INVITED REVIEW SERIES:
UNRAVELLING THE MANY FACES OF COPD TO
OPTIMIZE ITS CARE AND OUTCOMES
SERIES EDITORS: GREGORY G KING AND DON SIN

Acute exacerbation of COPD

FANNY W. KO,[1] KA PANG CHAN,[1] DAVID S. HUI,[1] JOHN R. GODDARD,[2,3] JANET G. SHAW,[2,3]
DAVID W. REID[2,3,4] AND IAN A. YANG[2,3]

[1]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, [2]School of Medicine, The University of Queensland, [3]Department of Thoracic Medicine, The Prince Charles Hospital, Metro North Hospital and Health District, and [4]Lung Infection and Inflammation Laboratory, QIMR Berghofer Medical Research Institute, Brisbane, Australia

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.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common disease worldwide[1–3] 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,

Japan, reported an exacerbation frequency ranging from 0.06 to 0.78 events per person per year.[5] Patients with exacerbations in the first year of the study had more frequent AECOPD during follow-up and worse quality of life (QOL).[5]

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.[6] In Hong Kong, COPD ranked as the third leading cause of respiratory death, after respiratory infection and cancer.[7] 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.[8] 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).[9] 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).[10] 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.[10]

AETIOLOGIES OF AECOPD

The triggering factors of AECOPD include infectious and noninfectious precipitants. However, up to 30% of AECOPD is of unknown aetiology.[11]

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.[12] 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.[13]

Viral infections

In a systematic review involving the Asia-Pacific countries, the weighted mean prevalence of respiratory viral infections in AECOPD was 34%.[14] 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.[14] Other relatively common causative viruses included respiratory syncytial virus, coronaviruses, parainfluenza, adenovirus and human metapneumovirus.[14,15] 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.[14] Multiple studies have also found that AECOPD due to viral infection is more common in the spring and winter seasons.[13,16,17]

Bacterial infections

Bacterial infection is a major cause of infective AECOPD, with prevalence ranging from 26% to 81%.[6,9–11] *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Haemophilus influenzae* were the three most common pathogens identified in mainland China[18] and Taiwan.[19,20] In Hong Kong and Australia, *H. influenzae*, *P. aeruginosa* and *Moraxella catarrhalis* were the major pathogens.[13,20] The most common causative microbes from a Korean study were *Streptococcus pneumoniae*, *P. aeruginosa* and *K. pneumoniae*.[12] Although more than 80% of the *Pseudomonas* strains were susceptible to common antipseudomonal antibiotics in China,[18] pseudomonal infection itself was associated with poor clinical outcome in a study in Taiwan.[19]

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.[20] 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.[13]

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 (SO_2),[21,22] nitrogen dioxide (NO_2),[21–24] ozone (O_3),[21,22]

small-diameter particulate matter (PM)$_{2.5}$,[22,24,25] PM$_{10}$[22] and coarse PM (2.5–10-µm aerodynamic diameter)[25] 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$_{2.5}$,[26] PM$_{10}$[27,28] and NO$_2$.[26,27] 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.[29]

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.[24,30] 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,[30] a reduction in sputum eosinophils or improvement of bronchial responsiveness.[31] 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.[32] 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.[33]

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.[34] Winter season and low humidity are confirmed triggers for AECOPD[34,35] and hospital admissions[36] in cities such as Hong Kong and Shanghai, and the lag effect could be as long as 14 days.[35] The peak seasons for AECOPD were spring and autumn from a study in Hokkaido, Japan.[5] 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.[21,22,36] The detrimental effect of lower temperature on AECOPD can be potentiated by a concomitant increase in NO$_2$, O$_3$ and SO$_2$ levels.[36] Increased barometric pressure, greater hours of sunshine and lower levels of humidity have been associated with increased risk of AECOPD.[34] 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.[37]

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%).[12] 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 thrombo-embolism ranged from 8% to 16%[12,38–41] 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.[3] 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 (Table 1). 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, compared with more intensive workup if the patient is hospitalized with a severe exacerbation and respiratory failure.

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).[42] In this study, noninferiority of the procalcitonin-guided approach, compared with the standard guideline-based approach, was not conclusively proven.

RELEVANCE OF THE COPD MICROBIOME TO EXACERBATIONS

With the development of molecular, culture-independent techniques, it is now evident that the healthy lung has its own site-specific population of microbes and is not a sterile organ as previously thought. The community composition of microbial flora can be determined by sequencing the variable

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 • C-reactive protein	• White cell count and differential (neutrophils, eosinophils and lymphocytes) • Systemic inflammation
Infection	• Sputum microscopy, culture and sensitivity • Nasal pharyngeal aspirate or swab for respiratory viral PCR • Chest X-ray	• For suspected bacterial infection • For suspected viral infection • To image suspected pneumonia or other pulmonary or cardiac causes of exacerbation, for example, pneumothorax, pleural effusion or heart failure
Impaired gas exchange	• Oximetry • Arterial blood gases	• Simple noninvasive measurement of oxygenation • 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.[43] 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.[43,44]

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.[45] A complex microbiome with diverse bacterial communities has been demonstrated both in endotracheal aspirates from mechanically ventilated patients with severe AECOPD[46] and in sputum samples obtained from patients experiencing a moderate exacerbation.[47] Bacterial community composition may be relatively stable in sputum samples at the start of an exacerbation and during recovery over 3 months.[48] 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.[49]

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.[50] 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)[49] 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.[51] 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 β_2 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) guideline[3] and respiratory societies in the Asia-Pacific region are shown in Table 2.[60–63]

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

GOLD[3]	Oral prednisolone 40 mg/day × 5 days
JRS[60]	Oral prednisolone 30–40 mg/day × 7–10 days
TSANZ[61]	Oral prednisolone 30–50 mg/day × 5 days (tapering dose required for those receiving > 14 days)
MTS[62]	Oral corticosteroids, no longer than 14 days, dose not specified
PCCP[63]	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.

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.[64] A Cochrane review[65] 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 methylprednisolone[66] 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.[67] The scarcity of data is also indirectly reflected by the inconsistent corticosteroids regimens noted in a Taiwanese observational study of AECOPD.[68] 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 an 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.[3] 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

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.[69] 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.[70]

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.[71] 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 FiO_2 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.[71,72]

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.[73]

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.[3,60–63] The criteria for initiation of NIV include respiratory acidosis (arterial $pH \leq 7.35$ and/or partial arterial carbon dioxide concentration $(PaCO_2) \geq 6.0\,kPa$ 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.[3]

When NIV is used together with effective pharmacological treatment, many patients will demonstrate recovery and be able to be weaned from NIV, with mean duration of use ranging from 2 to 10 days.[74–76] 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.[77]

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

	GOLD[3]	JRS[60]	TSANZ[61]	MTS[62]
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

[†]Inability to walk between rooms when previously mobile and inability to eat or sleep because of dyspnoea.

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[8,9,78–80] and was as high as 25% for patients requiring ICU admission.[81]

Increasing age[8,78,79,81] and impaired respiratory gas exchange were risk factors for in-hospital mortality. Acidotic pH, high $PaCO_2$ and low partial arterial oxygen concentration were all associated with higher in-hospital mortality.[78,80,82] Other risk factors include abnormal clinical findings (increased dyspnoea,[8] lower BMI,[8] altered mental status[8,78] and lower systolic blood pressure[82]), presence of comorbidities (congestive heart failure, liver disease, hyponatraemia < 130 mmol/L,[8,78] chronic renal failure,[8] hypoalbuminaemia[81] and high Charlson comorbidity index[79]), nursing home residency,[78]

requirement of NIV,[80] elevated troponin,[80] elevated D-dimer with exclusion of venous thromboembolism,[83] long-term use of corticosteroids[81] and high Acute Physiology and Chronic Health Evaluation (APACHE) II score.[81]

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%.[9,84] The 1-year mortality rate was 16% to 22% in patients not requiring NIV support or ICU care.[9,79,84,85] 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.[81]

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.[86] 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.[87] 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.[88] 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[89]	Salbutamol: tremor, palpitations, tachycardia[90] and hypokalaemia[3] Ipratropium: dry mouth and prostatic symptoms[3]
Systemic corticosteroids	Shorten recovery time, improve lung function and arterial hypoxemia, reduce treatment failure and decrease length of hospital stay[3]	Hyperglycaemia, worsened blood pressure control, mood disturbance, fluid retention and bruising[67]
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[3]	Claustrophobia, skin abrasion over the application site of mask interface, gastric distension and pneumonia[3]
Invasive mechanical ventilation	Support patient with respiratory failure (usually when NIV failed or not suitable)[3]	Ventilator-associated pneumonia, barotrauma and failure to wean to spontaneous ventilation[3]

NIV, noninvasive ventilation.

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 inpatient 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.[91] 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.[92] 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),[93] 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.[93] 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.[94]

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.[95] 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.[96]

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.[97] 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.[98] As treatment guidelines[99] 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.[100] 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.[101] 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.[102] 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.[103] Among these studies, only one study involved patients with recent AECOPD,[104] and this study also included other patients with congestive heart failure. Another study[105] 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.[106] 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.[92,96] 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.[107]

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.[108]

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.[109] 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,[110] including a range of inhaled, oral and injectable medicines that reduce the frequency of COPD exacerbations. Inhaled long-acting β_2 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.[111] Oral mucolytic agents such as *N*-acetylcysteine also reduce acute exacerbations.[112] 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.[113]

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.[51,114–121]

Furthermore, two systematic reviews found a statistically significant reduction in COPD exacerbations with the use of long-term macrolides.[122,123] 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.[122] 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; $P < 0.01$).[123] Subgroup analysis suggests that 6 months of macrolide therapy is the minimum treatment duration necessary to demonstrate significant reductions in COPD exacerbations.[122,123] 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.[122,123] Frequency of hospitalization and all-cause mortality did not differ between macrolide and placebo groups.[122,123]

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.

The Authors

FWK is a honorary clinical associate professor at the Chinese University of Hong Kong and a consultant of the Prince of Wales Hospital, Hong Kong. Her clinical work is in the field of adult respiratory medicine, and involves studying different aspects of COPD including etiologies and predictors for exacerbations, pulmonary rehabilitation, comorbidities and management programmes. KPC is a resident of the Respiratory Division of the Prince of Wales Hospital, Hong Kong. His clinical work is in the field of adult respiratory medicine, and research work in the field of airway diseases in particular in the predictors for exacerbation, comorbidities and management of COPD. DSH is a Stanley Ho professor of respiratory medicine at the Chinese University of Hong Kong and a honorary consultant physician at the Prince of Wales Hospital, Hong Kong. His research interests include clinical management of common airway diseases and emerging severe acute respiratory infections. JRG is a respiratory advanced trainee and a research scientist at The Prince Charles Hospital, and a PhD student at The University of Queensland, Brisbane, Australia. DWR is a thoracic and cystic fibrosis physician at The Prince Charles Hospital, an associate professor in the School of Medicine, The University of Queensland, and the team head of Lung Inflammation and Infection, QIMR Berghofer Medical Research Institute, Brisbane, Australia. IAY is a thoracic physician and director of thoracic medicine at The Prince Charles Hospital and a professor at UQ Thoracic Research Centre, School of Medicine, The University of Queensland, Brisbane, Australia. His clinical work is in the field of thoracic medicine, and his research team is studying gene–environmental interaction in COPD, asthma, lung cancer and air pollution.

REFERENCES

1 Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, Menezes AM, Sullivan SD, Lee TA, Weiss KB, *et al.* International variation in the prevalence of COPD (the BOLD study): a population-based prevalence study. *Lancet* 2007; **370**: 741-50.

2 Ko FW, Hui DS, Lai CK. Worldwide burden of COPD in high- and low-income countries. Part III. Asia-Pacific studies. *Int. J. Tuberc. Lung Dis.* 2008; **12**: 713-7.

3 Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease. Updated 2015. [Accessed 12 Jun 2015]. Available from URL: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2015_Apr2.pdf

4 Lim S, Lam DC, Muttalif AR, Yunus F, Wongtim S, Lan le TT, Shetty V, Chu R, Zheng J, Perng DW, *et al.* Impact of chronic obstructive pulmonary disease (COPD) in the Asia-Pacific region: the EPIC Asia population-based survey. *Asia Pac. Fam. Med.* 2015; **14**: 4.

5 Suzuki M, Makita H, Ito YM, *et al.* Clinical features and determinants of COPD exacerbation in the Hokkaido COPD cohort study. *Eur. Respir. J.* 2014; **43**: 1289-97.

6 World Health Organisation. Chronic respiratory diseases, burden of chronic obstructive pulmonary disease. [Accessed 27 Jul 2015]. Available from URL: http://wwwwhoint/respiratory/copd/burden/en/. 2015

7 Chan-Yeung M, Lai CK, Chan KS, Cheung AH, Yao TJ, Ho AS, Ko FW, Yam LY, Wong PC, Tsang KW, *et al.* The burden of lung disease in Hong Kong: a report from the Hong Kong Thoracic Society. *Respirology* 2008; **13** Suppl 4: S133-65.

8 Hasegawa W, Yamauchi Y, Yasunaga H, Sunohara M, Jo T, Matsui H, Fushimi K, Takami K, Nagase T. Factors affecting mortality following emergency admission for chronic obstructive pulmonary disease. *BMC Pulm Med.* 2014; **14**: 151.

9 Chang CL, Sullivan GD, Karalus NC, Mills GD, McLachlan JD, Hancox RJ. Predicting early mortality in acute exacerbation of chronic obstructive pulmonary disease using the CURB65 score. *Respirology.* 2011; **16**: 146–51.

10 Lou P, Zhu Y, Chen P, Zhang P, Yu J, Zhang N, Chen N, Zhang L, Wu H, Zhao J. Vulnerability, beliefs, treatments and economic burden of chronic obstructive pulmonary disease in rural areas in China: a cross-sectional study. *BMC Public Health.* 2012; **12**: 287.

11 Sapey E, Stockley RA. COPD exacerbations. 2: aetiology. *Thorax.* 2006; **61**: 250-8.

12 Choi KJ, Cha SI, Shin KM, Lee J, Hwangbo Y, Yoo SS, Lee Sy, Kim CH, Park JY, Jung TH. Prevalence and predictors of pulmonary embolism in Korean patients with exacerbation of chronic obstructive pulmonary disease. *Respiration* 2013; **85**: 203-9.

13 Wark PA, Tooze M, Powell H, Parsons K. Viral and bacterial infection in acute asthma and chronic obstructive pulmonary disease increases the risk of readmission. *Respirology* 2013; **18**: 996-1002.

14 Mohan A, Chandra S, Agarwal D, Guleria R, Broor S, Gaur B, Pandey RM. Prevalence of viral infection detected by PCR and RT-PCR in patients with acute exacerbation of COPD: a systematic review. *Respirology* 2010; **15**: 536-42.

15 Ko FW, Ip M, Chan PK, Fok JP, Chan MC, Ngai JC, Chan DP, Hui DS. A 1-year prospective study of the infectious etiology in patients hospitalized with acute exacerbations of COPD. *Chest* 2007; **131**: 44-52.

16 Ko FW, Ip M, Chan PK, Chan MC, To KW, Ng SS, Chau SS, Tang JW, Hui DS. Viral etiology of acute exacerbations of COPD in Hong Kong. *Chest* 2007; **132**: 900-8.

17 Cameron RJ, de Wit D, Welsh TN, Ferguson J, Grissell TV, Rye PJ. Virus infection in exacerbations of chronic obstructive pulmonary disease requiring ventilation. *Intensive Care Med.* 2006; **32**: 1022-9.

18 Ye F, He LX, Cai BQ, Wen FQ, Chen BY, Hadiarto M, Chen RC, Yuan JP, Sun HL. Spectrum and antimicrobial resistance of common pathogenic bacteria isolated from patients with acute exacerbation of chronic obstructive pulmonary disease in mainland of China. *Chin Med J (Engl)* 2013; **126**: 2207-14.

19 Lin SH, Kuo PH, Hsueh PR, Yang PC, Kuo SH. Sputum bacteriology in hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease in Taiwan with an emphasis on *Klebsiella pneumoniae* and *Pseudomonas aeruginosa. Respirology* 2007; **12**: 81-7.

20 Hui DS, Ip M, Ling T, Chang SC, Liao CH, Yoo CG, Kim DK, Yoon HI, Udompanich V, Mogmeud S, *et al.* A multicentre surveillance study on the characteristics, bacterial aetiologies and *in vitro* antibiotic susceptibilities in patients with acute exacerbation of chronic bronchitis. *Respirology* 2011; **16**: 532-9.

21 Lee IM, Tsai SS, Chang CC, Ho CK, Yang CY. Air pollution and hospital admissions for chronic obstructive pulmonary disease in a tropical city: Kaohsiung, Taiwan. *Inhal. Toxicol.* 2007; **19**: 393-8.

22 Ko FW, Tam W, Wong TW, Chan DP, Tung AH, Lai CK, Hui DS. Temporal relationship between air pollutants and hospital admissions for chronic obstructive pulmonary disease in Hong Kong. *Thorax* 2007; **62**: 780-5.

23 Zhang Z, Wang J, Chen L, Chen X, Sun G, Zhong N, Kan H, Lu W. Impact of haze and air pollution-related hazards on hospital admissions in Guangzhou, China. *Environ. Sci. Pollut. Res. Int.* 2014; **21**: 4236-44.

24 Tian L, Ho KF, Wang T, Qiu H, Pun VC, Chan CS, Louie PK, Yu IT. Ambient carbon monoxide and the risk of hospitalization due to chronic obstructive pulmonary disease. *Am J Epidemiol.* 2014; **180**: 1159–67.

25 Qiu H, Yu IT, Tian L, Wang X, Tse LA, Tam W, Wong TW. Effects of coarse particulate matter on emergency hospital admissions for respiratory diseases: a time-series analysis in Hong Kong. *Environ Health Perspect.* 2012; **120**: 572–6.

26 Li MH, Fan LC, Mao B, Yang JW, Choi AM, Cao WJ, Xu JF. Short Term Exposure to Ambient Fine Particulate Matter (PM2.5) Increases Hospitalizations and Mortality of Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. *Chest* 2015; DOI:10.1378/chest.15-0513 [Epub ahead of print]

27 Kan H, Chen B. Air pollution and daily mortality in Shanghai: a time-series study. *Arch Environ Health.* 2003; **58**: 360–7.

28 Meng X, Wang C, Cao D, Wong C, Han H. Short-term effect of ambient air pollution on COPD mortality in four Chinese cities. *Atmospheric Environment* 2013; **77**: 149–54.

29 Hedley AJ, Wong CM, Thach TQ, Ma S, Lam TH, Anderson HR. Cardiorespiratory and all-cause mortality after restrictions on sulphur content of fuel in Hong Kong: an intervention study. *Lancet.* 2002; **360**: 1646–52.

30 Tian L, Qiu H, Pun VC, Lin H, Ge E, Chan JC, Louie PK, Ho KF, Yu IT. Ambient carbon monoxide associated with reduced risk of hospital admissions for respiratory tract infections. *Am J Respir Crit Care Med.* 2013; **188**: 1240–5.

31 Bathoorn E, Slebos DJ, Postma DS, Koeter GH, van Oosterhout AJ, van der Toorn M, Boezen HM, Kerstjens HA. Anti-inflammatory effects of inhaled carbon monoxide in patients with COPD: a pilot study. *The European respiratory journal.* 2007; **30**: 1131–7.

32 Eisner MD, Iribarren C, Yelin EH, Sidney S, Katz PP, Sanchez G, Blanc PD. The impact of SHS exposure on health status and exacerbations among patients with COPD. *Int J Chron Obstruct Pulmon Dis.* 2009; **4**: 169–76.

33 Ko FW, Hui DS. Air pollution and chronic obstructive pulmonary disease. *Respirology.* 2012; **17**: 395–401.

34 Tseng CM, Chen YT, Ou SM, Hsiao YH, Li SY, Wang SJ, Yang AC, Chen TJ, Perng DW. The effect of cold temperature on increased exacerbation of chronic obstructive pulmonary disease: a nationwide study. *PLoS One.* 2013; **8**: e57066.

35 Huang F, Zhao A, Chen RJ, Kan HD, Kuang XY. Ambient temperature and outpatient visits for acute exacerbation of chronic bronchitis in Shanghai: a time series analysis. *Biomed Environ Sci.* 2015; **28**: 76–9.

36 Qiu H, Yu IT, Wang X, Tian L, Tse LA, Wong TW. Season and humidity dependence of the effects of air pollution on COPD hospitalizations in Hong Kong. *Atmospheric Environment.* 2013; **76**: 74–80.

37 Rea H, McAuley S, Jayaram L, Garrett J, Hockey H, Storey L, O'Donnell G, Haru L, Payton M, O'Donnell K. The clinical utility of long-term humidification therapy in chronic airway disease. *Respir Med.* 2010; **104**: 525–33.

38 Gunen H, Gulbas G, In E, Yetkin O, Hacievliyagil SS. Venous thromboemboli and exacerbations of COPD. *The European respiratory journal.* 2010; **35**: 1243–8.

39 Dutt TS, Udwadia ZF. Prevalence of venous thromboembolism in acute exacerbations of chronic obstructive pulmonary disease: an Indian perspective. *Indian J Chest Dis Allied Sci.* 2011; **53**: 207–10.

40 Duan SC, Yang YH, Li XY, Liang XN, Guo RJ, Xie WM, Kuang TG, Dai HP, Wang C. Prevalence of deep venous thrombosis in patients with acute exacerbation of chronic obstructive pulmonary disease. *Chin Med J (Engl).* 2010; **123**: 1510–4.

41 Erelel M, Cuhadaroglu C, Ece T, Arseven O. The frequency of deep venous thrombosis and pulmonary embolus in acute exacerbation of chronic obstructive pulmonary disease. *Respir Med.* 2002; **96**: 515–8.

42 Verduri A, Luppi F, D'Amico R, Balduzzi S, Vicini R, Liverani A, Ruggieri V, Plebani M, Barbaro MPF, Spanevello A *et al. et al.* Antibiotic Treatment of Severe Exacerbations of Chronic Obstructive Pulmonary Disease with Procalcitonin: A Randomized Noninferiority Trial. *PLoS ONE.* 2015; **10**: e0118241.

43 Sethi S. Chronic Obstructive Pulmonary Disease and Infection. Disruption of the Microbiome? *Annals of the American Thoracic Society* 2014; **11**: S43–S7.

44 Shaw JG, Vaughan A, Dent AG, O'Hare PE, Goh F, Bowman RV, Fong KM, Yang IA. Biomarkers of progression of chronic obstructive pulmonary disease (COPD). *Journal of Thoracic Disease.* 2014; **6**: 1532–47.

45 Molyneaux PL, Mallia P, Cox MJ, Footitt J, Willis-Owen SA, Homola D, Trujillo-Torralbo MB, Elkin S, Kon OM, Cookson WO *et al.* Outgrowth of the bacterial airway microbiome after rhinovirus exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2013; **188**: 1224–31.

46 Huang YJ, Kim E, Cox MJ, Brodie EL, Brown R, Wiener-Kronish JP, Lynch SV. A persistent and diverse airway microbiota present during chronic obstructive pulmonary disease exacerbations. *OMICS.* 2010; **14**: 9–59.

47 Millares L, Ferrari R, Gallego M, Garcia-Nuñez M, Pérez-Brocal V, Espasa M, Pomares X, Monton C, Moya A, Monsó E. Bronchial microbiome of severe COPD patients colonised by Pseudomonas aeruginosa. *Eur J Clin Microbiol Infect Dis.* 2014; **33**: 1–11.

48 Huang YJ, Sethi S, Murphy T, Nariya S, Boushey HA, Lynch SV. Airway Microbiome Dynamics in Exacerbations of Chronic Obstructive Pulmonary Disease. *Journal of Clinical Microbiology.* 2014; **52**: 2813–23.

49 Su J, Liu H-y, Tan X-l, Ji Y, Jiang Y-x, Prabhakar M, Rong Z-h, Zhou H-w, Zhang G-x. Sputum Bacterial and Fungal Dynamics during Exacerbations of Severe COPD. *PLoS ONE.* 2015; **10**: e0130736.

50 Smith DJ, Badrick AC, Zakrzewski M, Krause L, Bell SC, Anderson GJ, Reid DW. Pyrosequencing reveals transient cystic fibrosis lung microbiome changes with intravenous antibiotics. *Eur Respir J.* 2014; **44**: 922–30.

51 Simpson JL, Powell H, Baines KJ, Milne D, Coxson HO, Hansbro PM, Gibson PG. The effect of azithromycin in adults with stable

neutrophilic COPD: a double blind randomised, placebo controlled trial. *PLoS One.* 2014; **9**: e105609.

52 Brill SE, Law M, El-Emir E, Allinson JP, James P, Maddox V, Donaldson GC, McHugh TD, Cookson WO, Moffatt MF *et al.* Effects of different antibiotic classes on airway bacteria in stable COPD using culture and molecular techniques: a randomised controlled trial. *Thorax* 2015; **70**: 930–8.

53 Turner MO, Patel A, Ginsburg S, FitzGerald JM. Bronchodilator delivery in acute airflow obstruction. *A meta-analysis. Arch Intern Med.* 1997; **157**: 1736–44.

54 Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL, Smaldone GC, Guyatt G. Device selection and outcomes of aerosol therapy: Evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. *Chest.* 2005; **127**: 335–71.

55 Cates CJ, Welsh EJ, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. *Cochrane Database Syst Rev.* 2013; **9**: CD000052.

56 Mazhar SH, Ismail NE, Newton DA, Chrystyn H. Relative lung deposition of salbutamol following inhalation from a spacer and a Sidestream jet nebulizer following an acute exacerbation. *British journal of clinical pharmacology.* 2008; **65**: 334–7.

57 Simonds AK, Hanak A, Chatwin M, Morrell M, Hall A, Parker KH, Siggers JH, Dickinson RJ. Evaluation of droplet dispersion during non-invasive ventilation, oxygen therapy, nebuliser treatment and chest physiotherapy in clinical practice: implications for management of pandemic influenza and other airborne infections. *Health technology assessment (Winchester, England)* 2010; **14**(131): 72.

58 Holland A, Smith F, Penny K, McCrossan G, Veitch L, Nicholson C. Metered dose inhalers versus nebulizers for aerosol bronchodilator delivery for adult patients receiving mechanical ventilation in critical care units. *The Cochrane database of systematic reviews* 2013; **6**: Cd008863.

59 Woods JA, Wheeler JS, Finch CK, Pinner NA. Corticosteroids in the treatment of acute exacerbations of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis.* 2014; **9**: 421–30.

60 Japanese Respiratory Society. Guidelines for the Diagnosis and Treatment of COPD. 3rd edition. 2010. [Accessed 20 Nov 2015]. Available from URL: http://www.jrs.or.jp/uploads/uploads/files/photos/765.pdf

61 Thoracic Society of Australia and New Zealand. The COPD-X plan. [Accessed 26 Oct 2015]. Available from URL: http://copdx.org.au/copd-x-plan/

62 Malaysian Thoracic Society. Management of chronic obstructive pulmonary disease. 2nd edition. 2009 [Accessed 20 Nov 2015]. Available from URL: http://www.moh.gov.my/attachments/4749.pdf

63 Philippine College of Chest Physician. Clinical practice guidelines in the diagnosis and management of chronic obstructive pulmonary disease (COPD) in the Philippines, 2nd update. 2009 [Accessed 16 Nov 2015]. Available from URL: http://www.scribd.com/doc/99197030/PHILIPPINES-COPD-CPGuidelines-2009#scribd

64 Leuppi JD, Schuetz P, Bingisser R, Bodmer M, Briel M, Drescher T, Duerring U, Henzen C, Leibbrandt Y, Maier S *et al.* Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. *Jama.* 2013; **309**: 2223–31.

65 Walters JA, Tan DJ, White CJ, Wood-Baker R. Different durations of corticosteroid therapy for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2014; **12**: CD006897.

66 Ceviker Y, Sayiner A. Comparison of two systemic steroid regimens for the treatment of COPD exacerbations. *Pulm Pharmacol Ther.* 2014; **27**: 179–83.

67 de Jong YP, Uil SM, Grotjohan HP, Postma DS, Kerstjens HA, van den Berg JW. Oral or IV prednisolone in the treatment of COPD exacerbations: a randomized, controlled, double-blind study. *Chest.* 2007; **132**: 1741–7.

68 Wang PH, Cheng SL, Wang HC, Chang HT, Hsu YL, Chen YS, Chang CY. Systemic steroids in acute exacerbation of COPD - from guidelines to bedside. *Int J Clin Pharmacol Ther.* 2011; **49**: 705–8.

69 Vollenweider DJ, Jarrett H, Steurer-Stey CA, Garcia-Aymerich J, Puhan MA. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2012; **12**: CD010257.

70 Fanning M, McKean M, Seymour K, Pillans P, Scott I. Adherence to guideline-based antibiotic treatment for acute exacerbations of chronic obstructive pulmonary disease in an Australian tertiary hospital. *Intern Med J.* 2014; **44**: 903–10.

71 Beasley R, Chien J, Douglas J, Eastlake L, Farah C, King G, Moore R, Pilcher J, Richards M, Smith S *et al.* Thoracic Society of Australia and New Zealand oxygen guidelines for acute oxygen use in adults: 'Swimming between the flags'. *Respirology.* 2015; **20**: 1182–91.

72 Edwards L, Perrin K, Williams M, Weatherall M, Beasley R. Randomised controlled crossover trial of the effect on PtCO2 of oxygen-driven versus air-driven nebulisers in severe chronic obstructive pulmonary disease. *Emergency medicine journal : EMJ.* 2012; **29**: 894–8.

73 Ram FS, Picot J, Lightowler J, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2004; **1**: CD004104.

74 Collaborative Research Group of Non-invasive Mechanical Ventilation for Chronic Obstructive Pulmonary Disease. Early use of non-invasive positive pressure ventilation for acute exacerbations of chronic obstructive pulmonary disease: a multicentre randomized controlled trial. *Chin Med J (Engl).* 2005; **118**: 2034-40.

75 Verma AK, Mishra M, Kant S, Kumar A, Verma SK, Chaudhri S, Prabhuram J. Noninvasive mechanical ventilation: An 18-month experience of two tertiary care hospitals in north India. *Lung India.* 2013; **30**: 307–11.

76 Lun CT, Chan VL, Leung WS, Cheung AP, Cheng SL, Tsui MS, Chu CM. A pilot randomized study comparing two methods of non-invasive ventilation withdrawal after acute respiratory failure in chronic obstructive pulmonary disease. *Respirology.* 2013; **18**: 814–9.

77 Prasad SB, Chaudhry D, Khanna R. Role of noninvasive ventilation in weaning from mechanical ventilation in patients of chronic obstructive pulmonary disease: an Indian experience. *Indian J Crit Care Med.* 2009; **13**: 207–12.

78 Hu G, Zhou Y, Wu Y, Yu Y, Liang W, Ran P. The Pneumonia Severity Index as a Predictor of In-Hospital Mortality in Acute Exacerbation of Chronic Obstructive Pulmonary Disease. *PLoS One.* 2015; **10**: e0133160.

79 Ho TW, Tsai YJ, Ruan SY, Huang CT, Lai F, Yu CJ. In-hospital and one-year mortality and their predictors in patients hospitalized for first-ever chronic obstructive pulmonary disease exacerbations: a nationwide population-based study. *PLoS One.* 2014; **9**: e114866.

80 Kelly AM, Klim S. Is elevated troponin associated with in-hospital mortality in emergency department patients admitted with chronic obstructive pulmonary disease? *Eur J Emerg Med.* 2013; **20**: 54–7.

81 Ai-Ping C, Lee KH, Lim TK. In-hospital and 5-year mortality of patients treated in the ICU for acute exacerbation of COPD: a retrospective study. *Chest.* 2005; **128**: 518–24.

82 Soltani A, Reid D, Wills K, Walters EH. Prospective outcomes in patients with acute exacerbations of chronic obstructive pulmonary disease presenting to hospital: a generalisable clinical audit. *Intern Med J.* 2015; **45**: 925–33.

83 Fruchter O, Yigla M, Kramer MR. D-dimer as a prognostic biomarker for mortality in chronic obstructive pulmonary disease exacerbation. *Am J Med Sci.* 2015; **349**: 29–35.

84 Chang CL, Robinson SC, Mills GD, Sullivan GD, Karalus NC, McLachlan JD, Hancox RJ. Biochemical markers of cardiac dysfunction predict mortality in acute exacerbations of COPD. *Thorax.* 2011; **66**: 764–8.

85 Fruchter O, Yigla M. Cardiac troponin-I predicts long-term mortality in chronic obstructive pulmonary disease. *Copd.* 2009; **6**: 155–61.

86 Almagro P, Lopez Garcia F, Cabrera F, Montero L, Morchon D, Diez J, Soriano J. Comorbidity and gender-related differences in patients hospitalized for COPD. *The ECCO study. Respir Med.* 2010; **104**: 253–9.

87 Chung LP, Winship P, Phung S, Lake F, Waterer G. Five-year outcome in COPD patients after their first episode of acute exacerbation treated with non-invasive ventilation. *Respirology.* 2010; **15**: 1084–91.

88 Pavasini R, d'Ascenzo F, Campo G, Biscaglia S, Ferri A, Contoli M, Papi A, Ceconi C, Ferrari R. Cardiac troponin elevation predicts all-cause mortality in patients with acute exacerbation of chronic obstructive pulmonary disease: Systematic review and meta-analysis. *Int J Cardiol.* 2015; **191**: 187–93.

89 Belman MJ, Botnick WC, Shin JW. Inhaled bronchodilators reduce dynamic hyperinflation during exercise in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 1996; **153**: 967-75.

90 Nair S, Thomas E, Pearson SB, Henry MT. A randomized controlled trial to assess the optimal dose and effect of nebulized albuterol in acute exacerbations of COPD. *Chest* 2005; **128**: 48-54.

91 Bourbeau J, Nault D, Dang-Tan T. Self-management and behaviour modification in COPD. *Patient Educ. Couns.* 2004; **52**: 271-7.

92 Zwerink M, Brusse-Keizer M, van der Valk PD, Zielhuis GA, Monninkhof EM, van der Palen J, Frith PA, Effing T. Self management for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev.* 2014; **3**: CD002990.

93 Casas A, Troosters T, Garcia-Aymerich J, Roca J, Hernandez C, Alonso A, del Pozo F, de Toledo P, Anto JM, Rodriguez-Roisin R, *et al.* Integrated care prevents hospitalisations for exacerbations in COPD patients. *Eur. Respir. J.* 2006; **28**: 123-30.

94 Harrison SL, Janaudis-Ferreira T, Brooks D, Desveaux L, Goldstein RS. Self-management following an acute exacerbation of COPD: a systematic review. *Chest* 2015; **147**: 646-61.

95 Puhan MA, Gimeno-Santos E, Scharplatz M, Troosters T, Walters EH, Steurer J. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev.* 2011; **10**: CD005305.

96 Ko FW, Dai DL, Ngai J, Tung A, Ng S, Lai K, Fong R, Lau H, Tam W, Hui DS. Effect of early pulmonary rehabilitation on health care utilization and health status in patients hospitalized with acute exacerbations of COPD. *Respirology* 2011; **16**: 617-24.

97 Harrison SL, Robertson N, Graham CD, Williams J, Steiner MC, Morgan MD, Singh SJ. Can we identify patients with different illness schema following an acute exacerbation of COPD: a cluster analysis. *Respir. Med.* 2014; **108**: 319-28.

98 Maddocks M, Kon SS, Singh SJ, Man WD. Rehabilitation following hospitalization in patients with COPD: can it reduce readmissions? *Respirology* 2015; **20**: 395-404.

99 Nici L, Donner C, Wouters E, Zuwallack R, Ambrosino N, Bourbeau J, Carone M, Celli B, Engelen M, Fahy B, *et al.* American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am. J. Respir. Crit. Care Med.* 2006; **173**: 1390-413.

100 Mesquita R, Vanfleteren LE, Franssen FM, Sarv J, Taib Z, Groenen MT, Gaffron S, Bruijnzeel PL, Pitta F, Wouters EF, *et al.* Objectively identified comorbidities in COPD: impact on pulmonary rehabilitation outcomes. *Eur. Respir. J.* 2015; **46**: 545-8.

101 Gavish R, Levy A, Dekel OK, Karp E, Maimon N. The association between hospital readmission and pulmonologist follow-up visits in patients with COPD. *Chest* 2015; **148**: 375-81.

102 Sharma G, Kuo YF, Freeman JL, Zhang DD, Goodwin JS. Outpatient follow-up visit and 30-day emergency department visit and readmission in patients hospitalized for chronic obstructive pulmonary disease. *Arch. Intern. Med.* 2010; **170**: 1664-70.

103 Wong CX, Carson KV, Smith BJ. Home care by outreach nursing for chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev.* 2012; **4**: CD000994.

104 Aiken LS, Butner J, Lockhart CA, Volk-Craft BE, Hamilton G, Williams FG. Outcome evaluation of a randomized trial of the PhoenixCare intervention: program of case management and coordinated care for the seriously chronically ill. *J. Palliat. Med.* 2006; **9**: 111-26.

105 Kwok T, Lum CM, Chan HS, Ma HM, Lee D, Woo J. A randomized, controlled trial of an intensive community nurse-supported discharge program in preventing hospital readmissions of older patients with chronic lung disease. *J. Am. Geriatr. Soc.* 2004; **52**: 1240-6.

106 Kruis AL, Smidt N, Assendelft WJ, Gussekloo J, Boland MR, Rutten-van Molken M, Chavannes NH. Integrated disease management interventions for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev.* 2013; **10**: CD009437.

107 Ko FW, Ngai JC, Ng SS, Chan KP, Cheung R, Leung MY, Pun MC, Hui DS. COPD care programme can reduce readmissions and in-patient bed days. *Respir. Med.* 2014; **108**: 1771-8.

108 Jeppesen E, Brurberg KG, Vist GE, Wedzicha JA, Wright JJ, Greenstone M, Walters JA. Hospital at home for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev.* 2012; **5**: CD003573.

109 Jakobsen AS, Laursen LC, Rydahl-Hansen S, Ostergaard B, Gerds TA, Emme C, Schou L, Phanareth K. Home-based telehealth hospitalization for exacerbation of chronic obstructive pulmonary disease: findings from "the virtual hospital" trial. *Telemed. J. E. Health* 2015; **21**: 364-73.

110 Criner GJ, Bourbeau J, Diekemper RL, Ouellette DR, Goodridge D, Hernandez P, Curren K, Balter MS, Bhutani M, Camp PG, *et al.* Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society guideline. *Chest* 2015; **147**: 894-942.

111 Martinez FJ, Calverley PM, Goehring UM, Brose M, Fabbri LM, Rabe KF. Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multicentre randomised controlled trial. *Lancet* 2015; **385**: 857-66.

112 Zheng JP, Wen FQ, Bai CX, Wan HY, Kang J, Chen P, Yao WZ, Ma LJ, Li X, Raiteri L, *et al.* Twice daily N-acetylcysteine 600 mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON): a randomised, double-blind placebo-controlled trial. *Lancet Respir. Med.* 2014; **2**: 187-94.

113 Overington JD, Huang YC, Abramson MJ, Brown JL, Goddard JR, Bowman RV, Fong KM, Yang IA. Implementing clinical guidelines for chronic obstructive pulmonary disease: barriers and solutions. *J. Thorac. Dis.* 2014; **6**: 1586-96.

114 Suzuki T, Yanai M, Yamaya M, Satoh-Nakagawa T, Sekizawa K, Ishida S, Sasaki H. Erythromycin and common cold in COPD. *Chest* 2001; **120**: 730-3.

115 Banerjee D, Khair OA, Honeybourne D. The effect of oral clarithromycin on health status and sputum bacteriology in stable COPD. *Respir. Med.* 2005; **99**: 208-15.

116 Seemungal TA, Wilkinson TM, Hurst JR, Perera WR, Sapsford RJ, Wedzicha JA. Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. *Am. J. Respir. Care Med.* 2008; **178**: 1139-47.

117 Blasi F, Bonardi D, Aliberti S, Tarsia P, Confalonieri M, Amir O, Carone M, Di Marco F, Centanni S, Guffanti E. Long-term azithromycin use in patients with chronic obstructive pulmonary disease and tracheostomy. *Pulm. Pharmacol. Ther.* 2010; **23**: 200-7.

118 He ZY, Ou LM, Zhang JQ, Bai J, Liu GN, Li MH, Deng JM, MacNee W, Zhong XN. Effect of 6 months of erythromycin treatment on inflammatory cells in induced sputum and exacerbations in chronic obstructive pulmonary disease. *Respiration* 2010; **80**: 445-52.

119 Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA, Jr., Criner GJ, Curtis JL, Dransfield MT, Han MK, Lazarus SC, *et al.* Azithromycin for prevention of exacerbations of COPD. *N. Engl. J. Med.* 2011; **365**: 689-98.

120 Berkhof FF, Doornewaard-ten Hertog NE, Uil SM, Kerstjens HA, van den Berg JW. Azithromycin and cough-specific health status in patients with chronic obstructive pulmonary disease and chronic cough: a randomised controlled trial. *Respir. Res.* 2013; **14**: 125.

121 Uzun S, Djamin RS, Kluytmans JA, Mulder PG, van't Veer NE, Ermens AA, Pelle AJ, Hoogsteden HC, Aerts JG, van der Eerden MM. Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomised, double-blind, placebo-controlled trial. *Lancet Respir. Med.* 2014; **2**: 361-8.

122 Herath SC, Poole P. Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst. Rev.* 2013; **11**: Cd009764.

123 Ni W, Shao X, Cai X, Wei C, Cui J, Wang R, Liu Y. Prophylactic use of macrolide antibiotics for the prevention of chronic obstructive pulmonary disease exacerbation: a meta-analysis. *PLoS One* 2015; **10**: e0121257.