbations of patients with COPD.

**Meteorological effect**

A lower ambient temperature, even with a decrease of 1 °C, can lead to AECOPD. The effect is more marked when there is a significant drop (5 °C) in ambient temperature. Winter season and low humidity are confirmed triggers for AECOPD and hospital admissions in cities such as Hong Kong and Shanghai, and the lag effect could be as long as 14 days. The peak seasons for AECOPD were spring and autumn from a study in Hokkaido, Japan. It appears that the seasons associated with AECOPD differ among cities. Besides temperature as a seasonal factor, viral infection and air pollution can also interact with seasonal effects to influence risk of developing AECOPD.

The effect of air pollutants on the risk of AECOPD is also dependent on the ambient temperature. The detrimental effect of lower temperature on AECOPD can be potentiated by a concomitant increase in NO$_2$, O$_3$ and SO$_2$ levels. Increased barometric pressure, greater hours of sunshine and lower levels of humidity have been associated with increased risk of AECOPD. A study from New Zealand has shown that the use of long-term humidification therapy, with humidified, fully saturated air at 37 °C and a flow rate of 20–25 L/min, can lead to significantly fewer exacerbation days, increased time to first exacerbation and reduced exacerbation frequency for chronic airway diseases, including COPD.

**Other causes and comorbidities**

A recent Korean study has shown that noninfectious causes of AECOPD included pulmonary embolism (5%), congestive heart failure (2%) and discontinuation of COPD medications (1%). Causes could not be identified in 11% in this study, which did not assess other potential noninfectious causes including air pollution, meteorological effect and comorbidities of the patients. The prevalence of venous thromboembolism ranged from 8% to 16% in the screened AECOPD population, depending on the study objective and method of screening.

**DIAGNOSTIC APPROACH TO ACUTE EXACERBATIONS OF COPD**

Acute exacerbations of COPD are characterized by a worsening of the patient’s respiratory symptoms, dyspnoea, cough and/or sputum, more than the usual day-to-day variations and requiring changes to their medication. Depending on its severity, an AECOPD may be managed in primary care or as an outpatient or, if severe, may require hospitalization.

**Investigations**

After initial history and examination, a number of investigations may be useful in assessing the aetiology, severity and complications of an AECOPD. The selection of investigations will depend on the clinical setting in which the patient is being treated (e.g. primary care, emergency department or hospital), with fewer investigations needed in primary care if the patient has a mild to moderate exacerbation and respiratory failure or, if severe, may require hospitalization.

Other biomarkers of the bacterial aetiology of exacerbations have been tested in studies, but none is yet in routine clinical practice. The use of serum procalcitonin, which is a marker of bacterial infection, to guide prescription of antibiotic therapy was tested in a randomized controlled trial (RCT). In this study, noninferiority of the procalcitonin-guided approach, compared with the standard guideline-based approach, was not conclusively proven.
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Table 1 Useful investigations for patients with acute exacerbations of chronic obstructive pulmonary disease

| Pathophysiology          | Related investigations                                                                 | Rationale for the investigation                                                                 |
|--------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Inflammation             | • Full blood count<br>• C-reactive protein                                               | • White cell count and differential (neutrophils, eosinophils and lymphocytes)<br>• Systemic inflammation |
|                          | • Sputum microscopy, culture and sensitivity<br>• Nasal pharyngeal aspirate or swab for respiratory viral PCR<br>• Chest X-ray | • For suspected bacterial infection<br>• For suspected viral infection<br>• To image suspected pneumonia or other pulmonary or cardiac causes of exacerbation, for example, pneumothorax, pleural effusion or heart failure |
| Impaired gas exchange     | • Oximetry<br>• Arterial blood gases                                                    | • Simple noninvasive measurement of oxygenation<br>• To characterize type 1 or type 2 respiratory failure, if the exacerbation is severe or if there is preexisting respiratory failure |
| Airflow obstruction       | • Spirometry or peak expiratory flow rate                                               | • Performed if the patient is able to detect deterioration of airflow limitation, compared with baseline (spirometry may be difficult to perform during an exacerbation and would be considered optional in these circumstances) |
| Comorbidities             | • ECG                                                                                    | • If cardiac features are present, such as arrhythmia or coronary artery disease               |

ECG, electrocardiogram; PCR, polymerase chain reaction.

regions of the 16S gene, which encodes bacterial ribosomal ribonucleic acid. According to the ‘vicious cycle’ paradigm, chronic bacterial infection in the airways may drive inflammation, with significant implications for the pathogenesis and progression of COPD, including impact on exacerbations.

Alterations in the lung microbiome in COPD exacerbations

Several small studies have sampled the airway microbiome during AECOPD. Experimental infection with rhinovirus increased the total bacterial load in sputum samples of patients with COPD, with ‘outgrowth’ and dominance of *H. influenzae* occurring at 2 to 6 weeks after viral infection, which suggests that acute viral infection changes the community composition of the lung microbiome. A complex microbiome with diverse bacterial communities has been demonstrated both in endotracheal aspirates from mechanically ventilated patients with severe AECOPD and in sputum samples obtained from patients experiencing a moderate exacerbation. Bacterial community composition may be relatively stable in sputum samples at the start of an exacerbation and during recovery over 3 months. However, other studies have found that the structure and diversity of both bacterial and fungal genera in the sputum microbiome can change rapidly each day, as shown in hospitalized COPD patients with a severe exacerbation.

Similarly, we have observed dynamic and rapid changes of the airway microbiome in a study of 23 cystic fibrosis (CF) patients hospitalized for antibiotic therapy during an acute exacerbation. In the CF population, there was an increase in microbial diversity and a reduction in the relative abundance of *Pseudomonas* by day 3 of intravenous antibiotics, but by days 8 to 10 of the admission, bacterial community composition had returned to pretreatment levels. Whether similar changes occur in the lung microbiome with treatment during an AECOPD is not clear, but a recent small study (six patients only) suggests that this may indeed be the case.

Overall, these studies illustrate the dynamic nature of the lung microbiome during and after exacerbations of lung diseases that are characterized by chronic bacterial infection in the airway. However, most studies have been conducted in only small numbers of patients, and further investigation is needed to determine the relationship between composition of the lung microbiome and risk of AECOPD and progression. Moreover, adequately powered studies are required to determine whether restoration of the diversity of the microbiome with treatment may serve as a biomarker of recovery from exacerbation and how this relates to subsequent re-exacerbation rates and long-term lung function decline.

Effect of long-term antibiotics on the COPD microbiome

Continuous prophylactic antibiotics, especially macrolides, have been shown to reduce the frequency of AECOPD. As yet, no studies have examined the effects of long-term antibiotics on the COPD microbiome; however, several studies have measured changes in airway bacterial load. In a 12-week RCT of 30 stable COPD patients with neutrophilic airway inflammation, treatment with azithromycin tended to reduce the frequency of severe exacerbations and decreased sputum neutrophil counts and neutrophil chemokine (CXCL8) levels. Total bacterial load was reduced 10-fold with azithromycin, but this change did not reach statistical significance. In a 13-week study of 99 patients
with COPD, there was no change in airway bacterial load (measured by 16S quantitative polymerase chain reaction (qPCR)) with the use of azithromycin, pulsed moxifloxacin or doxycycline (compared with placebo).52

Despite no apparent reduction in bacterial load in these initial reports, characterization of changes in the airway microbiome remains an important goal in patients using long-term antibiotics, because beneficial changes in the community dynamics of the microbiome could occur, but without appreciable change in total bacterial load. More detailed, prospective studies of the lung microbiome and its impact on exacerbations are required.

MANAGEMENT OF ACUTE EXACERBATIONS OF COPD

Bronchodilators
Inhaled bronchodilators (short-acting β2 agonists and short-acting muscarinic antagonists) are effective in the treatment of AECOPD. Several methods of administration are available in the acute setting, including wet nebulizers and metered dose inhalers (MDI) with spacer device. Nebulizers and MDI with spacers have demonstrated equal efficacy in relieving acute airflow obstruction,53 with no significant difference in length of hospital stay.54 A recent Cochrane review found no difference in outcomes for nebulizers and MDI with spacers in patients with acute asthma;55 a similar appraisal of the evidence specific to COPD patients is awaited. In addition to clinical endpoints, the relative lung distribution of salbutamol appears to be similar for nebulizer versus MDI with spacer.56

There are theoretical benefits in favour of MDI with spacers, including faster administration, improved cost-effectiveness and increased opportunity for inhaler technique education. Nebulizers are known to generate aerosols,57 which may be important in the transmission of infection. The familiarity of staff and patients with each delivery method may vary, and patient factors including reduced level of consciousness or severe dyspnoea may be relevant, necessitating an individually tailored decision. For patients receiving mechanical ventilation, there is currently insufficient evidence to support one delivery method over the other.58

Systemic corticosteroids
The use of systemic corticosteroid in the treatment of AECOPD is well established, based on its effectiveness in suppressing airway inflammation.59 A prolonged course and high-dose systemic corticosteroids can give a longer and better anti-inflammatory effect. However, steroid use is associated with many adverse events, especially with the cumulative dose due to the recurrent nature of AECOPD. There is currently no consensus on the standard regimen of systemic corticosteroids, in regard to dose, route and duration for AECOPD. The recommended steroid regimens by the Global Obstructive Lung Disease (GOLD) guideline6 and respiratory societies in the Asia-Pacific region are shown in Table 2.

Studies suggest that use of oral corticosteroids at low dose is as effective as intravenous corticosteroids given at high dose, while minimizing the risk of adverse effects.59 The Reduction in the Use of Corticosteroids in Exacerbated COPD (REDUCE) trial showed that a 5-day course of oral corticosteroids was not inferior to a 14-day course in terms of exacerbation recurrence but with a shorter length of hospital stay.54 A Cochrane review55 suggested that a short course, 3 to 7 days, of systemic corticosteroids does not lead to increase in treatment failure or risk of relapse of AECOPD. Data regarding the use of systemic corticosteroids are limited in the Asia-Pacific region. A Turkish study comparing efficacy between oral steroid and intravenous methylprednisolone56 found that the improvement of blood gas parameters, symptom scores, length of stay and readmission due to AECOPD were comparable with these two treatments. However, the group receiving intravenous methylprednisolone had more events of recurrent AECOPD requiring attendance to emergency department, hyperglycaemia and worsened blood pressure control.57 The scarcity of data is also indirectly reflected by the inconsistent corticosteroids regimens noted in a Taiwanese observational study of AECOPD.58 There have been relatively few studies of the use of nebulized corticosteroids for exacerbations, as an alternative to systemic steroids.

Antibiotics
Given that bacteria are implicated in a substantial proportion of exacerbations (as discussed earlier in epidemiology), antibiotics are frequently used in the acute management of inpatients or outpatients with AECOPD. Broad-spectrum antibiotics covering common respiratory pathogens, based on local guidelines and microbial patterns, are recommended for patients who are experiencing at least two symptoms that are consistent with a greater likelihood of bacterial infection such as an increase in sputum purulence or volume and dyspnoea.6 Examples of commonly prescribed antibiotics include amoxycillin (with or without clavulanic acid), a macrolide or tetracycline, or a respiratory quinolone. Oral antibiotics are preferred, although intravenous antibiotics can be used

Table 2  Dose and duration of systemic corticosteroids for treatment of acute exacerbation of chronic obstructive pulmonary disease, as recommended by different clinical guidelines

| Region | Regimen |
|--------|---------|
| GOLD3 | Oral prednisolone 40 mg/day × 5 days |
| JRS50 | Oral prednisolone 30–40 mg/day × 7–10 days |
| TSANZ61 | Oral prednisolone 30–50 mg/day × 5 days (tapering dose required for those receiving >14 days) |
| MTS52 | Oral corticosteroids, no longer than 14 days, dose not specified |
| PCCP63 | Oral prednisolone 30–40 mg/day × 7–14 days |

GOLD, Global Obstructive Lung Disease; JRS, Japanese Respiratory Society; MTS, Malaysian Thoracic Society; PCCP, Philippine College of Chest Physicians; TSANZ, Thoracic Society of Australia and New Zealand.
if there is impaired mental state, swallowing difficulty, severe exacerbation or coexistent pneumonia. The optimal duration of antibiotic treatment is not certain from the available evidence, although antibiotics are usually recommended for 5 days.

Despite the widespread use of antibiotics for AECOPD in clinical practice, a Cochrane systematic review of 16 trials (2068 participants) of antibiotics versus placebo for AECOPD found inconsistent benefit for the use of antibiotics, depending on the clinical setting and severity of the exacerbation. For hospitalized patients, the pooled results showed that antibiotics reduced the risk of treatment failure (relative risk of 0.77). In contrast, for outpatient treatment, the quality of evidence for benefit was generally low and was not statistically significant when the analysis was restricted to currently available antibiotics (as opposed to antibiotics used in older studies). For patients admitted to intensive care units (ICU), there was high quality evidence from 1 trial which showed a statistically significant effect on mortality. A retrospective clinical audit in an Australian hospital found that inpatient antibiotic regimens frequently diverged from published clinical guidelines and that discordance was associated with longer length of stay and greater healthcare costs.

**Oxygen**

Supplemental oxygen therapy is often required in the treatment of AECOPD. The Thoracic Society of Australia and New Zealand has produced endorsed guidelines for acute oxygen use. To avoid the consequences of hypoxaemia and hyperoxaemia, supplemental oxygen should be titrated to target oxygen saturations of 88–92% in patients with COPD or other chronic respiratory diseases. Pulse oximetry should be employed routinely, and consideration given to arterial blood gas measurement. Patients with high or increasing FiO2 requirements may require close observation or admission to a high dependency unit/ICU facility. Where nebulizers are used for administration of bronchodilators, an air-driven nebulizer is preferred.

**Noninvasive ventilation**

One of the major breakthroughs in treating AECOPD patients in the last few decades is the application of noninvasive ventilation (NIV) for acute hypercapnic respiratory failure. Use of NIV effectively unloads the respiratory muscles and reduces the effort on the work of breathing. NIV reduces intubation rate, overall mortality due to respiratory failure and rates of invasive mechanical ventilation-related complications.

Based on the evidence from studies in the Asia-Pacific region and Western countries, NIV is now recommended by clinical guidelines as first-line treatment for acute type 2 respiratory failure due to AECOPD. The criteria for initiation of NIV include respiratory acidosis (arterial pH ≤ 7.35 and/or partial arterial carbon dioxide concentration (PaCO2) ≥ 6.0 kPa or 45 mm Hg), severe dyspnoea with clinical signs indicating fatigue of respiratory muscles, increased work of breathing or both. These signs include retraction of the intercostal spaces, use of respiratory accessory muscles and paradoxical movement of the abdomen.

When NIV is used together with effective pharmacological treatment, many patients will demonstrate early recovery and be able to be weaned from NIV, with mean duration of use ranging from 2 to 10 days. Regarding adverse effects, the use of NIV has been linked to claustrophobia, skin abrasion over the application site of the mask interface, gastric distension and pneumonia, although the incidence of pneumonia is less common than with invasive mechanical ventilation.

### Table 3 Criteria for hospitalization of patients with acute exacerbation of chronic obstructive pulmonary disease

| Criteria                                                                 | GOLD3 | JRS60 | TSANZ61 | MTS62 |
|--------------------------------------------------------------------------|-------|-------|---------|-------|
| Marked increase in intensity of symptoms such as sudden development of dyspnoea | X     | X     | X       | X     |
| Underlying severe COPD                                                   | X     | ND    | ND      | X     |
| Reduced alertness                                                        | ND    | ND    | X       | X     |
| Failure of exacerbation to respond to initial medical management         | X     | X     | X       | X     |
| Older age                                                                | X     | X     | ND      | X     |
| Development of new physical signs, for example, cyanosis and peripheral oedema | X     | X     | X       | X     |
| Haemodynamic instability                                                 | ND    | ND    | ND      | X     |
| Significant comorbidities                                                | X     | X     | X       | X     |
| Newly occurring cardiac arrhythmias                                      | ND    | X     | X       | X     |
| Insufficient home support                                                | X     | X     | X       | X     |
| Frequent exacerbations                                                   | X     | X     | ND      | ND    |
| Uncertain diagnosis requiring differential diagnoses                      | ND    | X     | ND      | ND    |

1. Inability to walk between rooms when previously mobile and inability to eat or sleep because of dyspnoea.
2. COPD, chronic obstructive pulmonary disease; GOLD, Global Obstructive Lung Disease; JRS, Japanese Respiratory Society; MTS, Malaysian Thoracic Society; ND, no data; TSANZ, Thoracic Society of Australia and New Zealand; X, presence of these factors suggest need for consideration of hospital admission.
Which patients with AECOPD should be hospitalized?

High-risk AECOPD patients are best managed in hospital, to aim to prevent the high rates of morbidity and mortality. The various admission criteria of the GOLD guidelines and from three Asia-Pacific respiratory societies are listed in Table 3. The criteria can be generally divided into three categories:

1. **Severe COPD symptoms**: increase in shortness of breath and increased frequency of exacerbation
2. **Development of new complications**: pulmonary hypertension, carbon dioxide retention (reduced alertness), haemodynamic instability or arrhythmia
3. **Inadequate outpatient treatment expected**: advanced age, failed initial medical or outpatient management and insufficient home support

Prognosis of inpatients with AECOPD

Unfortunately, death is not an uncommon outcome for hospitalized AECOPD patients. The mortality rate ranged from 4% to 14% in the Asia-Pacific region based on different cohorts, and was as high as 25% for patients requiring ICU admission. Increasing age, impaired respiratory exchange were risk factors for in-hospital mortality. Acidotic pH, high PaCO₂ and low partial arterial oxygen concentration were all associated with higher in-hospital mortality. Other risk factors include abnormal clinical findings (increased dyspnoea, lower BMI, altered mental status, and lower systolic blood pressure), presence of comorbidities (congestive heart failure, liver disease, hyponatraemia, chronic renal failure, hypoalbuminaemia and high Charlson comorbidity index), nursing home residency, requirement of NIV, elevated troponin, elevated D-dimer with exclusion of venous thromboembolism, long-term use of corticosteroids and high Acute Physiology and Chronic Health Evaluation (APACHE) II score.

There are few prospective cohort studies on the long-term prognosis for discharged AECOPD patients in the Asia-Pacific region. The 30-day mortality rate has been estimated to be around 8.5%. The 1-year mortality rate was 16% to 22% in patients not requiring NIV support or ICU care. For patients who required NIV support or ICU care during the index hospitalization, the 1-year mortality rates were 28% and 43%, respectively, with a very high overall mortality rate of 75% at 5 years after discharge.

Cardiovascular comorbidity in AECOPD

Cardiovascular comorbidity is common among COPD patients. In an Italian study of hospitalized AECOPD patients, 55% had arterial hypertension, 27% had chronic heart failure, and 17% had ischaemic heart disease. Only a limited number of studies have been conducted in the Asia-Pacific region regarding the cardiovascular comorbidity in AECOPD patients. A study from Australia observed that cardiovascular events contributed to 26% of long-term mortality following the first episode of AECOPD. A study from Italy found that in patients admitted to the hospital for AECOPD, cardiac troponin elevation emerged as an independent predictor of increased risk of all-cause mortality. It is not certain whether AECOPD increases cardiac stress and exacerbates cardiac comorbidity, therefore leading to excessive mortality related to cardiovascular events during or after an AECOPD.

### Table 4  Summary of treatment approaches for acute exacerbation of chronic obstructive pulmonary disease

| Principle of therapy | Treatment effect | Potential side effects |
|----------------------|------------------|------------------------|
| Short-acting inhaled bronchodilators (salbutamol/ ipratropium) | Reduce breathlessness by reducing dynamic pulmonary hyperinflation | Salbutamol: tremor, palpitations, tachycardia and hypokalaemia Ipratropium: dry mouth and prostatic symptoms |
| Systemic corticosteroids | Shorten recovery time, improve lung function and arterial hypoxemia, reduce treatment failure and decrease length of hospital stay | Hyperglycaemia, worsened blood pressure control, mood disturbance, fluid retention and bruising |
| Antibiotics | Antimicrobial action | Adverse effects of specific antibiotics, antibiotic-associated diarrhoea, candidiasis and antibiotic resistance (repeated or prolonged use) |
| Oxygen therapy | Improve gas exchange | Risk of carbon dioxide retention with hyperoxia and adverse effects of delivery methods (e.g. dry nasal passages with nasal prongs) |
| NIV | Improve respiratory acidosis and decrease respiratory rate, work of breathing, severity of breathlessness, complication such as ventilator-associated pneumonia and length of hospital stay, mortality and intubation | Claustrophobia, skin abrasion over the application site of mask interface, gastric distension and pneumonia |
| Invasive mechanical ventilation | Support patient with respiratory failure (usually when NIV failed or not suitable) | Ventilator-associated pneumonia, barotrauma and failure to wean to spontaneous ventilation |

NIV, noninvasive ventilation.

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Treatment approaches for AECOPD are summarized in Table 4.

**Nonpharmacological interventions for patients who have had a recent exacerbation**

There is recent strong interest in the nonpharmacological interventions for patients who have recently experienced an AECOPD. As this is a high-risk group of patients, studies of intervention strategies both during hospital stay and shortly after discharge have been undertaken, with the aim of decreasing readmission rates and improving QOL. These interventions include disease-specific self-management, pulmonary rehabilitation, early medical follow-up, home visits by respiratory health workers, integrated care programmes and telehealth-assisted hospital at home.

**Self-management**

Self-management describes formalized patient education programmes aimed at teaching skills and providing support for health-promoting behaviour. A Cochrane review has found that self-management interventions (in the absence of supervised exercise) are effective in patients with COPD and are associated with improved health-related QOL, a reduction in respiratory-related and all-cause hospital admissions, and improvement in dyspnoea. However, heterogeneity among interventions, study populations, follow-up time and outcome measures have made it difficult to formulate clear recommendations regarding the most effective form and content of self-management in COPD. In the only study that has recruited patients immediately following an AECOPD (155 patients with AECOPD after hospital discharge from centres in Spain and Belgium), intervention consisted of an individually tailored care plan upon discharge that was shared with the primary care team, as well as accessibility to a specialized nurse case manager through a web-based call centre. The intervention resulted in lower rates of hospitalization and readmissions, although there was no difference in mortality at 12-month follow-up. Another systematic review that examined the effects of self-management alone delivered during hospitalization for an AECOPD or within 1 month of hospital discharge found no effects on mortality rate, depressive symptoms, primary care usage or exercise capacity. Minimal effects were found on self-efficacy, anxiety symptoms and health-promoting behaviour.

Self-management interventions delivered immediately post-AECOPD vary widely, and outcome measures are inconsistent. Such variations have made it difficult to draw strong recommendations regarding effectiveness. Further studies on self-management interventions, preferably delivered by trained healthcare professionals to selected patients with structured follow-up, are required.

**Pulmonary rehabilitation**

A Cochrane review of nine small heterogeneous trials of peri-hospitalization and early post-hospitalization pulmonary rehabilitation showed wide-ranging benefits including a significantly reduced risk of readmission. An RCT in Hong Kong showed that an early rehabilitation programme for 8 weeks following AECOPD led to improvement in QOL for up to 6 months but did not reduce healthcare utilization at 1 year.

Although pulmonary rehabilitation appears useful for post-hospitalization COPD patients, a recent observational study reported that only 9% of people completed a post-hospitalization pulmonary rehabilitation programme over a 6-month period. From the patient perspective, a common reason for nonparticipation in pulmonary rehabilitation is transport difficulties, particularly in the immediate post-discharge setting where patients often feel too ill and/or breathless to engage. As treatment guidelines have recommended 20 sessions of exercise training to be effective, this may be a difficult task for many patients without adequate social support.

A recent study noted that comorbidities do not seem to preclude patients with COPD from obtaining significant and clinically meaningful improvements in functional exercise capacity and health status following pulmonary rehabilitation. Complex patients with COPD and comorbidities thus should not be excluded from pulmonary rehabilitation. Encouraging patients immediately post-AECOPD to participate in pulmonary rehabilitation and obtaining the resources required for a pulmonary rehabilitation programme remain critical challenges in the care of COPD patients.

**Early medical follow-up**

Early clinic follow-up by pulmonologists appears to reduce exacerbation-related rehospitalization rates of COPD patients. A retrospective cohort study in Israel of 195 patients discharged from hospital following treatment of AECOPD found that early clinic follow-up by a pulmonologist within a month from hospital discharge could reduce exacerbation-related rehospitalization rates within 90 days from discharge. Another retrospective cohort study using data of Medicare beneficiaries in the USA involving 62,746 patients admitted for AECOPD found that a follow-up visit with their primary care physician or pulmonologist within 30 days of discharge could lower rates of emergency room visits and readmission in patients with COPD. Additional RCT are needed to assess the beneficial effects of the specific components of care in the early clinic consultation for these patients who are recently discharged after an AECOPD.

**Outreach service**

A Cochrane review analysing data of 1498 COPD patients from nine RCT that provided interventions by an outreach nurse (visiting patients in their homes, providing support and education, monitoring health and liaising with physicians) found that outreach nursing programmes for COPD improved disease-specific health-related QOL. However, the effect on hospitalizations was heterogeneous, reducing...
admissions in one study but increasing them in others. Among these studies, only one study involved patients with recent AECOPD, and this study also included other patients with congestive heart failure. Another study involved patients who had experienced AECOPD within the past 6 months. There are currently inadequate data to recommend this service for patients shortly post-AECOPD.

Integrated disease management
A recent meta-analysis of data from 26 trials involving 2997 people, with a follow-up ranging from 3 to 24 months, has shown that integrated disease management of COPD improved disease-specific QOL and exercise capacity, and reduced hospital admissions and hospital days per person. The trials included in this meta-analysis varied greatly with participants being treated in all types of healthcare settings (mostly primary or secondary with one trial in tertiary care) and with different programmes. The studies included in this meta-analysis consisted of stable COPD patients who had received a programme provided by caregivers from at least two disciplines, with two different components (e.g. exercise, education or self-management) and with a duration of at least 3 months. No RCT has specifically assessed the effect of a comprehensive programme with multidisciplinary input for patients who have had a recent admission for AECOPD. However, there are studies suggesting that a post-AECOPD rehabilitation programme and self-management may help to decrease exacerbations and improve the QOL of patients. Ko et al recently reported an audit of patients undergoing a 16-week comprehensive COPD care programme shortly post-AECOPD and found that patients had a reduction in hospital admissions at 1 year after the programme compared with the year prior to the commencement of programme.

Further studies are needed to assess if integrated disease management for patients shortly after AECOPD can help to decrease readmissions. The cost-effectiveness of these labour-intensive programmes should also be assessed.

Hospital at home
Treatment of AECOPD at home may lead to fewer readmissions in comparison with conventional hospital treatment. However, this is not suitable for all COPD patients as many AECOPD patients are too unwell to be managed at home, at least initially. Mortality, in addition to patients’ or relatives’ satisfaction, is not significantly altered by either method of care in this group of selected patients who can be considered for receiving home care.

With advancement in technology, telemedicine is expanding in its application. A recent RCT compared the effects of home-based telehealth hospitalization with conventional hospitalization in 57 patients with severe AECOPD. The study found that home-based telehealth hospitalization was noninferior to conventional hospitalization when the noninferiority margin was set at 20% of the control group’s risk of readmission. The data suggest that a subgroup of patients with severe COPD may be treated for acute exacerbation at home using telehealth, without the physical presence of health professionals but with a proper organizational ‘backup’. Further studies are needed to assess patient selection, and the safety and cost-effectiveness of such approaches. In particular, the population in the Asia-Pacific region may have education levels and socioeconomic conditions that are different from those of other countries.

REDUCING FUTURE RISK OF EXACERBATIONS
Evidence-based clinical guidelines for COPD include recommendations for interventions targeted at preventing exacerbations, including a range of inhaled, oral and injectable medicines that reduce the frequency of COPD exacerbations. Inhaled long-acting β2 agonists, alone or in combination with inhaled corticosteroids, and inhaled long-acting muscarinic antagonists all reduce exacerbation rates. The oral phosphodiesterase-4 inhibitor, roflumilast, is associated with fewer exacerbations in COPD patients with a phenotype of chronic bronchitis and history of prior exacerbations. Oral mucolytic agents such as N-acetylcysteine also reduce acute exacerbations. Vaccination against both influenza and pneumococcal infections is advocated as part of overall care of COPD patients. A checklist of recommendations can help to remind clinicians about the importance of preventing future exacerbations, especially at the time of hospital discharge.

Despite such treatment recommendations, AECOPD still occurs frequently and is associated with significant morbidity and mortality. There is thus an urgent need for more effective strategies to prevent exacerbations. Macrolide antibiotics have shown promise in other chronic lung diseases, prompting recent interest in prophylactic use in patients with COPD. Nine RCT have reported the effects of prophylactic macrolide antibiotics on risk of exacerbations of COPD. Furthermore, two systematic reviews found a statistically significant reduction in COPD exacerbations with the use of long-term macrolides. In the Cochrane systematic review of Herath and Poole, covering five of the studies, the number needed to treat to prevent one exacerbation was eight. In the meta-analysis of Ni et al, the unadjusted risk ratio of an acute exacerbation with macrolide treatment was 0.70 (95% confidence interval: 0.56-0.87; P < 0.01). Subgroup analysis suggests that 6 months of macrolide therapy is the minimum treatment duration necessary to demonstrate significant reductions in COPD exacerbations. Although these pooled analyses demonstrated a statistically significant improvement in total score for the St George Respiratory Questionnaire with macrolide use, this failed to reach the minimal clinically important difference. Frequency of hospitalization and all-cause mortality did not differ between macrolide and placebo groups. These systematic reviews suggest that more studies are required to determine optimal treatment regimen...
(dose, individual agent and duration) and that patient selection needs to be further explored as perhaps subpopulations of patients with COPD may derive greater benefit. Adverse effects are an important concern given that patients with COPD are generally older with associated multimorbidities, and the potential for increased antimicrobial resistance needs to be considered. In summary, while emerging evidence suggests that continuous macrolide therapy reduces exacerbation frequency in COPD, there are many questions that remain to be addressed before this treatment can be routinely recommended in clinical practice. The challenge is to identify the patients with COPD who will benefit the most from macrolides while minimizing the risk of adverse effects.

**CONCLUSIONS**

The AECOPD poses a major health and economic burden to society. Infectious etiologies that are related to AECOPD involve a wide variety of viruses and bacteria. Environmental factors including air pollution and meteorological effects also influence the rate of AECOPD. The approach to diagnostic tests for AECOPD consists of characterizing gas exchange, infection and inflammation. Acute management typically involves use of bronchodilators, antibiotics and/or systemic steroids and, if severe, oxygen and NIV. Further studies are needed to assess the different types of non-pharmacological interventions available shortly post-AECOPD, as well as pharmacotherapy to reduce future risk of exacerbations, for identification of the efficacious components and overall cost-effectiveness.

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