NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC) GUIDELINE SYNTHESIS

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) PART II. DIAGNOSIS AND MANAGEMENT OF ACUTE EXACERBATIONS

Guidelines

1. **Finnish Medical Society Duodecim**. Chronic obstructive pulmonary disease (COPD). In: EBM Guidelines. Evidence-Based Medicine. Helsinki, Finland: Duodecim Medical Publications Ltd.; 2007 Feb 7 [various].
2. **Global Initiative for Chronic Obstructive Lung Disease (GOLD)**. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease, World Health Organization, National Heart, Lung and Blood Institute; 2007. [420 references]
3. **National Collaborating Centre for Chronic Conditions, National Institute for Health and Clinical Excellence (NCCCC/NICE)**. Chronic obstructive pulmonary disease. Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. Thorax 2004 Feb;59 Suppl 1:1-232. [491 references]
4. **Singapore Ministry of Health**. Chronic obstructive pulmonary disease. Singapore: Singapore Ministry of Health; 2006 Oct. 84 p. [155 references]

INTRODUCTION

A direct comparison of the Finnish Medical Society Duodecim (FMS), the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (a collaborative project of the World Health Organization and the National Heart, Lung, and Blood Institute), the National Collaborating Centre for Chronic Conditions (a collaborating center for the National Institute for Health and Clinical Excellence [NCCCC/NICE]), and the Singapore Ministry of Health (SMOH) recommendations for the diagnosis and management of acute exacerbation of COPD is provided in the tables below.

The guidelines are broad in scope. In addition to addressing the diagnosis and management of acute exacerbations, all four guidelines also address stable COPD. The GOLD guideline also addresses prevention strategies. GOLD, NCCCC/NICE and SMOH provide recommendations for pulmonary rehabilitation. These topics, however, are beyond the scope of this synthesis. Recommendations concerning diagnosis and management of stable COPD are compared in Part I of this synthesis. Recommendations for pulmonary rehabilitation of patients with COPD are addressed in Part III of this synthesis.

The FMS and GOLD guidelines are updates of previous versions. In developing their guidelines both GOLD and SMOH reviewed the 2004 NCCCC/NICE guideline; SMOH also reviewed the 2005 version of the GOLD guideline.

The tables below provide a side-by-side comparison of key attributes of each guideline, including specific interventions and practices that are addressed. The language used in these tables, particularly that which is used in Table 3, Table 4, and Table 5 is in most cases taken verbatim from the original guidelines:

- Table 1 provides a quick-view glance at the primary interventions considered by each group and which make up the focus of this guideline synthesis.
- Table 2 provides a comparison of the overall scope of the included guidelines.

  Table 3 provides a more detailed comparison of the specific recommendations offered by each group for the topics under consideration in this synthesis, including:

  - Diagnosis and Initial Assessment
    - Signs and Symptoms of Acute Exacerbation
    - Causes of Exacerbation
    - Assessing Severity of Exacerbation
    - Diagnostic Testing
  - Management of Acute Exacerbations
    - Outpatient/Home Management vs. Inpatient Management
  - Pharmacologic Treatment
    - Bronchodilators
    - Combination Therapy
    - Corticosteroids
    - Antibiotics
  - Non-Pharmacologic Interventions
    - Oxygen
    - Noninvasive and Invasive Ventilation
  - Hospital Discharge and Follow-Up
- Table 4 lists the potential benefits associated with the implementation of each guideline as stated in the original guidelines.
- Table 5 presents the rating schemes used by the guideline groups to rate the level of evidence and the strength of the recommendations.

A summary discussion of the areas of agreement and areas of differences among the guidelines is presented following the content comparison tables.

Abbreviations used in the text and tables:

- COPD, Chronic obstructive pulmonary disease
- ECG, Electrocardiogram
- FMS, Finnish Medical Society Duodecim
- FEV_1, Forced expiratory volume in one second
- GOLD, Global Initiative for Chronic Obstructive Lung Disease
- ICU, Intensive Care Unit
- NCCCC, National Collaborating Centre for Chronic Conditions
- NICE, National Institute for Health and Clinical Excellence
- NIPPV, Noninvasive positive pressure ventilation

- NIV, Noninvasive ventilation
- PEF, Peak expiratory flow
- SMOH, Singapore Ministry of Health

TABLE 1: COMPARISON OF INTERVENTIONS AND PRACTICES CONSIDERED
("✓" indicates topic is addressed)

	FMS (2007)	GOLD (2007)	NCCCC/NICE (2004)	SMOH (2006)
Diagnosis and Initial Assessment	✓	✓	✓	✓
Outpatient vs. Inpatient Management	✓	✓	✓	✓
Pharmacologic Interventions	✓	✓	✓	✓
Non-Pharmacologic Interventions	✓	✓	✓	✓
Hospital Discharge and Follow-Up		✓	✓	

TABLE 2: COMPARISON OF SCOPE AND CONTENT

Objective and Scope	
FMS (2007)	• Evidence-Based Medicine Guidelines collect, summarize, and update the core clinical knowledge essential in general practice. The guidelines also describe the scientific evidence underlying the given recommendations.
GOLD (2007)	• To increase awareness of COPD and decrease morbidity and mortality from the disease • To improve prevention and management of COPD through a concerted worldwide effort of people involved in all facets of health care and health care policy • To encourage an expanded level of research interest in this highly prevalent disease • To work toward combating the nihilistic attitude toward COPD by disseminating information about available

	treatments (both pharmacologic and nonpharmacologic) and by working with a network of experts—the Global Initiative for Chronic Obstructive Lung Disease (GOLD) National Leaders—to implement effective COPD management programs developed in accordance with local health care practices
NCCCC/NICE (2004)	• To develop a clinical guideline on the management of chronic obstructive pulmonary disease for use in the National Health Service (NHS) in England and Wales • To offer best practice advice on the identification and care of patients with COPD • To define the symptoms, signs, and investigations required to establish a diagnosis of COPD • To define the factors that are necessary to assess the severity of COPD, provide prognostic information, and guide best management • To provide guidance on the pharmacological and non-pharmacological treatment of patients with stable COPD and on the management of exacerbations • To discuss the interface with surgery and intensive therapy units
SMOH (2006)	• To give physicians a practical approach and guide to the care of chronic obstructive pulmonary disease (COPD) patients
Target Population	
FMS (2007)	• Finland • Adults with COPD
GOLD (2007)	• Individuals with COPD
NCCCC/NICE (2004)	• England and Wales • Adults who have a clinical working diagnosis of COPD, including chronic bronchitis, emphysema, and chronic airflow limitation/obstruction **Note**: The guideline does not cover the management of people with asthma, bronchopulmonary dysplasia, and bronchiectasis, nor does it cover children.
SMOH (2006)	• Singapore • Patients with known or suspected chronic obstructive pulmonary disease (COPD)

Intended Users	
FMS (2007)	Health Care Providers Physicians
GOLD (2007)	Advanced Practice Nurses Allied Health Personnel Nurses Physician Assistants Physicians Public Health Departments Respiratory Care Practitioners
NCCCC/NICE (2004)	Advanced Practice Nurses Allied Health Personnel Dietitians Health Care Providers Hospitals Nurses Occupational Therapists Patients Physical Therapists Physicians Public Health Departments Respiratory Care Practitioners Students
SMOH (2006)	Physicians

TABLE 3: COMPARISON OF RECOMMENDATIONS FOR ACUTE EXACERBATION OF COPD	
DIAGNOSIS AND INITIAL ASSESSMENT	
Signs and Symptoms of Acute Exacerbation	
FMS (2007)	Although not specifically stated in the guideline, factors that indicate the initiation of treatment for the management of an acute infection include: • Increased dyspnoea • Increased sputum • Purulent sputum

GOLD (2007)	**Key Points**: • An exacerbation of COPD is defined as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD. **Medical History** Increased breathlessness, the main symptom of an exacerbation, is often accompanied by wheezing and chest tightness, increased cough and sputum, change of the color and/or tenacity of sputum, and fever. Exacerbations may also be accompanied by a number of nonspecific complaints, such as tachycardia and tachypnea, malaise, insomnia, sleepiness, fatigue, depression, and confusion. A decrease in exercise tolerance, fever, and/or new radiological anomalies suggestive of pulmonary disease may herald a COPD exacerbation. An increase in sputum volume and purulence points to a bacterial cause, as does prior history of chronic sputum production. **Differential Diagnoses** Ten to 30% of patients with apparent exacerbations of COPD that do not respond to treatment. In such cases the patient should be re-evaluated for other medical conditions that can aggravate symptoms or mimic COPD exacerbations. These conditions include pneumonia, congestive heart failure, pneumothorax, pleural effusion, pulmonary embolism, and cardiac arrhythmia. Noncompliance with the prescribed medication regimen can also cause increased symptoms that may be confused with a true exacerbation. Elevated serum levels of brain-type natriuretic peptide, in conjunction with other clinical information, identifies patients with acute dyspnea secondary to congestive heart failure and enables them to be distinguished from patients with COPD exacerbations.
NCCCC/NICE (2004)	**Definition** An exacerbation is a sustained worsening of the patient's symptoms from his or her usual stable state that is beyond normal day-to-day variations and is acute in onset. Commonly reported symptoms are worsening breathlessness, cough, increased sputum production, and change in sputum colour. The change in these symptoms often necessitates a change in medication.

	Sign and Symptoms Exacerbations of COPD can be associated with the following symptoms: • Increased dyspnoea • Increased sputum purulence • Increased sputum volume • Increased cough • Upper airway symptoms (e.g., colds and sore throats) • Increased wheeze • Chest tightness • Reduced exercise tolerance • Fluid retention • Increased fatigue • Acute confusion Chest pain and fever are uncommon features of COPD exacerbations and should prompt a search for other aetiologies. **Differential Diagnosis of an Exacerbation** Other conditions may present with similar symptoms in patients with COPD. These must be considered and excluded when making a diagnosis of an exacerbation. Other causes of similar symptoms in patients with COPD are: • Pneumonia • Pneumothorax • Left ventricular failure/pulmonary oedema • Pulmonary embolus • Lung cancer • Upper airway obstruction • Pleural effusion • Recurrent aspiration
SMOH (2006)	**Definition of an Acute Exacerbation** There is no widely accepted definition of acute exacerbation of COPD. Most published definitions describe an exacerbation as an acute event with worsening of the patient's symptoms from their usual stable state, which is beyond normal day-to-day variations. Commonly reported symptoms are worsening breathlessness, cough, increased sputum volume and sputum purulence.

	An acute exacerbation of COPD is a clinical diagnosis. **Differential Diagnoses of Acute Exacerbations** • Pneumonia • Pneumothorax • Left ventricular failure/pulmonary oedema • Pulmonary embolism • Lung cancer • Upper airway obstruction • Pleural effusion • Recurrent aspiration
Causes of Exacerbation	
FMS (2007)	Symptoms of COPD are aggravated by respiratory infection.
GOLD (2007)	The most common causes of an exacerbation are infection of the tracheobronchial tree and air pollution, but the cause of about one-third of severe exacerbations cannot be identified (**Evidence B**). The role of bacterial infections is controversial, but recent investigations with newer research techniques have begun to provide important information. Bronchoscopic studies have shown that at least 50% of patients have bacteria in high concentrations in their lower airways during exacerbations. However, a significant portion of these patients also have bacteria colonizing their lower airways in the stable phase of the disease. There is some indication that the bacterial burden increases during exacerbations, and that acquisition of strains of the bacteria that are new to the patient is associated with exacerbations. Development of specific immune responses to the infecting bacterial strains, and the association of neutrophilic inflammation with bacterial exacerbations, also support the bacterial causation of a proportion of exacerbations.
NCCCC/NICE (2004)	A number of factors are known to cause exacerbations of COPD. Although bacteria can be cultured from the sputum of patients with stable COPD there is evidence that they are also responsible for exacerbations. Viruses are also important aetiological agents, particularly during winter months. Non-infectious agents are also responsible for some exacerbations. The following factors are known causes of exacerbations of

	COPD:
	
	• Infections
	  • Rhinoviruses (common cold)
	  • Influenza
	  • Parainfluenza
	  • Coronavirus
	  • Adenovirus
	  • Respiratory syncytial virus
	  • *Chlamydia pneumoniae*
	  • *Haemophilus influenzae*
	  • *Streptococcus pneumoniae*
	  • *Moraxella catarrhalis*
	  • *Staphylococcus aureus*
	  • *Pseudomonas aeruginosa*
	• Common pollutants
	  • Nitrogen dioxide
	  • Particulates
	  • Sulphur dioxide
	  • Ozone
	
	The cause of the exacerbation may be unidentifiable in up to 30% of exacerbations.

SMOH (2006)	**Causes of Acute Exacerbation of COPD** The most common causes of an exacerbation are infection of the tracheo-bronchial tree (often viral) and air pollution. Other contributing factors may be co-existing diseases like: • Pneumonia • Right or left heart failure or arrhythmias • Pulmonary embolism • Spontaneous pneumothorax • Inappropriate oxygen administration • Drugs (hypnotics, tranquillisers, diuretics, etc.) • Metabolic diseases (diabetes, electrolyte disturbances, etc.) • Poor nutritional state • Other diseases (gastrointestinal bleeding, etc.) • End-stage respiratory disease (fatigue of respiratory muscles, etc.)
Assessing Severity of Exacerbation	
FMS (2007)	Not addressed in the guideline

GOLD (2007)	Assessment of the severity of an exacerbation is based on the patient's medical history before the exacerbation, preexisting comorbidities, symptoms, physical examination, arterial blood gas measurements, and other laboratory tests (Figure 5.4-1 in the original guideline document). Specific information is required on the frequency and severity of attacks of breathlessness and cough, sputum volume and color, and limitation of daily activities. When available, prior arterial blood gas measurements are extremely useful for comparison with those made during the acute episode, as an acute change in these tests is more important than their absolute values. Thus, where possible, physicians should instruct their patients to bring the summary of their last evaluation when they come to the hospital with an exacerbation. In patients with *Stage IV: Very Severe* COPD, the most important sign of a severe exacerbation is a change in the mental status of the patient and this signals a need for immediate evaluation in the hospital.
NCCCC/NICE (2004)	Some exacerbations are mild and self-limiting. These are frequently managed by patients at home without consulting healthcare professionals. Other exacerbations are severe, carry a risk of death, and require hospitalisation. A number of factors can be used to assess the severity of an exacerbation. Not all will be present, but the occurrence of any of these should alert the clinician. The following signs are features of a severe exacerbation: • Marked dyspnoea • Tachypnoea • Purse lip breathing • Use of accessory muscles (sternomastoid and abdominal) at rest • Acute confusion • New onset cyanosis • New onset peripheral oedema • Marked reduction in activities of daily living
SMOH (2006)	Signs of severe exacerbation (any of the following) (refer to algorithm on p. 51 of the original guideline document) • Marked dyspnoea and tachypnoea (>30 respirations/minute) • Use of accessory muscles (sternomastoid and abdominal) at rest • Cyanosis • Confusion

	• SaO_2 < 90%
Diagnostic Testing	
FMS (2007)	Not addressed in the guideline
GOLD (2007)	***Spirometry and PEF.*** Even simple spirometric tests can be difficult for a sick patient to perform properly. These measurements are not accurate during an acute exacerbation; therefore their routine use is not recommended. ***Pulse oximetry and arterial blood gas measurement.*** Pulse oximetry can be used to evaluate a patient's oxygen saturation and need for supplemental oxygen therapy. For patients that require hospitalization, measurement of arterial blood gases is important to assess the severity of an exacerbation. A PaO_2 < 8.0 kPa (60 mm Hg) and/or SaO_2 < 90% with or without $PaCO_2$ > 6.7 kPa (50 mmHg) when breathing room air indicate respiratory failure. In addition, moderate-to-severe acidosis (pH < 7.36) plus hypercapnia ($PaCO_2$ > 6 to 8 kPa, 45 to 60 mm Hg) in a patient with respiratory failure is an indication for mechanical ventilation. ***Chest X-ray and ECG.*** Chest radiographs (posterior/anterior plus lateral) are useful in identifying alternative diagnoses that can mimic the symptoms of an exacerbation. Although the history and physical signs can be confusing, especially when pulmonary hyperinflation masks coexisting cardiac signs, most problems are resolved by the chest X-ray and ECG. An ECG aids in the diagnosis of right heart hypertrophy, arrhythmias, and ischemic episodes. Pulmonary embolism can be very difficult to distinguish from an exacerbation, especially in advanced COPD, because right ventricular hypertrophy and large pulmonary arteries lead to confusing ECG and radiographic results. A low systolic blood pressure and an inability to increase the PaO_2 above 8.0 kPa (60 mm Hg) despite high-flow oxygen also suggest pulmonary embolism. If there are strong indications that pulmonary embolism has occurred, it is best to treat for this along with the exacerbation. ***Other laboratory tests.*** The whole blood count may identify polycythemia (hematocrit > 55%) or bleeding. White blood cell counts are usually not very informative. The presence of purulent sputum during an exacerbation of symptoms is sufficient indication for starting empirical antibiotic treatment. Streptococcus pneumoniae, Hemophilus influenzae, and Moraxella catarrhalis are the most common bacterial

	pathogens involved in COPD exacerbations. If an infectious exacerbation does not respond to the initial antibiotic treatment, a sputum culture and an antibiogram should be performed. Bio- chemical test abnormalities can be associated with an exacerbation and include electrolyte disturbance(s) (e.g., hyponatremia, hypokalemia), poor glucose control, metabolic acid-base disorder. These abnormalities can also be due to associated co-morbid conditions (see below "Differential Diagnoses").
NCCCC/NICE (2004)	The diagnosis of an exacerbation is made clinically and does not depend on the results of investigations; however, in certain situations, investigations may assist in ensuring appropriate treatment is given. Different investigation strategies are required for patients managed in hospital (who will tend to have more severe exacerbations) and those managed in the community. Changes in lung function at the time of an exacerbation are usually small and are not helpful in routine practice. Patients may present for the first time with an exacerbation of COPD. In this situation patients need assessing and their diagnosis confirmed as described in section 6 of the original guideline, Diagnosing COPD (see also Part I of this synthesis). Sending sputum samples for culture in primary care is of very limited value because empirical therapy is effective and should be prescribed promptly if the sputum is purulent. **D - Recommendations for Primary Care** In patients with an exacerbation managed in primary care: • Sending sputum samples for culture is not recommended in routine practice. • Pulse oximetry is of value if there are clinical features of a severe exacerbation. **D** - Recommendations for Patients Referred to Hospital In all patients with an exacerbation referred to hospital: • A chest radiograph should be obtained. • Arterial blood gas tensions should be measured and the inspired oxygen concentration must be recorded. • An ECG should be recorded (to exclude comorbidities). • A full blood count should be performed and urea and electrolyte concentrations should be measured. • A theophylline level should be measured in patients on theophylline therapy at admission.

	• If sputum is purulent, a sample should be sent for microscopy and culture. • Blood cultures should be taken if the patient is pyrexial.
SMOH (2006)	**Investigations for Patients with Exacerbation** **C** - Chest radiography is recommended in an acute exacerbation, when other diagnoses like pneumonia or heart failure need to be excluded. (**Grade C, Level 2+**) **D** - Sputum culture is not recommended for routine investigation of patients with exacerbation. (**Grade D, Level 3**) **D** - Pulse oximetry, if available, can assist doctors in identifying patients with hypoxaemia when oxygen saturation (SaO_2) is less than 90%. (**Grade D, Level 3**)
MANAGEMENT OF ACUTE EXACERBATIONS	
Outpatient/Home Management vs. Inpatient Management	

FMS (2007)	**Basics**
	
	• Oxygen therapy at home can be used to prevent elevation of pulmonary arterial pressure in advanced COPD and to extend the life of the patient.
	• The effect of oxygen therapy on symptoms (e.g., shortness of breath) is quite limited.
	• Oxygen therapy at home is meant only for patients with chronic hypoxaemia (i.e., arterial desaturation).
	• Treatment decisions should be made after critical consideration.
	• When initiating oxygen therapy at home, appropriate monitoring of treatment must be ensured. Treatment decisions and implementation of treatment should be the responsibility of the local pulmonary clinic.
	
	Initiation Criteria for Oxygen Therapy
	
	• Chronic, advanced pulmonary disease (FEV_1)
	• The partial pressure of oxygen in arterial blood, measured with the patient in stable phase of the disease breathing room air is
	• Partial pressure of oxygen can also be 7.3 to 8.0 kPa if one of the following criteria is involved:
	  • Signs of increased pulmonary arterial pressure (e.g., oedema)
	  • Secondary polycythaemia (haematocrit >55)

	• Significant nocturnal hypoxaemia established by oximetry and reversible by oxygen therapy and not caused by concomitant sleep apnoea syndrome • Significant neuropsychological symptoms reversible by oxygen therapy • Oxygen therapy gives the desired response (PaO_2 >8.0 kPa) without unfavourable increase in the partial pressure of carbon dioxide in arterial blood. • The patient does not smoke and is sufficiently cooperative. **Implementation of Treatment** • Oxygen therapy at home is implemented in most cases using an electric oxygen concentrator. The oxygen concentrator eliminates nitrogen from room air and provides the patient with over 90%-proof oxygen. • Portable liquid oxygen is suitable for a minority of patients. Primarily these are patients who are in the working life and/or who are motivated for rehabilitation through physical exercise. • All oxygen therapy necessitates good cooperation by the patient and willingness for long-term cooperation with the treating unit. • Home calls made by a rehabilitation instructor are an essential part of the monitoring of patients receiving oxygen therapy at home.
GOLD (2007)	**Home Management** There is increasing interest in home care for end-stage COPD patients, although economic studies of home care services have yielded mixed results. Four randomized clinical trials have shown that nurse-administered home care (also known as "hospital-at-home" care) represents an effective and practical alternative to hospitalization in selected patients with exacerbations of COPD without acidotic respiratory failure. However, the exact criteria for this approach as opposed to hospital treatment remain uncertain and will vary by health care setting. The algorithm reported in Figure 5.4-2 in the original guideline document may assist in the management of an exacerbation at home; a stepwise therapeutic approach is recommended. **Hospital Management** The risk of dying from an exacerbation of COPD is closely related to the development of respiratory acidosis, the

presence of significant comorbidities, and the need for ventilatory support. Patients lacking these features are not at high risk of dying, but those with severe underlying COPD often require hospitalization in any case. Attempts at managing such patients entirely in the community have met with only limited success, but returning them to their homes with increased social support and a supervised medical care package after initial emergency room assessment has been much more successful. Savings on inpatient expenditures offset the additional costs of maintaining a community-based COPD nursing team. However, detailed cost-benefit analyses of these approaches are awaited.

A range of criteria to consider for hospital assessment/admission for exacerbations of COPD are shown in Figure 5.4-3 (below). Some patients need immediate admission to an intensive care unit (ICU) (Figure 5.4-4 in the original guideline document). Admission of patients with severe COPD exacerbations to intermediate or special respiratory care units may be appropriate if personnel, skills, and equipment exist to identify and manage acute respiratory failure successfully.

Indications for Hospital Assessment or Admission for Exacerbations of COPD (Figure 5.4-3 in the original guideline document)

- Marked increase in intensity of symptoms, such as sudden development of resting dyspnea
- Severe underlying COPD
- Onset of new physical signs (e.g., cyanosis, peripheral edema)
- Failure of exacerbation to respond to initial medical management
- Significant comorbidities
- Frequent exacerbations
- Newly occurring arrhythmias
- Diagnostic uncertainty
- Older age
- Insufficient home support

Indications for ICU Admission of Patients with Exacerbations of COPD (Figure 5.4-4 in the original guideline document)

- Severe dyspnea that responds inadequately to initial emergency therapy
- Changes in mental status (confusion, lethargy, coma)
- Persistent or worsening hypoxemia (PaO_2 <5.3 kPa, 40 mm Hg), and/or severe/worsening hypercapnia ($PaCO_2$ >8.0 kPa, 60 mm Hg), and/or severe/worsening

	respiratory acidosis (pH <7.25) despite supplemental oxygen and noninvasive ventilation • Need for invasive mechanical ventilation • Hemodynamic instability—need for vasopressors **Emergency Department or Hospital** The first actions when a patient reaches the emergency department are to provide supplemental oxygen therapy and to determine whether the exacerbation is life threatening (Figure 5.4-4 in the original guideline document). If so, the patient should be admitted to the ICU immediately. Otherwise, the patient may be managed in the emergency department or hospital as detailed in Figure 5.4-5 in the original guideline document.
NCCCC/NICE (2004)	**D** - Factors that should be considered when deciding whether to treat the patient in the home or in a hospital are listed below: **Treat at Home** • Able to cope at home - Yes • Breathlessness - Mild • General condition - Good • Level of activity - Good • Cyanosis - No • Worsening peripheral oedema - No • Level of consciousness - Normal • Already receiving long-term oxygen therapy (LTOT) - No • Social circumstances - Good • Acute confusion - No • Rapid rate of onset - No • Significant comorbidity (particularly cardiac disease and insulin-dependent diabetes) - No • SaO_2 <90% - No • Changes on the chest radiograph - No • Arterial pH level - $\geq$7.35 • Arterial PaO_2 - $\geq$7 kPa **Treat in Hospital** • Able to cope at home - No • Breathlessness - Severe • General condition - Poor/deteriorating • Level of activity - Poor/confined to bed • Cyanosis - Yes • Worsening peripheral oedema - Yes • Level of consciousness - Impaired • Already receiving long-term oxygen therapy (LTOT) - Yes

	• Social circumstances - Living alone/not coping • Acute confusion - Yes • Rapid rate of onset - Yes • Significant comorbidity (particularly cardiac disease and insulin-dependent diabetes) - Yes • Changes on the chest radiograph - Present • Arterial pH level - $\geq$7.35 • Arterial PaO_2 - $\leq$7 kPa **A** - Hospital-at-home and assisted-discharge schemes are safe and effective and should be used as an alternative way of managing patients with exacerbations of COPD who would otherwise need to be admitted or stay in hospital. **D** - The multi-professional team required to operate these schemes should include allied health professionals with experience in managing patients with COPD, and may include nurses, physiotherapists, occupational therapists, and generic health workers. **D** - There are currently insufficient data to make firm recommendations about which patients with an exacerbation are most suitable for hospital-at-home or early discharge. Patient selection should depend on the resources available and absence of factors associated with a worse prognosis, such as acidosis. **D** - Patient's preferences about treatment at home or in hospital should be considered.
SMOH (2006)	**When to Refer to the Emergency Department (ED)** **GPP** - Any one of the following signs may indicate severe exacerbations requiring urgent referral to the Emergency Department: 1. Marked dyspnoea and tachypnoea (> 30 respirations/minute) 2. Use of accessory muscles (sternomastoid and abdominal) at rest 3. Cyanosis 4. Confusion 5. SaO_2 <90% **(GPP)**
PHARMACOLOGIC TREATMENT	
Bronchodilators (Including Delivery Systems)	

FMS (2007)	An inhaled sympathomimetic (salbutamol 2.5 to 5 milligrams or terbutaline 5 to 10 milligrams) by a dosing device or a spray. Inhaled ipratropium bromide 0.5 mg is usually added to it. There is no evidence of a significant effect of theophylline infusion (**C**) and its usage is not recommended. It may sometimes be used at a dose of 0.5 mg/kg/h if response to other treatments is poor. Serum theophylline concentration should be monitored if possible.
GOLD (2007)	**Key Points**: • Inhaled bronchodilators (particularly inhaled $beta_2$-agonists with or without anticholinergics) and oral glucocorticosteroids are effective treatments for exacerbations of COPD (**Evidence A**). **Home Management** *Bronchodilator Therapy* Home management of COPD exacerbations involves increasing the dose and/or frequency of existing short-acting bronchodilator therapy, preferably with a $beta_2$-agonist (**Evidence A**). There is not sufficient evidence, however, to indicate a difference in efficacy between the different classes of short-acting bronchodilators, or to indicate additional benefit of combinations of short-acting bronchodilators. However, if not already used, an anticholinergic can be added until the symptoms improve. There is no difference in the clinical response between bronchodilator therapy delivered by MDI with a spacer and by hand held nebulizer. **Hospital Management** ***Bronchodilator therapy.*** Short-acting inhaled $beta_2$-agonists are usually the preferred bronchodilators for treatment of exacerbations of COPD (**Evidence A**). If a prompt response to these drugs does not occur, the addition of an anticholinergic is recommended, even though evidence concerning the effectiveness of this combination is controversial. Despite its wide-spread clinical use, the role of methylxanthines in the treatment of exacerbations of COPD remains controversial. Methylxanthines (theophylline or aminophylline) is currently considered second-line intravenous therapy, used when there is inadequate or insufficient response to short-acting bronchodilators (**Evidence B**). Possible beneficial effects in terms of lung function and clinical endpoints are modest and inconsistent, whereas adverse effects are significantly

	increased. There are no clinical studies that have evaluated the use of inhaled long-acting bronchodilators (either 12-agonists or anticholinergics) with or without inhaled glucocorticosteroids during an acute exacerbation.
NCCCC/NICE (2004)	Increased breathlessness is a common feature of an exacerbation of COPD. This is usually managed by taking increased doses of short-acting bronchodilators. As well as taking increased doses of bronchodilators at the time of an exacerbation, these drugs may be given using different delivery systems. **Note**: The guideline does not offer recommendations specific to the use of beta$_2$ agonists in acute exacerbation. **Delivery Systems for Inhaled Therapy During Exacerbations** **A** - Both nebulisers and hand-held inhalers can be used to administer inhaled therapy during exacerbations of COPD. **D** - The choice of delivery system should reflect the dose of drug required, the ability of the patient to use the device, and the resources available to supervise the administration of the therapy. **D** - Patients should be changed to hand-held inhalers as soon as their condition has stabilised because this may permit earlier discharge from hospital. **D** - If a patient is hypercapnic or acidotic, the nebuliser should be driven by compressed air, not oxygen (to avoid worsening hypercapnia). If oxygen therapy is needed, it should be administered simultaneously by nasal cannulae. **D** - The driving gas for nebulised therapy should always be specified in the prescription. **Theophylline and Other Methylxanthines** **D** - Intravenous theophylline should only be used as an adjunct to the management of exacerbations of COPD if there is an inadequate response to nebulised bronchodilators. **D** - Care should be taken when using intravenous theophylline because of interactions with other drugs and potential toxicity if the patient has been on oral theophylline. **D** - Theophylline levels should be monitored within 24 hours of starting treatment and subsequently as frequently as indicated

	by the clinical circumstances.
SMOH (2006)	**A** - Inhaled anticholinergic bronchodilators or inhaled short-acting beta$_2$-agonists are beneficial and should be used in the treatment of patients presenting with acute exacerbation of COPD. (**Grade A, Level 1+**) Since the inhaled anticholinergic bronchodilators have fewer and more benign side effects, consider these agents first. Only after the initial bronchodilator is at maximum dose is the addition of a second inhaled bronchodilator beneficial. **D** - Both nebulisers and hand-held inhalers can be used to administer inhaled therapy during exacerbations of COPD, as they are equally effective in achieving bronchodilation in COPD exacerbations. (**Grade D, Level 4**) The choice of delivery system should depend on the dose of drug required, the ability of the patient to use the device and the resources available to supervise the administration of the therapy.
Combination Therapy	
FMS (2007)	An inhaled sympathomimetic (salbutamol 2.5 to 5 mg or terbutaline 5 to 10 mg) by a dosing device or a spray. Inhaled ipratropium bromide 0.5 mg is usually added to it.
GOLD (2007)	**<u>Home Management</u>** **Bronchodilator Therapy** There is not sufficient evidence, however, to indicate a difference in efficacy between the different classes of short-acting bronchodilators, or to indicate additional benefit of combinations of short-acting bronchodilators. However, if not already used, an anticholinergic can be added until the symptoms improve. **Glucocorticosteroids** They should be considered in addition to bronchodilators if the patient's baseline FEV_1 is < 50% predicted. **<u>Hospital Management</u>** **Bronchodilator Therapy**. If a prompt response to beta$_2$ agonists does not occur, the addition of an anticholinergic is recommended, even though evidence concerning the

	effectiveness of this combination is controversial. **Glucocorticosteroids**. Oral or intravenous glucocorticosteroids are recommended as an addition to other therapies in the hospital management of exacerbations of COPD (**Evidence A**).
NCCCC/NICE (2004)	The guideline does not offer specific recommendations regarding combination therapy with inhaled anticholinergics and short-acting beta$_2$-agonists in an acute exacerbation of COPD.
SMOH (2006)	**Bronchodilators** Since the inhaled anticholinergic bronchodilators have fewer and more benign side effects, consider these agents first. Only after the initial bronchodilator is at maximum dose is the addition of a second inhaled bronchodilator beneficial. **Systemic Corticosteroids** **A** - In the absence of significant contraindications, oral corticosteroids should be used, in conjunction with other therapies, in all patients admitted to hospital with an exacerbation of COPD. (**Grade A, Level 1+**)
Corticosteroids	
FMS (2007)	Methyl prednisolone 0.5 mg/kg every 6 hours is probably beneficial. Also oral corticosteroids (prednisolone 30 to 40 mg/day) are empirically recommended for 7 to 14 days.
GOLD (2007)	**Key Points**: • Inhaled bronchodilators (particularly inhaled beta$_2$-agonists with or without anticholinergics) and oral glucocorticosteroids are effective treatments for exacerbations of COPD (**Evidence A**). **Home Management** ***Glucocorticosteroids***. Systemic glucocorticosteroids are beneficial in the management of exacerbations of COPD. They shorten recovery time, improve lung function (FEV_1) and hypoxemia (PaO_2) (**Evidence A**), and may reduce the risk of early relapse, treatment failure, and length of hospital stay. They should be considered in addition to bronchodilators if the patient's baseline FEV_1 is < 50% predicted. A dose of 30 to 40 mg prednisolone per day for 7 to 10 days is recommended. Nebulized budesonide may be an alternative (although more

	expensive) to oral glucocorticosteroids in the treatment of non-acidotic exacerbations and is associated with significant reduction of complications such as hyperglycemia. Randomized clinical trials in the outpatient office set-up are not available. **Hospital Management** ***Glucocorticosteroids***. Oral or intravenous glucocorticosteroids are recommended as an addition to other therapies in the hospital management of exacerbations of COPD (**Evidence A**). The exact dose that should be recommended is not known, but high doses are associated with a significant risk of side effects. Thirty to 40 mg of oral prednisolone daily for 7 to 10 days is effective and safe (**Evidence C**). Prolonged treatment does not result in greater efficacy and increases the risk of side effects (e.g., hyperglycemia, muscle atrophy).
NCCCC/NICE (2004)	**A** - In the absence of significant contraindications, oral corticosteroids should be used, in conjunction with other therapies, in all patients admitted to hospital with an exacerbation of COPD. **B** - In the absence of significant contraindications, oral corticosteroids should be considered in patients managed in the community who have an exacerbation with a significant increase in breathlessness which interferes with daily activities. **D** - Patients requiring corticosteroid therapy should be encouraged to present early to get maximum benefits. **D** - Prednisolone 30 mg orally should be prescribed for 7 to 14 days. **A** - It is recommended that a course of corticosteroids treatment should not be longer than 14 days as there is no advantage in prolonged therapy. **D** - For guidance on stopping oral corticosteroid therapy it is recommended that clinicians refer to the British National Formulary. **D** - Osteoporosis prophylaxis should be considered in patients requiring frequent courses of oral corticosteroids. **D** - Patients should be made aware of the optimum duration of treatment and the adverse effects of prolonged therapy.

	D - Patients, particularly those discharged from hospital, should be given clear instructions about why, when, and how to stop their corticosteroid treatment.
SMOH (2006)	**Systemic Corticosteroids** **A** - In the absence of significant contraindications, oral corticosteroids should be used, in conjunction with other therapies, in all patients admitted to hospital with an exacerbation of COPD. (**Grade A, Level 1+**) **A** - In the absence of significant contraindications, oral corticosteroids should be considered in patients managed in the community who have an exacerbation with a significant increase in the breathlessness which interferes with daily activities. (**Grade A, Level 1+**) **A** - Prednisolone 30 mg orally should be prescribed for 7 to 14 days to patients with an exacerbation. It is recommended that a course of corticosteroid treatment should not be longer than 14 days as there is no advantage in prolonged therapy. (**Grade A, Level 1+**)
Antibiotics	

FMS (2007)	• Antimicrobial treatment in an exacerbation of COPD is controversial. Factors that indicate starting antimicrobial treatment include:
	  • Increased dyspnoea
	  • Increased sputum
	  • Purulent sputum
	• If the patient exhibits two of the three symptoms listed above, an antimicrobial drug is usually indicated (**A**).
	• Alternatives in antimicrobial treatment:
	  • Amoxicillin 500 mg three times daily for 10 days
	  • Doxycycline 150 mg once daily for 10 days
	  • Sulpha-trimethoprim, dose of trimethoprim 160 mg twice daily for 10 days
	• Antibiotics have no place in the basic maintenance therapy of COPD.

GOLD (2007)	**Key Points**: • Patients experiencing COPD exacerbations with clinical signs of airway infection (e.g., increased sputum purulence) may benefit from antibiotic treatment (**Evidence B**).

	Hospital Management *Antibiotics* Based on the current available evidence, antibiotics should be given to: • Patients with exacerbations of COPD with three of the following cardinal symptoms: increased dyspnea, increased sputum volume, and increased sputum purulence (**Evidence B**) • Patients with exacerbations of COPD with two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms (**Evidence C**) • Patients with a severe exacerbation of COPD that requires invasive mechanical ventilation (invasive or noninvasive) (**Evidence B**) The infectious agents in COPD exacerbations can be viral or bacterial. The predominant bacteria recovered from the lower airways of patients with COPD exacerbations are H. influenzae, S. pneumoniae, and M. catarrhalis. So-called atypical pathogens, such as Mycoplasma pneumoniae and Chlamydia pneumoniae, have been identified in patients with COPD exacerbations, but because of diagnostic limitations the true prevalence of these organisms is not known. Figure 5.4-7 in the original guideline document provides recommended antibiotic treatment for exacerbations of COPD, although it must be emphasized that most of the published studies related to the use of antibiotics were done in chronic bronchitis patients. The route of administration (oral or intravenous) depends on the ability of the patient to eat and the pharmacokinetics of the antibiotic. The oral route is preferred; if the IV route must be used, switching to the oral route is recommended when clinical stabilization permits. Based on studies of the length of use of antibiotics for chronic bronchitis, antibiotic treatment in patients with COPD exacerbations could be given for 3 to 7 days (**Evidence D**).
NCCCC/NICE (2004)	**A** - Antibiotics should be used to treat exacerbations of COPD associated with a history of more purulent sputum. **B** - Patients with exacerbations without more purulent sputum do not need antibiotic therapy unless there is consolidation on a chest radiograph or clinical signs of pneumonia. **D** - Initial empirical treatment should be an aminopenicillin, a macrolide, or a tetracycline. When initiating empirical antibiotic treatment, prescribers should always take account of

	any guidance issued by their local microbiologists. **D** - When sputum has been sent for culture, the appropriateness of antibiotic treatment should be checked against laboratory culture and sensitivities when they become available.
SMOH (2006)	**A** - Antibiotics should be used to treat exacerbations of COPD when (Saint et al. 1995): 1. There is history of purulent sputum 2. There are clinical signs of pneumonia 3. There is consolidation on a chest radiograph **(Grade A, Level 1+)** Initial empirical treatment can be a beta lactam-beta lactamase inhibitor combination, a 2nd generation macrolide, a 2nd generation cephalosporin, or a quinolone. When initiating empirical antibiotic treatment, prescribers should always take account of any guidance issued by their local microbiologists.
NON-PHARMACOLOGIC INTERVENTIONS	
Oxygen	
FMS (2007)	Oxygen by nasal catheter or by venturi mask. Caution should be exercised when dosing (if the result of an arterial blood gas analysis is not available, the concentration of mask oxygen should not exceed 28%, or nasal catheter flow should not exceed more than 2 L/minutes in patients above 50 years of age).
GOLD (2007)	**Hospital Management** ***Controlled oxygen therapy***. Oxygen therapy is the cornerstone of hospital treatment of COPD exacerbations. Supplemental oxygen should be titrated to improve the patient's hypoxemia. Adequate levels of oxygenation (PaO_2 >8.0 kPa, 60 mm Hg, or SaO_2 >90%) are easy to achieve in uncomplicated exacerbations, but CO_2 retention can occur insidiously with little change in symptoms. Once oxygen is started, arterial blood gases should be checked 30 to 60 minutes later to ensure satisfactory oxygenation without CO_2 retention or acidosis. Venturi masks (high-flow devices) offer more accurate delivery of controlled oxygen than do nasal prongs but are less likely to be tolerated by the patient.
NCCCC/NICE	**D** - The oxygen saturation should be measured in patients

(2004)	with an exacerbation of COPD, if there are no facilities to measure arterial blood gases. **C** - If necessary, oxygen should be given to keep the SaO_2 greater than 90%. **D** - Pulse oximeters should be available to all healthcare professionals managing patients with exacerbations of COPD, and they should be trained in their use. Clinicians should be aware that pulse oximetry gives no information about the PCO_2 or pH. **D** - In the interim period while the recommendation on the availability of oximeters is implemented, oxygen should be given to all patients with an exacerbation of COPD who are breathless, if the oxygen saturations are not known. **D** - During the transfer to hospital the following points should be considered: • It is not desirable to exceed an oxygen saturation of 93%. Oxygen therapy should be commenced at approximately 40% and titrated upwards if saturation falls below 90% and downwards if the patient becomes drowsy or if the saturation exceeds 93 to 94%. • Patients with known type II respiratory failure need special care, especially if they require a long ambulance journey or if they are given oxygen at home for a prolonged period before the ambulance arrives. **D** - When the patient arrives at hospital, arterial blood gases should be measured and the inspired oxygen concentration noted in all patients with an exacerbation of COPD. Arterial blood gas measurements should be repeated regularly, according to the response to treatment. **D** - The aim of supplemental oxygen therapy in exacerbations of COPD is to maintain adequate levels of oxygenation (SaO_2 greater than 90%), without precipitating respiratory acidosis or worsening hypercapnia. Patients with pH <7.35 should be considered for ventilatory support.
SMOH (2006)	**GPP** - Oxygen therapy should be considered if patient is known, or suspected, to have hypoxaemia. This can be administered via nasal prongs, or venturi mask. One should exercise caution in the oxygen dose for patients, such that the lowest possible oxygen concentration to maintain oxygen saturation above 90% is provided. If pulse oximetry is not available, the concentration of the oxygen mask should not exceed 28%, or the nasal prong oxygen flow rate should be

	kept at 2L/min. (**GPP**)
Noninvasive and Invasive Ventilation	
FMS (2007)	Non-invasive positive pressure ventilation using a mask improves recovery in severe acute exacerbation of COPD (**A**).
GOLD (2007)	**Key Points**: • Noninvasive mechanical ventilation in exacerbations improves respiratory acidosis, increases pH, decreases the need for endotracheal intubation, and reduces $PaCO_2$, respiratory rate, severity of breathlessness, the length of hospital stay, and mortality (**Evidence A**). **Hospital Management** Noninvasive mechanical ventilation. Noninvasive intermittent ventilation (NIV) has been studied in several randomized controlled trials in acute respiratory failure, consistently providing positive results with success rates of 80 to 85%. These studies provide evidence that NIV improves respiratory acidosis (increases pH, and decreases $PaCO_2$), decreases respiratory rate, severity of breathlessness, and length of hospital stay (**Evidence A**). More importantly, mortality—or its surrogate, intubation rate—is reduced by this intervention. However, NIV is not appropriate for all patients, as summarized in Figure 5.4-8 (see below). **Indications and Relative Contraindications for NIV** (figure 5.4-8 in the original guideline document) *Selection Criteria* • Moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion • Moderate to severe acidosis (pH $\leq$ 7.35) and/or hypercapnia ($PaCO_2$ >6.0 kPa, 45 mmHg) • Respiratory frequency > 25 breaths per minute *Exclusion Criteria (any may be present)* • Respiratory arrest • Cardiovascular instability (hypotension, arrhythmias, myocardial infarction) • Change in mental status; uncooperative patient • High aspiration risk • Viscous or copious secretions • Recent facial or gastroesophageal surgery • Craniofacial trauma

- Fixed nasopharyngeal abnormalities
- Burns
- Extreme obesity

Invasive Mechanical Ventilation.

During exacerbations of COPD the events occurring within the lungs include bronchoconstriction, airway inflammation, increased mucus secretion, and loss of elastic recoil, all of which prevent the respiratory system from reaching its passive functional residual capacity at the end of expiration, enhancing dynamic hyperinflation and increasing the work of breathing. The indications for initiating invasive mechanical ventilation during exacerbations of COPD are shown in Figure 5.4-9 (see below), including failure of an initial trial of NIV. As experience is being gained with the generalized clinical use of NIV in COPD, several of the indications for invasive mechanical ventilation are being successfully treated with NIV. Figure 5.4-10 in the original guideline document details some other factors that determine the use of invasive ventilation.

The use of invasive ventilation in end-stage COPD patients is influenced by the likely reversibility of the precipitating event, the patient's wishes, and the availability of intensive care facilities. When possible, a clear statement of the patient's own treatment wishes—an advance directive or "living will"—makes these difficult decisions much easier to resolve. Major hazards include the risk of ventilator-acquired pneumonia (especially when multi-resistant organisms are prevalent), barotrauma, and failure to wean to spontaneous ventilation.

Indications for Invasive Mechanical Ventilation (Figure 5.4-9 in the original guideline document)

- Unable to tolerate NIV or NIV failure (for exclusion criteria, see Figure 5.4-8 above)
- Severe dyspnea with use of accessory muscles and paradoxical abdominal motion
- Respiratory frequency >35 breaths per minute
- Life-threatening hypoxemia
- Severe acidosis (pH <7.25) and/or hypercapnia ($PaCO_2$ >8.0 kPa, 60 mmHg)
- Respiratory arrest
- Somnolence, impaired mental status
- Cardiovascular complications (hypotension, shock)
- Other complications (metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion)
- NIPPV failure (or exclusion criteria [see above])

	* FiO_2: Fractional concentration of oxygen in dry inspired gas Weaning or discontinuation from mechanical ventilation can be particularly difficult and hazardous in patients with COPD. The most influential determinant of mechanical ventilatory dependency in these patients is the balance between the respiratory load and the capacity of the respiratory muscles to cope with this load. By contrast, pulmonary gas exchange by itself is not a major difficulty in patients with COPD. Weaning patients from the ventilator can be a very difficult and prolonged process and the best method (pressure support or a T-piece trial) remains a matter of debate. In COPD patients that failed extubation, noninvasive ventilation facilitates weaning and prevents reintubation, but does not reduce mortality. A report that included COPD and non-COPD patients showed that noninvasive mechanical ventilation in patients that failed extubation was not effective in averting the need for reintubation and did not reduce mortality.
NCCCC/NICE (2004)	**Non-invasive Ventilation (NIV) and COPD Exacerbations** **A** - NIV should be used as the treatment of choice for persistent hypercapnic ventilatory failure during exacerbations despite optimal medical therapy. **D** - It is recommended that NIV should be delivered in a dedicated setting with staff who have been trained in its application, who are experienced in its use, and who are aware of its limitations. **D** - When patients are started on NIV, there should be a clear plan covering what to do in the event of deterioration and ceilings of therapy should be agreed. **Invasive Ventilation and Intensive Care** **C** - Patients with exacerbations of COPD should receive treatment on intensive care units, including invasive ventilation when this is thought to be necessary. **D** - During exacerbations of COPD, functional status, body mass index (BMI), requirement for oxygen when stable, comorbidities, and previous admissions to intensive care units should be considered, in addition to age and FEV_1, when assessing suitability for intubation and ventilation. Neither age nor FEV_1 should be used in isolation when assessing suitability. **A** - NIV should be considered for patients who are slow to wean from invasive ventilation.

SMOH (2006)	**A** - Non-invasive ventilation should be used as the treatment of choice in the hospital, for persistent hypercapnic ventilatory failure during exacerbations despite optimal medical therapy. (**Grade A, Level 1+**) **Note**: Refer to the original guideline document for a discussion of air travel in COPD patients.
HOSPITAL DISCHARGE AND FOLLOW-UP	
FMS (2007)	No recommendations offered
GOLD (2007)	**Key Points:** • Medications and education to help prevent future exacerbations should be considered as part of follow-up, as exacerbations affect the quality of life and prognosis of patients with COPD. **Hospital Discharge and Follow-Up** Insufficient clinical data exist to establish the optimal duration of hospitalization in individual patients developing an exacerbation of COPD although units with more respiratory consultants and better quality organized care have lower mortality and reduced length of hospital stay following admission for acute COPD exacerbation. Consensus and limited data support the discharge criteria listed in Figure 5.4-11 in the original guideline document. Figure 5.4-12 in the original guideline document provides items to include in a follow-up assessment 4 to 6 weeks after discharge from the hospital. Thereafter, follow-up is the same as for stable COPD, including supervising smoking cessation, monitoring the effectiveness of each drug treatment, and monitoring changes in spirometric parameters. Home visits by a community nurse may permit earlier discharge of patients hospitalized with an exacerbation of COPD, without increasing readmission rates. Use of a written action plan in COPD increased appropriate therapeutic interventions for exacerbations of COPD, an effect that does not decrease health-care resource utilization (**Evidence B**). In patients hypoxemic during a COPD exacerbation, arterial blood gases and/or pulse oximetry should be evaluated prior to hospital discharge and in the following 3 months. If the patient remains hypoxemic, long-term supplemental oxygen therapy may be required. Opportunities for prevention of future exacerbations should be

reviewed before discharge, with particular attention to smoking cessation, current vaccination (influenza, pneumococcal vaccines), knowledge of current therapy including inhaler technique, and how to recognize symptoms of exacerbations.

Pharmacotherapy known to reduce the number of exacerbations and hospitalizations and delay the time of first/next hospitalization, such as long-acting inhaled bronchodilators, inhaled glucocorticosteroids, and combination inhalers, should be specifically considered. Early outpatient pulmonary rehabilitation after hospitalization for a COPD exacerbation is safe and results in clinically significant improvements in exercise capacity and health status at 3 months. Social problems should be discussed and principal caregivers identified if the patient has a significant persisting disability.

Discharge Criteria for Patients with Exacerbations of COPD (Figure 5.4-11 in the original guideline document)

- Inhaled $beta_2$-agonst therapy is required no more frequently than every 4 hours.
- Patient, if previously ambulatory, is able to walk across room.
- Patient is able to eat and sleep without frequent awakening by dyspnea.
- Patient has been clinically stable for 12 to 24 hours.
- Arterial blood gases have been stable for 12 to 24 hours.
- Patient (or home caregiver) fully understands correct use of medications.
- Follow-up and home care arrangements have been completed (e.g., visiting nurse, oxygen delivery, meal provisions).
- Patient, family, and physician are confident patient can manage successfully at home.

Items to Assess at Follow-Up Visit 4 to 6 Weeks After Discharge from Hospital for Exacerbations of COPD (Figure 5.4-12 in the original guideline document)

- Ability to cope in usual environment
- Measurement of FEV_1
- Reassessment of inhaler technique
- Understanding of recommended treatment regimen
- Need for long-term oxygen therapy and/or home nebulizer (for patients with *Stage IV: Very Severe* COPD)

NCCCC/NICE (2004)	**Monitoring Recovery from an Exacerbation** **D** - Patient's recovery should be monitored by regular clinical assessment of their symptoms and observation of their functional capacity. **D** - Pulse oximetry should be used to monitor the recovery of patients with nonhypercapnic, nonacidotic respiratory failure. **D** - Intermittent arterial blood gas measurements should be used to monitor the recovery of patients with respiratory failure who are hypercapnic or acidotic, until they are stable. **D** - Daily monitoring of PEF or FEV_1 should not be performed routinely to monitor recovery from an exacerbation because the magnitude of changes is small compared with the variability of the measurement. **Discharge Planning** **D** - Spirometry should be measured in all patients before discharge. **D** - Patients should be re-established on their optimal maintenance bronchodilator therapy before discharge. **D** - Patients who have had an episode of respiratory failure should have satisfactory oximetry or arterial blood gas results before discharge. **D** - All aspects of the routine care that patients receive (including appropriateness and risk of side effects) should be assessed before discharge. **D** - Patients (or home carers) should be given appropriate information to enable them to fully understand the correct use of medications, including oxygen, before discharge. **D** - Arrangements for follow-up and home care (such as visiting nurse, oxygen delivery, referral for other support) should be made before discharge. **D** - Before the patient is discharged, the patient, family, and physician should be confident that he or she can manage successfully. When there is remaining doubt a formal activities of daily living assessment may be helpful.
SMOH (2006)	No recommendations offered.

TABLE 4: BENEFITS AND HARMS	
Benefits	
FMS (2007)	Appropriate management and treatment of COPD may help relieve patient symptoms, improve exercise capacity, improve lung function, reduce morbidity and mortality, improve quality of life, and reduce frequency and severity of exacerbations.

GOLD (2007)	**Overall**
	• COPD prevention
	• The goals of effective COPD management are to:
	  • Prevent disease progression
	  • Relieve symptoms
	  • Improve exercise tolerance
	  • Improve health status
	  • Prevent and treat complications
	  • Prevent and treat exacerbations
	  • Reduce mortality

NCCCC/NICE (2004)	• If adopted, these guideline recommendations should lead to better standards of care and thus better outcomes from chronic obstructive pulmonary disease. • The frequency of exacerbations should be reduced by appropriate use of inhaled corticosteroids and bronchodilators and vaccinations.
SMOH (2006)	Appropriate diagnosis and management of patients with COPD
Harms	
FMS (2007)	Not stated
GOLD (2007)	**Arterial Blood Gas Measurement**: Adequate pressure must be applied at the arterial puncture site for at least one minute, as failure to do so can lead to painful bruising. **Beta$_2$-agonists**: Stimulation of beta$_2$-receptors can produce resting sinus tachycardia and has the potential to precipitate cardiac rhythm disturbances in very susceptible patients, although this appears to be a remarkably rare event with inhaled therapy. Exaggerated somatic tremor is troublesome in some

older patients treated with higher doses of $beta_2$-agonists, whatever the route of administration, and this limits the dose that can be tolerated. Although hypokalemia can occur, especially when treatment is combined with thiazide diuretics, and oxygen consumption can be increased under resting conditions, these metabolic effects show tachyphylaxis unlike the bronchodilator actions. Mild falls in PaO_2 occur after administration of both short- and long-acting $beta_2$-agonists, but the clinical significance of these changes is doubtful. Despite the concerns raised some years ago, further detailed study has found no association between $beta_2$-agonist use and an accelerated loss of lung function or increased mortality in COPD.

Anticholinergics: Anticholinergic drugs are poorly absorbed, which limits the troublesome systemic effects seen with atropine. Extensive use of this class of inhaled agents in a wide range of doses and clinical settings has shown them to be very safe. The main side effect is dryness of the mouth. Twenty-one days of inhaled tiotropium, 18 micrograms a day as a dry powder, does not retard mucus clearance from the lungs. Although occasional prostatic symptoms have been reported, there are no data to prove a true causal relationship. A bitter, metallic taste is reported by some patients using ipratropium. An unexpected small increase in cardiovascular events in COPD patients regularly treated with ipratropium bromide has been reported and requires further investigation.

Use of wet nebulizer solutions with a face mask has been reported to precipitate acute glaucoma, probably by a direct effect of the solution on the eye. Mucociliary clearance is unaffected by theses drugs, and respiratory infection rates are not increased.

Methylxanthines: Toxicity is dose related, a particular problem with the xanthine derivatives because their therapeutic ratio is small and most of the benefit occurs only when near-toxic doses are given. Methylxanthines are nonspecific inhibitors of all phosphodiesterase enzyme subsets, which explains their wide range of toxic effects. Problems include the development of atrial and ventricular arrhythmias (which can prove fatal) and grand mal convulsions (which can occur irrespective of prior epileptic history). More common and less dramatic side effects include headaches, insomnia, nausea, and heartburn, and these may occur within the therapeutic range of serum theophylline. Unlike the other bronchodilator classes, xanthine derivatives may involve a risk of overdose (either intentional or accidental).

Oral Glucocorticosteroids: A side effect of long-term treatment with systemic glucocorticosteroids is steroid myopathy, which contributes to muscle weakness, decreased functionality, and respiratory failure in subjects with advanced

	COPD. **Narcotics (morphine)**: Some clinical studies suggest that morphine used to control dyspnea may have serious adverse effects and its benefits may be limited to a few sensitive subjects. **Lung Transplantation**: The common complications seen in COPD patients after lung transplantation, apart from operative mortality, are acute rejection and bronchiolitis obliterans, cytomegalovirus (CMV), other opportunistic fungal (Candida, Aspergillus, Cryptococcus, Carinii) or bacterial (Pseudomonas, Staphylococcus species) infections, lymphoproliferative disease, and lymphomas. **Invasive Mechanical Ventilation**: Major hazards include the risk of ventilator-acquired pneumonia (especially when multi-resistant organisms are prevalent), barotrauma, and failure to wean to spontaneous ventilation.
NCCCC/NICE (2004)	• Particular caution needs to be taken with the use of theophylline in elderly patients because of differences in pharmacokinetics, the increased likelihood of comorbidities, and the use of other medications. • Clinicians should be aware of the potential risk of developing osteoporosis and other side effects in patients treated with high-dose inhaled corticosteroids (especially in the presence of other risk factors) and should discuss the risk with patients. • Patients should be warned about the risks of fire and explosion if they continue to smoke when prescribed oxygen. • The technology appraisal also notes that zanamivir should be used with caution in people with COPD because of risk of bronchospasm. If people with COPD are prescribed zanamivir they should be made aware of the risks and have a fast-acting bronchodilator available. • Care should be taken when using intravenous theophylline because of interactions with other drugs and potential toxicity if the patient has been on oral theophylline.
SMOH (2006)	• Side effects of medication • Complications related to surgery • Risk of fire and explosion when using oxygen therapy. Patients requiring oxygen therapy should be advised against smoking cigarettes.

TABLE 5: EVIDENCE RATING SCHEMES AND REFERENCES	
FMS (2007)	**Classification of the Quality of Evidence** A. **Quality of Evidence: High** • Further research is very unlikely to change our confidence in the estimate of effect. • Several high-quality studies with consistent results • In special cases: one large, high-quality multi-centre trial B. **Quality of Evidence: Moderate**. • Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. • One high-quality study • Several studies with some limitations C. **Quality of Evidence: Low**. • Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. • One or more studies with severe limitations D. **Quality of Evidence: Very Low**. • Any estimate of effect is very uncertain. • Expert opinion • No direct research evidence • One or more studies with very severe limitations
GOLD (2007)	**Levels of Evidence** A. Randomized controlled trials. Rich body of data. *Definition:* Evidence is from endpoints of well-designed randomized controlled trials that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants. B. Randomized controlled trials. Limited data. *Definition:* Evidence is from endpoints of intervention studies that include only a limited number of patients, posthoc or subgroup analysis of randomized controlled trials, or meta-analysis of randomized controlled trials. In general, Category B pertains when few randomized trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat

	inconsistent. C. Nonrandomized trials. Observational studies. *Definition:* Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies. D. Panel consensus. Judgment. *Definition:* This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was deemed insufficient to justify placement in one of the other categories. The Panel Consensus is based on clinical experience or knowledge that does not meet the above-listed criteria.
NCCCC/NICE (2004)	**Levels of Evidence** **Ia**: Evidence from systematic reviews or meta-analysis of randomised controlled trials **Ib**: Evidence from at least one randomised controlled trial **IIa**: Evidence from at least one controlled study without randomisation **IIb**: Evidence from at least one other type of quasi-experimental study **III**: Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies **IV**: Evidence from expert committee reports or opinions and/or clinical experience of respected authorities **NICE**: Evidence from NICE guidelines or Health Technology Appraisal Programme **HSC**: Evidence from Health Service Circulars **Grading of Recommendations** **Grade A**: Based on hierarchy I evidence **Grade B**: Based on hierarchy II evidence or extrapolated from hierarchy I evidence **Grade C**: Based on hierarchy III evidence or extrapolated from hierarchy I or II evidence

	Grade D: Directly based on hierarchy IV evidence or extrapolated from hierarchy I, II, or III evidence
SMOH (2006)	**Grades of Recommendations** **Grade A**: At least one meta-analysis, systematic review of randomized controlled trials (RCTs), or RCT rated as 1+ + and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results **Grade B**: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1+ + or 1+ **Grade C**: A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2+ + **Grade D**: Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+ **GPP (good practice points)**: Recommended best practice based on the clinical experience of the guideline development group. **Levels of Evidence** **Level 1++**: High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias. **Level 1+**: Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias. **Level 1-**: Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias **Level 2++**: High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability

	that the relationship is causal **Level 2+**: Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal **Level 2-**: Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal **Level 3**: Non-analytic studies (e.g. case reports, case series) **Level 4**: Expert opinion

GUIDELINE CONTENT COMPARISON

The Finnish Medical Society Duodecim (FMS), the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (a collaborative project of the World Health Organization and the National Heart, Lung, and Blood Institute), the National Collaborating Centre for Chronic Conditions (a collaborating center for the National Institute for Health and Clinical Excellence [NCCCC/NICE]), and the Singapore Ministry of Health (SMOH) present recommendations for management of acute exacerbations of COPD and provide explicit reasoning behind their judgments. All four guidelines identify the type of supporting evidence for selected recommendations.

The scope and format of the guidelines vary somewhat. All four guidelines address both management of stable COPD and acute exacerbation.

The GOLD guideline, however, differs from the other guidelines in its global perspective and in its emphasis on prevention strategies. This guideline presents a COPD management plan with four components: (1) assessment and monitoring of disease, (2) reduction of risk factors, (3) management of stable COPD, and (4) management of exacerbations.

The NCCCC/NICE guideline, like the GOLD guideline, is broad in scope, extensively covering the diagnosis and management of both chronic and acute exacerbation of COPD. This guideline also includes discussion of the evidence (and recommendations) related to the use of respiratory stimulants and respiratory physiotherapy for exacerbations of COPD.

The GOLD, NCCCC/NICE, and SMOH guidelines differ from the FMS guideline by including recommendations for pulmonary rehabilitation which is addressed in Part III of this synthesis (currently under development). The FMS and GOLD guidelines are updates of previous versions. In developing their guidelines both GOLD and SMOH reviewed the 2004 NCCCC/NICE guideline; SMOH also reviewed the 2005 version of the GOLD guideline.

Areas of Agreement

Signs and Symptoms of Acute Exacerbation

Although there is some difference among the guidelines in the specific symptoms noted for acute exacerbation of COPD, all groups recognize worsening dyspnea, increase in sputum purulence, and increase in sputum volume as cardinal symptoms of acute exacerbation.

Diagnostic Testing

Chest X-ray and ECG

GOLD, NCCCC/NICE, and SMOH recommend chest x-ray in the initial evaluation of patients with suspected acute exacerbation. Both GOLD and NCCCC/NICE also recommend ECG. FMS does not address initial evaluation or diagnostic testing.

Measurement of Arterial Blood Gases

GOLD, NCCCC/NICE and SMOH agree that pulse oximetry can be a beneficial diagnostic test to perform, with GOLD and NCCCC/NICE also recommending arterial blood gas analysis to assess severity of acute exacerbations and to gauge the need for oxygen therapy or ventilatory support. FMS does not offer recommendations.

Indications for Hospital Management

GOLD, NCCCC/NICE and SMOH agree that certain patients require hospitalization and/or even, according to GOLD, admission to ICUs. The specific criteria for hospital admission vary, although generally, they agree that hospitalization is necessary for a marked increase in intensity of symptoms. NCCCC/NICE discusses hospital-at-home and assisted discharge schemes as an alternative way of managing patients with exacerbations of COPD who would otherwise need to be admitted or stay in the hospital.

Pharmacological Management

Bronchodilator Therapy

FMS and GOLD both recommend short-acting $beta_2$ agonists as initial pharmacologic management of acute exacerbations, followed by the addition of an inhaled anticholinergic if a patient fails to respond to initial single-agent therapy. GOLD acknowledges that the evidence for the effectiveness of this combination remains controversial.

SMOH, in contrast, states that both inhaled anticholinergic bronchodilators and inhaled short-acting $beta_2$-agonists are beneficial in the treatment of acute exacerbation of COPD, and that anticholinergic bronchodilators should be considered first because they have fewer and more benign side effects. NCCCC/NICE acknowledges use of short-acting bronchodilators without specifying type.

The guidelines are in general agreement that methylxanthines (theophylline, aminophylline) cannot be routinely recommended in patients with acute exacerbation of COPD because of their adverse effects. All of the guidelines note, however, that they may be used as an adjunct to other therapies when response to other treatments is poor. Monitoring of serum theophylline levels is recommended if clinicians choose to use these agents.

Corticosteroids

GOLD, NCCCC/NICE and SMOH agree that systemic corticosteroids are beneficial in both hospitalized as well as home managed patients with acute exacerbation. FMS is in agreement regarding the effectiveness of corticosteroids, but does not directly specify if its recommendations apply to hospitalized patients or outpatients. All four groups recommend a course of 30-40mg daily of oral prednisolone for the treatment of acute exacerbations, but for different durations: 7 to 10 days (GOLD), 7 to 14 days (FMS, NCCCC/NICE, and SMOH).

Antibiotics

There is general agreement among all four guidelines that antibiotics are beneficial in patients with at least two of the three cardinal symptoms of severe exacerbation (i.e., those with increased dyspnea, increased sputum volume, and sputum purulence). Benefits of antibiotics are less clear in patients without severe exacerbation. FMS states that antimicrobial treatment in exacerbation of COPD is controversial; however, when antibiotics are deemed necessary, they recommend amoxicillin, doxycycline, or sulpha-trimethoprim. GOLD states that the choice of antibiotic should be based on the severity of the exacerbation, which is an important determinant of the type of microorganism present. In general, GOLD recommends oral treatment with beta-lactams (penicillin; ampicillin/amoxicillin), tetracycline, or trimethoprim/sulfamethoxazole for mild exacerbations with no risk factors for poor outcomes; beta-lactam/beta-lactamase inhibitor for moderate exacerbation with risk factor(s) for poor outcome, and fluoroquinolones (ciprofloxacin, levofloxacin - high dose) for severe exacerbation with risk factors for *P. aeruginosa* infection. GOLD provides additional recommendations for alternative oral regimens (particularly for areas with high incidence of *S. pneumoniae* resistant to penicillin) and parental treatment. NCCCC/NICE recommends initial empirical treatment with an aminopenicillin, a macrolide, or a tetracycline. In addition, NCCCC/NICE cautions that when initiating empirical antibiotic treatment, prescribers should always take account of any guidance issued by their local microbiologists. When sputum has been sent for culture, the appropriateness of antibiotic treatment should be checked against laboratory culture and sensitivities when they become available.

Non-Pharmacologic Treatment

Oxygen Therapy

The guidelines are unanimous in their recommendations for oxygen therapy in all patients with acute exacerbation and hypoxemia. They also recommend blood gas monitoring to guard against hypercarbia and subsequent respiratory failure.

Mechanical Ventilation

All of the guidelines agree that noninvasive mechanical ventilation is a beneficial therapeutic option for patients with severe exacerbations to prevent respiratory failure. Use of noninvasive methods can reduce the need for intubation. GOLD also provides explicit indications for the use of invasive mechanical ventilation.

Hospital Discharge and Follow-Up

Discharge Criteria

GOLD and NCCCC/NICE are in general agreement on the discharge criteria for patients with acute exacerbation of COPD. These include stability of the patient's condition, need for bronchodilators not more frequent than every 4 hours or the re-establishment of optimal maintenance bronchodilator therapy before discharge, and follow-up and home care arrangements completed. FMS and SMOH do not offer any recommendations regarding discharge criteria for patients with acute exacerbation of COPD.

Areas of Differences

Bronchodilator Therapy

FMS and GOLD both recommend short-acting beta$_2$ agonists as initial pharmacologic management of acute exacerbations, followed by the addition of an inhaled anticholinergic if a patient fails to respond to initial single-agent therapy. GOLD acknowledges that the evidence for the effectiveness of this combination remains controversial. SMOH, in contrast, states that both inhaled anticholinergic bronchodilators and inhaled short-acting beta$_2$-agonists are beneficial in the treatment of acute exacerbation of COPD, and that anticholinergic bronchodilators should be considered first because they have fewer and more benign side effects. NCCCC/NICE acknowledges use of short-acting bronchodilators without specifying type.

This Synthesis was prepared by ECRI on October 8, 2001. It was reviewed by the guideline developers as of November 15, 2001. It was updated to include NCCCC/NICE and FMS and updated GOLD recommendations on March 24, 2005. The information was verified by NICE on May 3, 2005. This Synthesis was updated on October 20, 2005 to reflect updated GOLD guidelines. This synthesis was updated on April 19, 2006 to reflect revised FMS guidelines. This synthesis was updated on December 18, 2006 to withdraw guidelines from ACP/ACCP which were archived due to their age. This synthesis was updated most recently on June 3, 2008 to update GOLD recommendations.

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