MINISTRY OF HEALTH
SINGAPORE

Chronic Obstructive Pulmonary Disease

MOH Clinical Practice Guidelines 2/2017

Chapter of Family Medicine Physicians
Academy of Medicine,
Singapore

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Singapore

Chronic Obstructive Pulmonary
Disease Association,
Singapore

SINGAPORE THORACIC SOCIETY

December 2017

Levels of evidence and grades of recommendation

Levels of evidence

Level	Type of Evidence
1^{++}	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1^{+}	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
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
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
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendation

Grade	Recommendation
A	At least one meta-analysis, systematic review of 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
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^{+}
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^{++}
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.

CLINICAL PRACTICE GUIDELINES

Chronic obstructive pulmonary disease

MOH Clinical Practice Guidelines 2/2017

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Statement of Intent

These guidelines are intended to guide clinical practice and is based on the best available evidence at the time of development. Clinical practice might change depending on current evidence from science and the way care is delivered. As such, there can be other acceptable methods of care not covered in these guidelines. A specific individual case with clinical data that differ sufficiently from the general population might require medical care deviating from recommendations in these guidelines.

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Foreword

According to the WHO, Chronic Obstructive Pulmonary Disease (COPD) has remained the third leading cause of death globally between 2000 and 2012, killing over 3 million people a year. COPD is becoming particularly challenging in developing countries where the number of people smoking is increasing and the effect of household and industrial pollutants is most felt.

In Singapore, COPD is currently the 10th leading cause of death in 2014. COPD is unfortunately under-diagnosed nationally with an estimate of only 2% of diagnosed patients having had a COPD diagnosis based on airflow limitation. Improving diagnosis rates is something which needs to be addressed.

Like other chronic diseases, Singapore's clinicians need to offer a strong response against this disease based on prevention, early diagnosis and aggressive initial treatment. The impact of COPD on a patient's life can be significantly improved when appropriate care and treatment is given from the outset.

In recent years there has been a lot of work undertaken nationally regarding improving the prognosis of people with COPD in Singapore. At the national level, the launch of the Integrated Care Pathway (MOH) for COPD as well as The Airways Programme (NHG) are two examples. However ensuring that basic clinical standards are met will be key to winning the battle against COPD nationally.

These guidelines should provide clinicians with the latest best practice information regarding how to manage COPD across both primary and secondary care. A range of international literature has been reviewed by the workgroup to develop these guidelines. Clinical colleagues will particularly welcome the extensive sections on pharmacological and non-pharmacological treatment as well as a brand new section on palliative care.

I am sure these updated guidelines will assist doctors and other clinicians in improving the management of patients with COPD.

A/PROF BENJAMIN ONG
DIRECTOR OF MEDICAL SERVICES

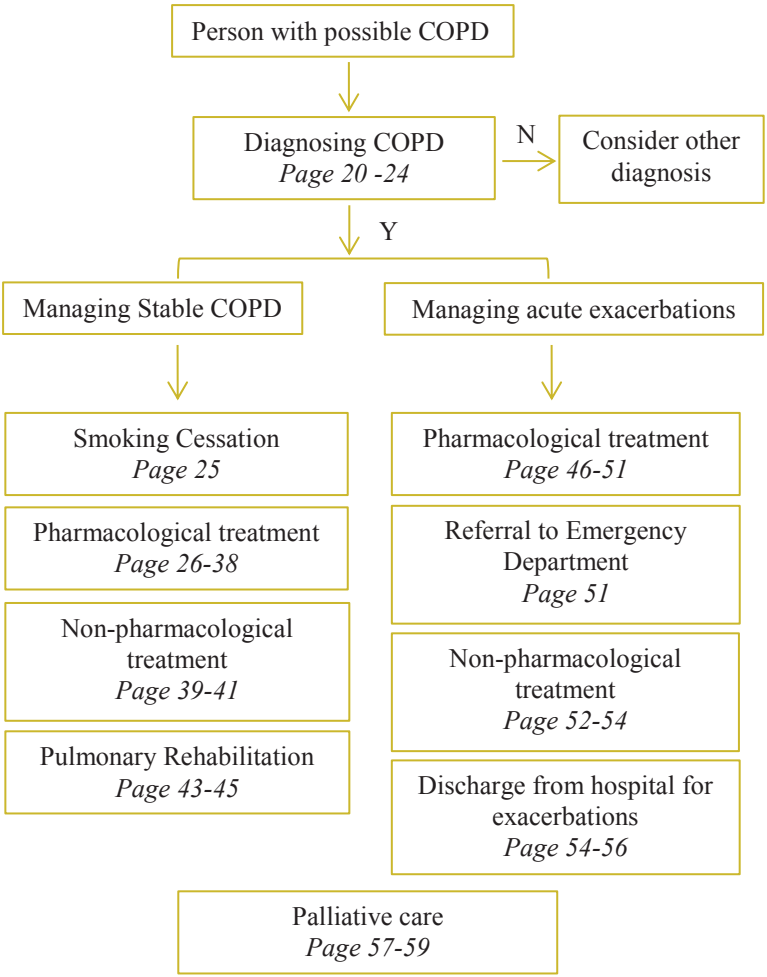
Commonly used abbreviations

The following is a list of abbreviations commonly used in this set of guidelines (arranged in alphabetical order), and a description of what they represent:

- CAT — COPD Assessment Test
- COPD — Chronic Obstructive Pulmonary Disease
- PEF — Peak Expiratory Flow
- FEV_1 — Forced Expiratory Volume in 1 second
- ΔFEV_1 — Change in FEV_1 (difference between post-bronchodilator and pre-bronchodilator FEV_1)
- FEV_1/FVC — Forced Expiratory Ratio
- FVC — Forced Vital Capacity (Volume of lungs from full inspiration to forced maximal expiration)
- GOLD — Global Initiative for Chronic Obstructive Lung Disease
- ICS — Inhaled Corticosteroid
- LABA — Long-Acting $Beta_2$ Agonist
- LAMA — Long-Acting Muscarinic receptor Antagonist
- PaO_2 — Partial pressure arterial oxygen
- SABA — Short-Acting $Beta_2$ Agonist
- SAMA — Short-Acting Muscarinic receptor Antagonist

Executive summary of recommendations

Figure 1 Flowchart illustrating the possible treatment algorithm for a suspected case of COPD



Details of recommendations can be found in the main text at the pages indicated. Key recommendations are highlighted in yellow.

3. Assessment and monitoring

No.	Recommendation	Grade, Level of Evidence	CPG page no.
	Considering a diagnosis of COPD		
1	Patients who are older than 40 years of age and who are current or ex-smokers should undertake spirometry if they answer yes to any one of the following questions: • Do you cough regularly? • Do you cough up phlegm regularly? • Do even simple chores or light exertion make you short of breath? • Do you wheeze when you exert yourself, or at night? • Do you get frequent "colds" that persist longer than those of other people you know?	GPP	20
	Utility of spirometry		
2	All patients who are suspected to have COPD based on symptoms must be evaluated by spirometry.	Grade D, Level 4	20
	Clinical assessment		
3	The exacerbation history is crucial to the proper classification of COPD patients, and hence should be carefully elucidated.	GPP	21

No.	Recommendation	Grade, Level of Evidence	CPG page no.
	Symptom quantification		
4	COPD symptoms should be quantified using the COPD Assessment Test (CAT) score upon diagnosis and repeated every 3 to 6 months during follow-up.	Grade D, Level 4	21
	Combined assessment of COPD		
5	COPD patients should be classified into Group A, B, C and D using the combined COPD assessment framework in accordance with GOLD 2017 guidelines.	Grade D, Level 4	22
	Assessment of comorbidities		
6	Assessment of co-morbidities should be performed for patients diagnosed with COPD.	GPP	23
	Role of chest x-ray		
7	A chest x-ray should be done when a diagnosis of COPD is suspected.	Grade D, Level 4	23
	Monitoring of COPD patients		
8	COPD patients should be followed up every 3 to 6 months. The CAT score should be used at each visit to track symptoms related to COPD. Routine yearly chest x-rays are not required.	GPP	24

4. Smoking cessation

No.	Recommendation	Grade, Level of Evidence	CPG page no.
9	Smoking cessation is a vital intervention in COPD which will preserve lung function and improve survival. It is recommended for all patients with COPD.	Grade A, Level 1+	25

5. Pharmacological treatment

No.	Recommendation	Grade, Level of Evidence	CPG page no.
	Bronchodilators		
10	Short-acting bronchodilators are prescribed on an as-needed basis and should be the initial empirical treatment for the relief of breathlessness and exercise limitation.	Grade A, Level 1+	27
11	Patients with persistent breathlessness (GOLD Group B) should receive a LABA or a LAMA. If a LAMA is started, SAMA (including nebulisations) should be stopped. Patients with persistent breathlessness should be escalated to a LABA/LAMA combination.	Grade A, Level 1+	31
12	Patients with minimal symptoms but frequent exacerbations (GOLD Group C) should receive a LAMA as first line treatment. If further exacerbations occur, treatment should preferably be escalated to a LAMA/LABA combination; a LABA/ICS combination can also be used. Patients with persistent symptoms and frequent exacerbations (GOLD Group D) should be started first on a LABA/LAMA combination.	Grade A, Level 1+	31

No.	Recommendation	Grade, Level of Evidence	CPG page no.
	Steroids		
13	Addition of ICS to standard therapy should be considered for patients with moderate to severe COPD (GOLD Group C and D) with frequent exacerbations. The expected benefit of reduction in exacerbations should be balanced against risk of pneumonia. Standalone ICS is not recommended for COPD patients.	Grade A, Level 1+	32
14	For patients with frequent exacerbations (2 or more per year) and persistent breathlessness with $FEV_1 < 50\%$ of predicted (GOLD Group C and D), the use of combination therapy (LABA/ICS or LABA/LAMA) is recommended.	Grade A, Level 1+	32
15	Combination of ICS and LABA in one inhaler should be considered for patients in whom both ICS and LABA are indicated.	Grade A, Level 1+	33
16	Long-term oral steroids are discouraged in view of unfavourable risk-benefit ratio.	Grade A, Level 1+	33
	Methylxanthines		
17	Low-dose theophylline may be considered in patients with COPD where symptom control is still not achieved with existing inhaled bronchodilator therapy.	Grade D, Level 4	35
	Roflumilast		
18	Addition of roflumilast to inhaled bronchodilator therapy may provide benefits in reducing exacerbations in patients with FEV1 < 50% and chronic bronchitis who have recurrent exacerbations despite triple inhaler therapy. However, this must be weighed in the context of increased risk of adverse events.	Grade B, Level 1-	36

No.	Recommendation	Grade, Level of Evidence	CPG page no.
	Long-term macrolides		
19	Long-term macrolide treatment (6-12 months) may be considered in a select group of patients who have multiple exacerbations which are refractory to standard therapy. There is insufficient data to recommend routine use of macrolides in the treatment of COPD.	Grade B, Level 1+	36
	Mucolytics		
20	Mucolytic drug therapy should be considered in patients with a chronic cough productive of sputum, and should be continued if there is symptomatic improvement.	Grade B, Level 1+	37

6. Non-pharmacological treatment

No.	Recommendation	Grade, Level of Evidence	CPG page no.
	Long term oxygen therapy		
21	Long term oxygen therapy is indicated in patients with severe COPD who are in chronic respiratory failure [blood oxygen saturation (SpO_2) $\leqslant$ 88%].	Grade A, Level 1+	39
	Surgical treatments		
22	Lung Volume Reduction Surgery is indicated in selected patients with upper lobe emphysema and poor exercise capacity after rehabilitation.	Grade A, Level 1+	39
23	Bullectomy may be beneficial in selected COPD patients with bullae occupying more than one-third of the hemithorax.	Grade D, Level 3	40

No.	Recommendation	Grade, Level of Evidence	CPG page no.
	Bronchoscopic lung volume reduction		
24	Bronchoscopic lung volume reduction treatment may have a role only in carefully selected COPD patients.	Grade A, Level 1+	40
	Lung transplantation		
25	Lung transplantation may be indicated in selected patients with advanced COPD.	Grade D, Level 3	40
	Vaccinations in COPD		
26	COPD patients should be offered annual vaccination with the seasonal inactivated influenza vaccine.	Grade A, Level 1+	41
	Pneumococcal vaccination		
27	Pneumococcal vaccination should be considered in COPD patients.	Grade C, Level 2+	41

7. Community care, co-morbidities and rehabilitation

No.	Recommendation	Grade, Level of Evidence	CPG page no.
	Screening in the community		
28	All patients ≥ 40 years of age with a history of smoking should be assessed on a yearly basis for symptoms of COPD i.e., dyspnoea, chronic cough or chronic sputum production.	GPP	42
29	Patients with any symptoms of COPD (i.e. dyspnoea, chronic cough or chronic sputum production) should undergo a spirometry to assess for the presence of COPD.	Grade D, Level 4	42
30	Screening spirometry in the general asymptomatic population is not recommended.	Grade D, Level 4	42

No.	Recommendation	Grade, Level of Evidence	CPG page no.
31	Where practicable, General Practitioners should arrange for their patients to undergo spirometry to help in the diagnosis of COPD in the community as a standard practice.	GPP	43
32	Personnel conducting spirometry testing should be trained in the conduct of the test, and be familiar with the machines they are using.	Grade D, Level 4	43
33	Spirometries should be undertaken when patients are clinically stable and free from respiratory tract infections.	Grade D, Level 4	43
	Co-morbidities		
34	All patients with a history of COPD should be screened for cardiovascular risk factors.	Grade D, Level 4	43
	Pulmonary rehabilitation		
35	In-patient pulmonary rehabilitation should be started once the patient is medically stable after acute exacerbation of COPD.	Grade A, Level 1++	45

8. Management of acute exacerbations

No.	Recommendation	Grade, Level of Evidence	CPG page no.
	Management of acute exacerbations		
36	In all patients with an exacerbation referred to hospital, a chest radiograph should be obtained and is useful in excluding alternative diagnoses.	Grade C, Level 2+	47
37	Sending sputum samples for culture in primary care is not recommended.	Grade D, Level 4	47

No.	Recommendation	Grade, Level of Evidence	CPG page no.
38	Measuring arterial blood gas tensions should be considered and the inspired oxygen concentration should be recorded.	Grade B, Level 2++	47
39	Theophylline level should be measured in patients on theophylline therapy at admission to rule out toxicity.	Grade D, Level 4	47
40	Spirometric tests are not recommended during an exacerbation of COPD.	Grade D, Level 4	47
Pharmacological management of an acute exacerbation			
41	Inhaled SABA with or without inhaled SAMA are the preferred bronchodilators for treatment of an exacerbation of COPD.	Grade C, Level 2+	49
42	Both nebulisers and hand-held inhalers can be used to administer inhaled therapy during exacerbations of COPD.	Grade A, Level 1+	49
43	Patients should be changed to hand-held inhalers as soon as their condition has stabilised.	Grade D, Level 4	49
44	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.	Grade A, Level 1+	49
45	Systemic corticosteroids should be used, in conjunction with other therapies, in all patients admitted to hospital with an exacerbation of COPD.	Grade A, Level 1+	50
46	In the absence of significant contraindications, oral corticosteroids should be considered in patients in the community who have an exacerbation with a significant increase in breathlessness which interferes with daily activities.	Grade A, Level 1+	50

No.	Recommendation	Grade, Level of Evidence	CPG page no.
47	For COPD patients with acute exacerbation, prednisolone 30 mg orally should be administered for 5-10 days. There is no added clinical benefit of duration of systemic corticosteroids beyond 14 days.	Grade A, Level 1+	50
48	Antibiotics should be used to treat exacerbations of COPD associated with a history of more purulent sputum.	Grade A, Level 1+	50
49	Antibiotics should be given in exacerbations of COPD if the patient requires mechanical ventilation (invasive or noninvasive).	Grade A, Level 1+	50
50	The length of antibiotic therapy need not exceed 5 days for mild to moderate exacerbations of COPD.	Grade A, Level 1+	51
51	For moderate to severe exacerbations of COPD, a 7 to 10 day course of antibiotics is recommended.	Grade A, Level 1+	51
52	Indications for hospital assessment or admission: • 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 an exacerbation to respond to initial medical management • Presence of serious comorbidities (e.g., heart failure or newly occurring arrhythmias) • Frequent exacerbations • Older age • Insufficient home support	GPP	51

No.	Recommendation	Grade, Level of Evidence	CPG page no.
	Non-pharmacological therapy		
53	For COPD patients with acute exacerbation, controlled oxygen should be given to keep the blood oxygen saturation, SaO_2 within a target saturation of 88 – 92%.	Grade A, Level 1	52
54	Indications for ICU admissions: • Severe dyspnoea that responds inadequately to initial emergency therapy. • Changes in mental status (confusion, lethargy, coma). • Persistent or worsening hypoxaemia (PaO_2< 40 mm Hg) and/or severe worsening respiratory acidosis (pH <7.25) despite supplemental oxygen and non-invasive ventilation. • Need for invasive mechanical ventilation. • Haemodynamically unstable COPD patients who need vasopressors.	Grade D, Level 4	52
55	Non-invasive ventilation should be used as the treatment of choice for persistent hypercapnic ventilatory failure during exacerbations of COPD despite optimal medical therapy.	Grade A, Level 1++	53
56	When patients are started on non-invasive ventilation, there should be a clear plan covering what to do in the event of deterioration and ceilings of therapy should be agreed.	Grade D, Level 4	53
57	Indications for non-invasive mechanical ventilations (at least 1 of the following): • Respiratory acidosis (arterial pH < 7.35 and/or $PaCO_2$ > 45 mm Hg) • Severe dyspnea	Grade A, Level 1++	53

No.	Recommendation	Grade, Level of Evidence	CPG page no.
58	Indications for invasive mechanical ventilations: • Unable to tolerate non-invasive ventilation or non-invasive ventilation failure • Respiratory or cardiac arrest • Respiratory pauses with loss of consciousness or gasping for air • Diminished consciousness, psychomotor agitation inadequately controlled by sedation • Massive aspiration • Persistent inability to remove respiratory secretions • Heart rate < 50/min with loss of alertness • Severe hemodynamic instability without response to fluids and vasoactive drugs • Severe ventricular arrhythmias • Life-threatening hypoxemia in patients unable to tolerate non-invasive ventilation	Grade D, Level 4	54
59	Non-invasive ventilation should be used to facilitate liberation from invasive ventilation in patients recovering from an exacerbation of COPD but who fail spontaneous breathing trials.	Grade A, Level 1+	54
Discharge from hospitalisation for exacerbations			
60	Patients should be re-established on their optimal maintenance bronchodilator therapy before discharge.	Grade D, Level 4	54
61	Patients who have had an episode of respiratory failure should have satisfactory oximetry or arterial blood gas results before discharge. If peripheral saturation is <92% arterial blood gases should be assessed.	Grade D, Level 4	55
62	All aspects of the routine care that patients receive (including appropriateness and risk of side effects) should be assessed before discharge.	Grade D, Level 4	55

No.	Recommendation	Grade, Level of Evidence	CPG page no.
63	Patients (or home carers) should be given appropriate information to enable them to fully understand the correct use of medications, including oxygen, before discharge.	Grade D, Level 4	55
64	Arrangements for follow-up and home care (such as visiting nurse, oxygen delivery, referral for other support) should be made before discharge.	Grade D, Level 4	55
65	Hospital-at-home and assisted-discharge schemes are safe and effective and should be used as an alternative way of caring for patients with exacerbations of COPD who would otherwise need to be admitted or stay in hospital.	Grade A, Level 1+	55

9. Palliative care

No.	Recommendation	Grade, Level of Evidence	CPG page no.
66	Clinicians who care for patients with chronic or advanced respiratory diseases should be trained in, and be capable of providing basic palliative care to prevent and relieve suffering by controlling symptoms.	Grade D, Level 4	57
67	Clinicians should consult with palliative care specialists as appropriate for managing palliative care situations beyond their level of competence.	Grade D, Level 4	57
	Advance care planning		
68	COPD patients with two or more of the following criteria are candidates for end-of-life discussion and advance care planning: • FEV_1 30% or less • Starting on long term oxygen therapy	Grade D, Level 4	58

No.	Recommendation	Grade, Level of Evidence	CPG page no.
	• Repeated admissions for COPD exacerbation • Unintended progressive weight loss or cachexia • Functional decline • Development of significant comorbidities • A positive answer to the 'surprise' question: "Will you be surprised if your patient dies in the next 1 year?" • Lack of additional treatment options		
	Symptom management		
69	Opioids (oral or parenteral) are effective therapy for the management of refractory dyspnea and should be considered on an individual basis.	Grade D, Level 4	59
70	Anxiety and depression accompany dyspnea and should be evaluated and treated accordingly. Benzodiazepines, tricyclic anti-depressants and major tranquilizers may be useful in this context.	Grade D, Level 4	59
71	Oxygen and fans blowing air onto the face can relieve breathlessness.	Grade B, Level 2++	59
72	Fatigue can be improved by self-management education, pulmonary rehabilitation, and mind-body interventions.	Grade A, Level 2++	59

1 Introduction

1.1 Objectives and scope of guideline

These guidelines provide an update on the management of Chronic Obstructive Pulmonary Disease (COPD) in Singapore, and take into account the new evidence which has emerged since the publication of the previous guidelines in 2006.

1.2 Target group

The guidelines are intended for all healthcare professionals who care for patients with COPD. These include physicians, nurses, pharmacists, rehabilitation and respiratory therapists.

1.3 Guideline development

These guidelines have been produced by a committee comprising senior respiratory physicians, general practitioners, polyclinic physicians, pharmacists, physiotherapists and a patient representative, appointed by the Ministry of Health. They were developed using the best available current evidence and expert opinion.

1.4 What is new in the revised guidelines

The following is a list of major revisions or additions to the guidelines:

1. A template for the combined assessment of COPD.
2. A simplified COPD quality of life test: The COPD Assessment Test (CAT) score.
3. Recommendations on pharmacological treatment based on results from recent clinical trials.
4. A chapter on community care and co-morbidities.

1.5 Review of guidelines

Evidence-based clinical practice guidelines are only as current as the evidence that supports them. Users must keep in mind that new evidence could supersede recommendations in these guidelines. The workgroup advises that these guidelines be scheduled for review 5 years after publication, or if new evidence appears that requires substantive changes to the recommendations.

2 Background and epidemiology

2.1 Epidemiology and risk factors

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality world-wide. In Singapore, COPD is currently the tenth leading cause of death in 2014.[1] COPD is under-recognised and under-diagnosed.[2] A study in the USA showed that less than 50% of individuals with COPD based on airflow limitation have a doctor's diagnosis of COPD.[3]

2.1.1 Morbidity

In United States of America (USA), hospitalisation for acute exacerbations of COPD accounts for a large part of the high healthcare expenditure for COPD.[4] Expenditure for inpatient hospitalizations of COPD per patient is more than twice that for other inpatients.[5] In a cross-sectional survey involving 186 patients in Singapore, approximately two-thirds had at least one previous hospital readmission for acutely exacerbated COPD, and half reported two or more previous hospital readmissions, some with 10 to 20 hospital admissions.[6] The mortality rate of COPD patients within one year following hospital discharge was 15%.[7]

2.1.2 Medical co-morbidity

More than three-quarters of hospitalised COPD patients have at least one co-morbid medical condition, such as cardiovascular disease, hypertension, diabetes, osteoporosis, chronic kidney disease, cognitive impairment and depression.[8]

2.1.3 Clinical profile

A local study on COPD inpatients shows that the majority of hospitalised patients were male (83%) and Chinese (81%).[6] Significantly large proportions were divorced, widowed or single (32%), or lived in low end public housing apartments (46% live in 1 to 3 room HDB flats). There were high prevalence of underweight (50% had Body Mass Index (BMI) <18), and depression (45%). The use of psychotropic drugs was particularly high among frequently readmitted patients (13%). Inadequate or

poor caregiver support was common (35% reported no caregiver support at all; only 38% subjects reported fair to good care giver support). Uptake of pulmonary rehabilitation was low at 13%. The large majority (88%) did not receive influenza or pneumococcal vaccination in the past one year. Male sex, longer disease duration (>5 years), poor pulmonary function (FEV_1 < 50% of predicted) and use of psychotropic drugs were associated with frequent readmissions for Acute Exacerbations of COPD (AECOPD).

2.1.4 Population prevalence and risk factors

The Burden of Obstructive Lung Disease (BOLD) studies showed COPD ($FEV_1/FVC < 0.70$) among adults aged 40 and over varied widely among 12 countries ranging from 11.4% to 26.1%.[9, 10] Although the higher prevalence of COPD among smokers than non-smokers is well established by these studies, it is important to note that about 3 to 10% of non-smokers also have COPD, indicating that non-smoking risk factors are also important.[3] An estimated 25% to 45% of individuals with COPD have never smoked.[3] Non-smoker risk factors include the use of biomass fuel, occupational exposure to dusts and gases, history of pulmonary tuberculosis, chronic asthma, respiratory-tract infections during childhood, outdoor air pollution, and poor socioeconomic status.[3] Data from the Singapore Longitudinal Ageing Studies show similar prevalence and pattern of risk factors.[10, 11] The prevalence of COPD shows no gender differences, but is higher among older people, and among smokers. Notably, 24% of the non-smokers in the study also had COPD, highlighting the importance of other non-smoking risk factors such as past occupational exposure and history of asthma.[10, 11]

Table 1 Prevalence of COPD* (FEV_1/FVC <0.70) among 2479 Chinese participants aged 55 and above in the Singapore Longitudinal Ageing Studies.[10, 11]

	COPD %	P value
Overall	26.0	
Male	26.1	
Female	25.9	0.89
Age: 55-64	20.9	
65-74	29.6	
75+	34.8	<0.001
1-3 Room public housing	34.4	
4-5 Room public housing	25.4	
Private and Landed housing	18.6	<0.001
Never Smoker	24.3	
Past Smoker	26.3	
Current Smoker	47.1	<0.001
Past occupational exposure to dust, fumes or gases:		
No	25.4	
Yes	37.7	0.002
History of asthma:		
No	25.1	
Yes	52.6	<0.001

*Data in the table was extracted from re-analysis of the data from the cited reference.

3 Assessment and monitoring

3.1 Considering a diagnosis of COPD

The characteristic symptoms of COPD are persistent and progressive exertional dyspnoea, cough, sputum production, wheezing and chest tightness that can vary from day-to-day. There should be a positive history of exposure to risk factors of tobacco smoke, smoke from home cooking and occupational dusts.

GPP Patients who are older than 40 years of age and who are current or ex-smokers should undertake spirometry if they answer yes to any one of the following questions:

1. Do you cough regularly?
2. Do you cough up phlegm regularly?
3. Do even simple chores or light exertion make you short of breath?
4. Do you wheeze when you exert yourself, or at night?
5. Do you get frequent "colds" that persist longer than those of other people you know?

GPP

3.2 Utility of spirometry

KEY RECOMMENDATION

D All patients who are suspected to have COPD based on symptoms must be evaluated by spirometry.[12]

Grade D, Level 4

Patients who are suspected to be suffering from COPD should undertake spirometry. A pre-bronchodilator FEV_1 should be measured, and the ΔFEV_1 (Difference between post-bronchodilator FEV_1 and pre-bronchodilator FEV_1) computed. A ΔFEV_1 of > 200ml is suggestive of asthma instead of COPD, and the patient should be managed in accordance to asthma guidelines.

The presence of a post-bronchodilator FEV_1/FVC ratio < 0.7 confirms the presence of expiratory airflow limitation. Such a result combined with the presence of characteristic symptoms and

positive risk factor exposure makes the diagnosis of COPD highly likely. Therefore, a FEV_1/FVC ratio < 0.7 and a ΔFEV_1 < 200ml after bronchodilators treatment, demonstrates expiratory airflow limitation and hence is highly suggestive of COPD. Peak expiratory flow (PEF) measurement alone cannot be reliably used as the only diagnostic test, because of its weak specificity.

3.3 Clinical assessment

Clinical assessment of the COPD patient involves a thorough history and physical examination. Occupational or environmental exposures to cigarette smoke and other lung irritants should be recorded. Symptoms and signs related to COPD, complications e.g. leg oedema in cor pulmonale, and comorbidities should be identified. Inquiry concerning frequent and severity of exacerbations is crucial to management

GPP The exacerbation history is crucial to the proper classification of COPD patients, and hence should be carefully elucidated.

GPP

3.4 Symptom quantification

Symptoms of COPD can be quantified using a validated structured questionnaire called the COPD Assessment Test (CAT). The CAT score is needed for the proper classification of COPD patients. The CAT instrument* can be found at http://www.catestonline.org/.[13]

D COPD symptoms should be quantified using the COPD Assessment Test (CAT) score upon diagnosis and repeated every 3 to 6 months during follow-up.[12]

Grade D, Level 4

3.5 Combined assessment of COPD

The goals of COPD assessment are to determine disease severity, its impact on the patient's health status and the risk of future events

* Due to copyright restrictions, the CAT instrument cannot be reproduced.

such as exacerbations, hospitalisations or death. This assessment will eventually guide treatment and other therapeutic measures.

A combined approach to COPD assessment considers the following aspects of the disease (Figure 1):

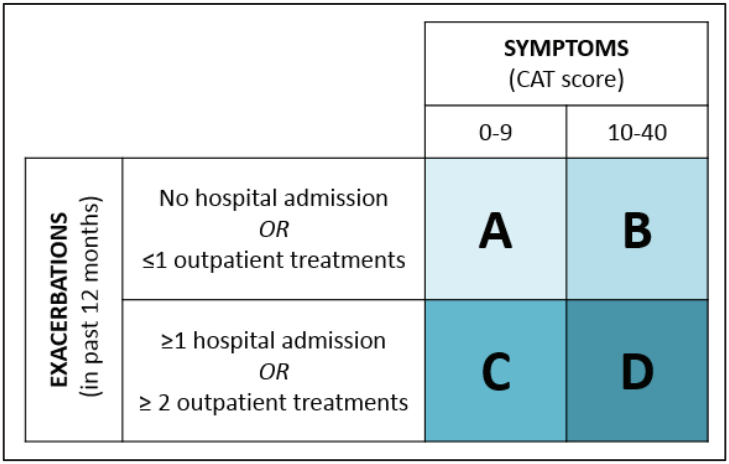
1. Current level of symptoms
2. Degree of FEV_1 reduction
3. Recent exacerbation profile

KEY RECOMMENDATION

D COPD patients should be classified into Group A, B, C and D using the combined COPD assessment framework in accordance with GOLD 2017 guidelines.[12]

Grade D, Level 4

Figure 1 Combined COPD assessment framework: Groups ABCD



3.6 Assessment of comorbidities

Although COPD is a lung disease, it is associated with systemic manifestations and co-morbid conditions. The most common co-

morbidities are ischemic heart disease, diabetes mellitus, skeletal muscle wasting, cachexia, osteoporosis, depression and lung cancer. These co-morbidities affect health outcomes and increase the risks of admission to hospital.

GPP Assessment of co-morbidities should be performed for patients diagnosed with COPD.

GPP

3.7 Role of chest x-ray

Chest x-rays are not diagnostic of COPD but are valuable in assessing comorbidities and excluding conditions, such as lung cancer and pulmonary tuberculosis – symptoms of which are similar to that of COPD.

D A chest x-ray should be done when a diagnosis of COPD is suspected.[12]

Grade D, Level 4

3.8 Assessment of oxygenation

If available, resting pulse oximetry should be performed. If the resting arterial oxygen saturation is less than 90%, an arterial blood gas measurement should be considered to quantify the severity of hypoxemia. COPD patients with a resting $pO_2 < 55$mmHg are likely to benefit from long term oxygen therapy.

3.9 Monitoring of COPD patients

COPD patients should be followed up every 3 to 6 months to assess for control or progression of the disease and comorbid conditions. The CAT score is a useful tool to track symptoms related to COPD. Stability and control of comorbid conditions should be assessed at each visit. If a patient reports acute or progressive worsening of respiratory symptoms, the following possibilities will need to be considered:

1. The patient is experiencing a COPD exacerbation
2. The COPD severity is worsening

3. There is a superimposed acute/sub-acute respiratory condition, e.g. pneumonia, pneumothorax, Pulmonary Tuberculosis (PTB), lung cancer
4. The comorbid conditions, e.g. Ischemic Heart Disease (IHD) and heart failure, are unstable

GPP COPD patients should be followed up every 3 to 6 months. The CAT score should be used at each visit to track symptoms related to COPD. Routine yearly chest x-rays are not required.

GPP

4 Smoking cessation

KEY RECOMMENDATION

A Smoking cessation is a vital intervention in COPD which will preserve lung function and improve survival. It is recommended for all patients with COPD.[14]

Grade A, Level 1+

5 Pharmacological treatment

5.1 Pharmacotherapy for stable COPD

5.1.1 Goals of pharmacotherapy in COPD

The goals of pharmacotherapy in COPD are as follows:
1. Relieve, reduce and abolish symptoms where possible
2. Increase exercise capacity
3. Reduce frequency and severity of acute exacerbations
4. Improve health related quality of life

Published data to date has not been able to conclusively prove any long-term effect on long-term decline in lung function with any of the existing medications, although there is a decrease in exacerbations and improvement in symptoms, quality of life and other parameters.[15] A meta-analysis has suggested that there may be an improvement in mortality with long-acting bronchodilators and/or steroids,[16] although these are post-hoc analyses that remain to be confirmed.

5.1.2 Principles of therapy

The principles of therapy in COPD are as follows:
1. Treatment needs to be maintained long-term.
2. Treatment needs to be tailored according to severity of symptoms, as well as risk of exacerbations, with step-wise increase usually required.
3. Attention should be given to the route of administration, especially via inhalational route.

When treatment is given via inhalational route, choice of device will depend on availability, cost, patient's ability and physician's preference. Attention must be paid to the choice of device, and training in inhaler device technique is essential. Elderly patients may have problems with co-ordination and COPD patients may have difficulty generating enough inspiratory flow rate even for dry powder devices. Use of a spacer with metered dose inhaler devices may overcome co-ordination problems and improve drug delivery.[15, 17] There have been a plethora of newer inhaler devices recently, and close attention should be paid to training patients and

caretakers in the use of the various devices. Table 2 (page 28) shows the inhaler formulations currently available in Singapore.

5.2 Bronchodilators

Recently, there have been a slew of inhalers that have been launched and the plethora of new options can be confusing to practitioners. We have listed as many of those that are currently available in this section. However the list is by no means exhaustive and there are likely to be even more options available in the near future.

In choosing among treatment options for patients, decision making can be guided by choosing the appropriate drug class according to GOLD guidelines, then selecting the most appropriate drug in that class according to inhaler device preference, cost, patient and practitioner preference.

5.2.1 Short-acting bronchodilators

Bronchodilator drugs relax bronchial muscles and relieve bronchospasm and symptoms. All categories of short-acting bronchodilators have been shown to improve post-bronchodilator lung function and dyspnoea scores. However, they do not decrease the rate of FEV_1 decline or improve mortality in COPD patients.[18]

KEY RECOMMENDATION

A Short-acting bronchodilators are prescribed on an as-needed basis and should be the initial empirical treatment for the relief of breathlessness and exercise limitation.[4,19]

Grade A, Level 1+

Table 2 Formulations of COPD medications

Drug	Inhaler	Nebuliser Solution	Oral	Injection	Duration of Action (hours)
Short-acting Beta$_2$-agonists					
Salbutamol	100 mcg per puff 200 mcg per puff (MDI & DPI)	0.5% solution	2 mg tablets 4 mg tablets 2 mg/5mL syrup	5 mg/5mL	4 – 6
Short-acting Muscarinic Receptor Antagonists					
Ipratropium	20 mcg per puff (MDI)	0.025% solution			6 – 8
Combination Short-acting Beta$_2$-agonists & Muscarinic Receptor Antagonists					
Salbutamol / Ipratropium		2.5/0.5 mg per 2.5 mL			6 – 8
Fenoterol / Ipratropium	50/20 mcg per puff (MDI)	0.5/0.25 mg per mL 1.25/0.5 mg per 4 mL			6 – 8
Long-Acting Beta$_2$-Agonist					
Indacaterol	150 mcg per puff 300 mcg per puff (DPI)				24
Olodaterol	2.5 mcg per puff (Respimat)				24
Formoterol	12 mcg per puff (MDI & DPI)				12
Long-Acting Muscarinic Receptor Antagonist					
Aclidinium	322 mcg per puff (DPI)				30
Tiotropium	18 mcg per puff (DPI) 2.5 mcg per puff (Respimat)				24
Glycopyrronium	50 mcg per puff (DPI)				24
Umeclidinium	62.5 mcg per puff (DPI)				24
Combination Long-Acting Beta$_2$-Agonist & Corticosteroids					
Formoterol / Beclomethasone	6/100 mcg per puff (MDI)				12
Formoterol / Budesonide	2.25/40 mcg per puff 2.25/80 mcg per puff 4.5/80 mcg per puff 4.5/160 mcg per puff (Rapihaler) 4.5/80 mcg per puff 4.5/160 mcg per puff 9/320 mcg per puff (DPI)				12
Formoterol / Mometasone	5/50 mcg per puff 5/100 mcg per puff 5/200 mcg per puff (MDI)				12

Drug	Inhaler	Nebuliser Solution	Oral	Injection	Duration of Action (hours)
Formoterol / Fluticasone	5/50 mcg per puff 5/125 mcg per puff 10/250 mcg per puff (MDI)				12
Salmeterol / Fluticasone	25/50 mcg per puff 25/125 mcg per puff 25/250 mcg per puff (MDI) 50/100 mcg per puff 50/250 mcg per puff 50/500 mcg per puff (DPI)				12
Vilanterol / Fluticasone	25/100 mcg per puff 25/200 mcg per puff (DPI)				24
Combination Long-Acting Beta$_2$-Agonist & Long-Acting Muscarinic Receptor Antagonist					
Formoterol/Aclinidium	12/340 mcg per puff (DPI)				30
Indacaterol / glycopyrronium	110/50 mcg per puff (DPI)				24
Vilanterol / Umeclidinium	25/62.5 mcg per puff (DPI)				24
Olodaterol / Tiotropium	2.5/2.5 mcg per puff (Respimat)				24
Inhaled Corticosteroids					
Beclomethasone	50 mcg per puff (MDI) 200 mcg per puff (DPI)				12
Budesonide	100 mcg per puff (DPI) 200 mcg per puff (MDI / DPI)	500 mcg per 2 mL 1mg per 2 mL			12
Fluticasone	50 mcg per puff (MDI & DPI) 100 mcg per puff (DPI) 200 mcg per puff (DPI) 125 mcg per puff (MDI) 250 mcg per puff (MDI & DPI) 500 mcg per puff (DPI)	500 mcg per 2 mL			
Systemic Corticosteroids					
Prednisolone			Tablet: 1 mg, 5 mg, 20 mg		
Methylxanthines					
Theophylline			Tablet: 100 mg, SR 125 mg, 200 mg, SR 250 mg, 300 mg Syrup: 80 mg/15 mL		
Aminophylline				250 mg/10 mL	

5.2.2 Long-acting bronchodilators

5.2.2.1 *Long-acting beta$_2$-agonists (LABA)*

LABAs have duration of action of 12 hours or more. Formoterol and salmeterol, especially in combination with inhaled steroids in the same inhaler, significantly improve FEV_1, lung volumes, dyspnoea, health-related quality of life and exacerbation rate but have no effect on mortality and rate of decline of lung function.[16, 20] LABA appear to be safe for long-term use in COPD.[22]

5.2.2.2 *Long-acting muscarinic receptor antagonist (LAMA)*

The currently available LAMAs are tiotropium, glycopyrronium bromide, aclidinium bromide and umeclidinium.

Tiotropium has been shown to be effective in reducing acute exacerbations, reducing symptoms and improving quality of life compared to placebo and to ipratropium bromide. It also improves the effectiveness of pulmonary rehabilitation.[23]

The UPLIFT trial, a large 4-year landmark clinical trial showed that tiotropium did not significantly reduce the annual rate of decline in FEV_1.[24] In another large trial, tiotropium was shown to be more effective than salmeterol in preventing exacerbations in patients with moderate-to-very-severe COPD.[25]

While spirometric improvements were observed when ipratropium was added in patients receiving tiotropium maintenance therapy, the clinical significance of these improvements had not been documented and the risk of anticholinergic adverse effects was increased with combination therapy.[26] Hence, co-administration of other anticholinergic-containing drugs with LAMAs is best avoided.

5.2.2.3 *Combining use of LAMA and LABA*

KEY RECOMMENDATION

A Patients with persistent breathlessness (GOLD Group B) should receive a LABA or a LAMA.[12, 27] If a LAMA is started, SAMA (including nebulisations) should be stopped.[26] Patients with persistent breathlessness should be escalated to a LABA/LAMA combination.[28]

Grade A, Level 1+

KEY RECOMMENDATION

A Patients with minimal symptoms but frequent exacerbations (GOLD Group C) should receive a LAMA as first line treatment[25]. If further exacerbations occur, treatment should preferably be escalated to a LAMA/LABA combination; a LABA/ICS combination can also be used. Patients with persistent symptoms and frequent exacerbations (GOLD Group D) should be started first on a LABA/LAMA combination[28].

Grade A, Level 1+

Various combinations of LAMA and LABA have been shown to improve lung function and quality of life.[29, 30]

Combination inhalers of LAMA and LABA have also become available, and in studies have been shown to provide improvement in bronchodilation compared to monotherapy.[31-33] A recent study showed that combination indacaterol-glycopyrronium was superior to salmeterol-fluticasone combination inhaler in reducing COPD exacerbations and increased the time to first exacerbation.[28]

5.3 Steroids

5.3.1 Inhaled corticosteroids (ICS)

ICS reduce the rate of exacerbation in COPD patients by 26%, and modestly slow the decline in quality of life in COPD patients. Lung

function tests (as measured by FEV_1) and mortality did not show a consistent response to ICS use.[38]

ICS have similar benefits to LABA for the majority of outcomes including rate of exacerbations and mortality.[39] However, the use of ICS is associated with increased risk of pneumonia compared to LABA. ICS are also associated with increased risk of oral candidiasis and dysphonia. A modest but statistically significant risk of fractures has also been associated with the use of budesonide and fluticasone.[40]

In view of the potential side effects, long-term ICS is recommended for patients with moderate to severe COPD (GOLD Group C and D) with frequent exacerbations only as an add-on to therapy with long-acting bronchodilators (LABA or LABA+LAMA).

Combination of ICS and LABA is more effective than use of either component alone.[15, 41] In patients with indications for both ICS and LABA, combination inhalers are suggested for convenience and compliance.

A Addition of ICS to standard therapy should be considered for patients with moderate to severe COPD (GOLD Group C and D) with frequent exacerbations. The expected benefit of reduction in exacerbations should be balanced against risk of pneumonia.[15, 38-40] Standalone ICS is not recommended for COPD patients.

Grade A, Level 1+

KEY RECOMMENDATION

A For patients with frequent exacerbations (2 or more per year) and persistent breathlessness with $FEV_1 < 50\%$ of predicted (GOLD Group C and D), the use of combination therapy (LABA/ICS or LABA/LAMA) is recommended.[15, 28, 41]

Grade A, Level 1+

A Combination of ICS and LABA in one inhaler should be considered for patients in whom both ICS and LABA are indicated.[15, 41]

Grade A, Level 1+

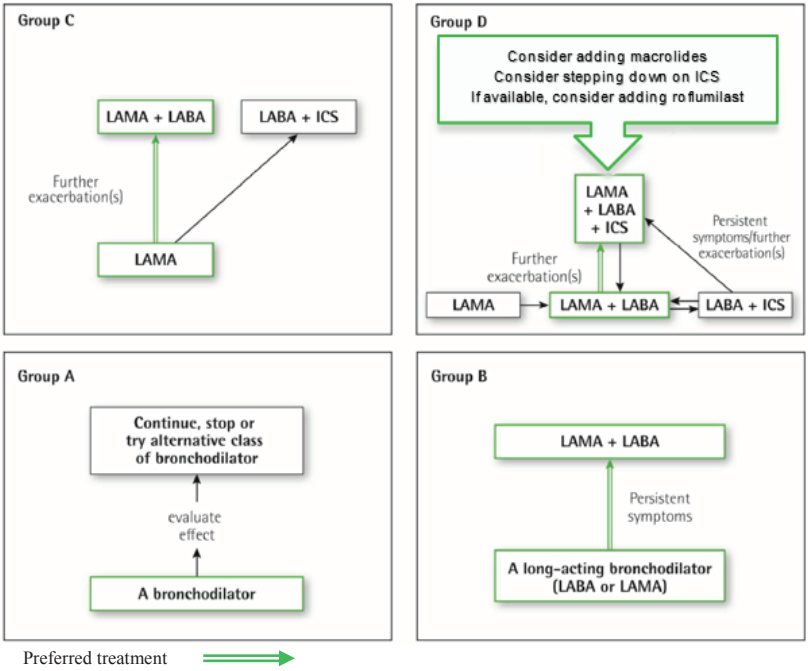
5.3.2 Oral steroids

Although a short course of high dose oral steroid (≥ 30mg/day of prednisolone) can improve lung function in some COPD patients, long-term doses of lower doses (< 10-15mg/day of prednisolone) do not prevent worsening of the condition and are associated with increased risk of adverse effects such as diabetes and osteoporosis.[42] Oral glucocorticoid use for maintenance has been found to be associated with increased mortality, albeit in an observational study.[43]

A Long-term oral steroids are discouraged in view of unfavourable risk-benefit ratio.[42, 43]

Grade A, Level 1+

Figure 2 Suggested algorithm for management and escalation of treatment in COPD (*modified from GOLD 2017 figure 4.1)



5.4 Methylxanthines

5.4.1 Theophylline

Theophylline, a non-selective phosphodiesterase inhibitor, has been used for more than 70 years for the treatment of obstructive airway diseases. In addition to its bronchodilator function, there is increasing evidence that theophylline has anti-inflammatory effects,[44, 45] and the possible benefit that systemic administration may exert on peripheral airways.[45]

Careful monitoring for side effects and drug interactions is needed in view of its narrow therapeutic index. Several brands of theophylline are available commercially, but due to different

release characteristics, it is advisable to stick to one brand. It is also important to be aware of factors which decrease its clearance, including potential drug interactions, and which may precipitate drug toxicity (Table 3). Signs of toxicity include arrhythmias and convulsions.[45]

Table 3 Drugs and physiological variables that affect theophylline metabolism in COPD

Increased clearance	Decreased clearance
1. Cigarette smoking 2. Anticonvulsant drugs 3. Rifampicin 4. Alcohol	1. Old age 2. Hypoxemia 3. Respiratory acidosis 4. Congestive cardiac failure 5. Liver cirrhosis 6. Erythromycin, clarithromycin 7. Quinolones 8. Cimetidine (not ranitidine) 9. Antifungals 10. Fluoxetine, fluvoxamine, sertraline 11. Viral infections 12. Some herbal remedies

D Low-dose theophylline may be considered in patients with COPD where symptom control is still not achieved with existing inhaled bronchodilator therapy.[46]

Grade D, Level 4

5.4.2 Roflumilast

Roflumilast is a selective phosphodiesterase-4 inhibitor which acts by inhibiting the breakdown of intracellular cyclic AMP. It is a once daily oral medication with no direct bronchodilator activity. It is currently not commercially available in Singapore but is mentioned in the GOLD 2017 treatment algorithms.

Roflumilast increases FEV1 modestly from baseline and has been shown to reduce moderate and severe exacerbations requiring oral corticosteroids by 15 – 20% in patients with severe – very severe COPD (GOLD Group D). However, it has no effect on mortality[10].

In the REACT study[47], roflumilast was added to combination ICS/LABA in patients with severe COPD and at least two exacerbations per year. There was a trend towards reduced exacerbations and hospital admissions in the treatment group.

Roflumilast is associated with fairly severe gastrointestinal side effects (nausea, diarrhoea and abdominal pain), headache, and weight loss[10], and psychiatric events such as insomnia, anxiety and depression[48].

Addition of roflumilast may be considered for patients with FEV1 < 50% and chronic bronchitis who have recurrent exacerbations despite triple inhaler therapy.[49] Roflumilast and theophylline should not be given together.

B Addition of roflumilast to inhaled bronchodilator therapy may provide benefits in reducing exacerbations in patients with FEV1 < 50% and chronic bronchitis who have recurrent exacerbations despite triple inhaler therapy. However, this must be weighed in the context of increased risk of adverse events.

Grade B, Level 1-

5.5 Long-term macrolides

Long-term macrolides (e.g. Azithromycin 250mg om or Clarithromycin 250mg om) may decrease COPD exacerbations in a select group of patients.[50, 51] However, effect on overall mortality is uncertain and there are significant side effects (hearing loss, increased QTc) as well as other considerations such as inducing macrolide resistance and masking underlying nontuberculous mycobacterial (NTM) infection.

B Long-term macrolide treatment (6-12 months) may be considered in a select group of patients who have multiple exacerbations which are refractory to standard therapy.[52,53] There is insufficient data to recommend routine use of macrolides in treatment of COPD.

Grade B, Level 1+

5.6 Mucolytics

Mucolytics such as N-acetylcysteine and bromhexine are frequently used in patients to loosen the phlegm for easier expulsion. Several trials in ethnic Chinese patients using carbocisteine and twice-daily N-acetylcysteine showed decrease in exacerbations.[54-56]

B Mucolytic drug therapy should be considered in patients with a chronic cough productive of sputum, and should be continued if there is symptomatic improvement.[57]

Grade B, Level 1+

5.7 Escalation and de-escalation of therapy

In patients who are persistently symptomatic or who have recurrent exacerbations, care should be taken to evaluate compliance, check inhaler technique, and exclude other concomitant pathology and co-morbidity (e.g. a COPD patient may also be suffering from ischaemic heart disease and congestive cardiac failure, or may have lung cancer or tuberculosis). If these are excluded, treatment of the COPD needs to be optimized.

A suggested algorithm for initiation and escalation of pharmacological treatment of stable COPD is presented in Figure 2. The algorithm as presented is straightforward, with the following points where treatment can be confusing:

1. GOLD C patients – the initial recommended treatment is for a single long-acting bronchodilator, and to escalate to a LABA/LAMA combination where patient has further exacerbations. However, an alternative treatment option is to add on an inhaled corticosteroid instead; it has been suggested that patients who have asthma-COPD overlap may be one group to benefit from this approach; some evidence also suggests that patients with higher eosinophil counts might benefit more from ICS although this approach remains to be defined (e.g. the cut-off which would indicate a more favorable response to ICS is not yet known)[58-61].

2. GOLD D patients – initial recommendation is for combination LABA/LAMA. In selected patients LABA/ICS may also be a good alternative (similar to point 1, the exact group is not well understood but may include patients with asthma/COPD overlap, or patients with relatively higher eosinophil counts).

   For patients with recurrent exacerbations despite LABA/LAMA or LABA/ICS, triple therapy with LABA/LAMA/ICS should be tried. If there are recurrent exacerbations in spite of this, consider addition of macrolides in ex-smokers (NB: GOLD guidelines suggest addition of roflumilast, although this drug is not currently registered in Singapore). Consideration can also be given to stepping down on the ICS in these patients given the evidence linking ICS to an increased risk of pneumonia.

3. In group D patients who appear to be well controlled on LAMA/LABA/ICS, one study has suggested that is safe to tail down the ICS component of the therapy to the lowest possible dose of ICS[37].

4. In any category of patients who are not responding as expected to pharmacotherapy, scrupulous attention to inhaler technique should be paid, especially with the many newer inhaler devices on the market. If patient is having difficulty with one device, it may be worthwhile to switch to another similar drug combination with a different inhaler technique.

6 Non-pharmacological treatment

6.1 Long term oxygen therapy (LTOT)

KEY RECOMMENDATION

A Long term oxygen therapy is indicated in patients with severe COPD who are in chronic respiratory failure [blood oxygen saturation (SpO_2) ≤ 88%].[62]

Grade A, Level 1+

Patients must be assessed during stable phase, at rest and on more than one visit. Patients who are not persistently hypoxic do not benefit from LTOT.[62]

LTOT delivers continuous oxygen at home for ≥ 15 hours per day. In appropriate patients LTOT improves quality of life and survival.[62]

6.2 Surgical treatments

6.2.1 Lung volume reduction surgery

Lung volume reduction surgery (LVRS) resects emphysematous lung bilaterally, improves airflow and mechanical efficiency of the diaphragm.[63]

A Lung Volume Reduction Surgery is indicated in selected patients with upper lobe emphysema and poor exercise capacity after rehabilitation.[64]

Grade A, Level 1+

In patients with heterogeneous, predominant upper lobe emphysema, LVRS improves quality of life and survival. By contrast, in patients with homogeneous emphysema and poor lung function, LVRS increases mortality.

6.2.2 Bullectomy for COPD

Bullectomy is a traditional surgical procedure which resects non-functioning emphysematous bulla.

D Bullectomy may be beneficial in selected COPD patients with bullae occupying more than one-third of the hemithorax.[65,66]

Grade D, Level 3

Selected COPD patients with large, non-functioning bulla which compresses adjacent normal lung may benefit from bullectomy.

6.3 Bronchoscopic lung volume reduction (BLVR)

BLVR results in improvements in lung function and symptoms but increases risk of exacerbations and other severe complications.

A Bronchoscopic lung volume reduction treatment may have a role only in carefully selected COPD patients.[67-69]

Grade A, Level 1+

6.4 Lung transplantation

COPD is the most common indication for lung transplantation.[63] A policy of single lung transplant for COPD improves access to organs for other potential recipients without significant reductions in total post-transplant survival.

D Lung transplantation may be indicated in selected patients with advanced COPD.[70]

Grade D, Level 3

6.5 Vaccinations in COPD

6.5.1 Influenza vaccination

Most acute exacerbations of COPD are triggered by community-acquired respiratory tract infections. Influenza is known to cause excess morbidity and mortality in COPD patients. A Cochrane review showed that inactivated influenza vaccine as compared to

placebo resulted in significantly decreased COPD exacerbations due to influenza.[57]

KEY RECOMMENDATION

A COPD patients should be offered annual vaccination with the seasonal inactivated influenza vaccine.[57]

Grade A, Level 1+

6.5.2 Pneumococcal vaccination

A 2013 Cochrane meta-analysis provided evidence to support the recommendation for the use of the pneumococcal polysaccharide vaccines (PPSVs) to prevent invasive pneumococcal disease in adults. There was however no clear evidence as to the effectiveness of this vaccine in preventing pneumonia or deaths in adults with chronic illness.[71] A recent large scale RCT showed the polysaccharide conjugate vaccine (PCV13) to be effective in preventing vaccine-type pneumococcal, bacteremic, and non-bacteremic community-acquired pneumonia and vaccine-type invasive pneumococcal disease in adults older than 65 years.[72]

A single RCT showed reduction in the incidence of community acquired pneumonia in COPD patients younger than 65 years old with presence of severe airflow obstruction.[73]

The US Advisory Committee on Immunization Practices (ACIP) provides guidance as to the recommended intervals for PCV13 and PPSV23 vaccines in adults.[74]

C Pneumococcal vaccination should be considered in COPD patients.[75-78]

Grade C, Level 2+

7 Community care, co-morbidities and rehabilitation

7.1 Preventing COPD exacerbations

Acute COPD exacerbations can be prevented. Smoking cessation, influenza and pneumococcal vaccination, current maintenance therapy including treatment with long-acting inhaled bronchodilators, and with or without inhaled corticosteroids will reduce the number of exacerbations and hospitalisations. Patients should be encouraged to maintain physical activity, and anxiety, depression, and social problems should be addressed effectively. Principal caregivers should be identified if the patient has a significant persisting disability.[79,80]

7.2 Screening in the community

7.2.1 Active case-finding

GPP All patients ≥ 40 years of age with a history of smoking should be assessed on a yearly basis for symptoms of COPD i.e. dyspnoea, chronic cough or chronic sputum production.

GPP

D Patients with any symptoms of COPD (i.e. dyspnoea, chronic cough or chronic sputum production) should undergo a spirometry to assess for the presence of COPD.[80]

Grade D, Level 4

7.2.2 Screening in the general population

D Screening spirometry in the general asymptomatic population is not recommended.[80]

Grade D, Level 4

7.2.3 Spirometry

GPP Where practicable, General Practitioners should arrange for their patients to undergo spirometry to help in the diagnosis of COPD in the community as a standard practice.

GPP

Primary care physicians are in an ideal position to be able to detect COPD in its early stages. Access to spirometry services will aid in diagnosis of such patients.

D Personnel conducting spirometry testing should be trained in the conduct of the test, and be familiar with the machines they are using.[81,82]

Grade D, Level 4

D Spirometries should be undertaken when patients are clinically stable and free from respiratory tract infections.[81]

Grade D, Level 4

7.3 Co-morbidities

D All patients with a history of COPD should be screened for cardiovascular risk factors.[83]

Grade D, Level 4

COPD often coexists with other diseases that may have a significant impact on prognosis. Some of these diseases arise independently of COPD while others may be causally related, either with shared risk factors or by one disease increasing the risk of the other. The presence of comorbidities should not alter COPD treatment, and comorbidities should be treated as if the patient did not have COPD.

7.4 Pulmonary rehabilitation

7.4.1 Definition of pulmonary rehabilitation

Pulmonary rehabilitation typically includes several different components, including exercise training, education, instruction in

various respiratory and chest physiotherapy techniques, and psychosocial support.[79]

Comprehensive pulmonary rehabilitation was defined as an patient-tailored intervention that includes one or more of these components beyond just exercise training,[77, 78] which is considered to be an essential, mandatory component.

7.4.2 Benefits of pulmonary rehabilitation

Pulmonary rehabilitation forms an important component of the management of COPD following exacerbations.[85,86]

Pulmonary rehabilitation has the following benefits:

1. Both statistical and clinical significant improvement in domains of quality of life, i.e. dyspnea, fatigue, emotions and patient control over disease[85,87-92]
2. Improves maximal exercise capacity, endurance time and walking distance[85,87-93]
3. Reduces anxiety and depression. Improves psychological well-being[85,88,91,92]
4. Reduces exertion and overall dyspnea[90,91]
5. Reduces acute exacerbation and hospitalisation[85,91]

7.4.3 Benefits of pulmonary rehabilitation after acute exacerbation of COPD

There was a significant reduction in odds of hospital re-admissions with pulmonary rehabilitation following acute exacerbations as well as demonstrating consistent improvements in Quality of Life and exercise capacity.

Pulmonary rehabilitation may induce therapeutic benefits to ameliorate clinical sequelae associated with acute exacerbations of COPD and comorbidities.[94,95] A randomised control trial found no statistically significant differences between early (started within 2 weeks) and late pulmonary rehabilitation (after 6 months of randomisation). However, the trial indicated that early rehabilitation may lead to faster recovery of health-related quality of life after exacerbations compared to rehabilitation later on.[96] There was also significant reduction in mortality in patients who

underwent pulmonary rehabilitation after acute exacerbation of COPD.[86,94,96-100]

7.4.4 Indications for Pulmonary Rehabilitation

Exercise, the main component of Pulmonary Rehabilitation, is beneficial for all patients with COPD.[101] Pulmonary rehabilitation is recommended for COPD patients who have symptoms limiting their activity.[84,85,87-93,101-106] COPD patients can commence pulmonary rehabilitation once they are medically stable after acute exacerbation of COPD.[85,86,94,96-100]

A In-patient pulmonary rehabilitation should be started once the patient is medically stable after acute exacerbation of COPD.[86,94,96-100]

Grade A, Level 1++

8 Management of acute exacerbations

8.1 Management of acute exacerbations

An exacerbation is a sustained worsening of the patient's symptoms from their usual stable state which is beyond normal day-to-day variations, and is acute in onset.[15]

The change in these symptoms often necessitates an addition or a change in medication.[107]

Commonly reported symptoms are worsening breathlessness, cough, increased sputum production and change in sputum colour.[107]

The differential diagnoses of acute exacerbations include pneumonia, pulmonary embolism, congestive heart failure, cardiac arrhythmia, pneumothorax, and pleural effusion.[15, 107]

Most common cause of acute exacerbations appear to be respiratory tract infection (either bacterial or viral). Exposure to air pollutants can also precipitate exacerbations. [15, 107] No cause can be identified in up to one-third of severe COPD exacerbations. Interruption of maintenance therapy can also result in an exacerbation.[15]

Exacerbations are defined as mild when there is a change of inhaled treatment by the patient, moderate when exacerbations of respiratory symptoms require medical intervention including a short course of antibiotic and/or oral steroids, and severe when exacerbations of respiratory symptoms require hospitalization.[15]

The goals of treatment for an acute exacerbation of COPD are to minimise the impact of the current exacerbation and prevent the development of subsequent exacerbations.[15]

Assessment of an acute exacerbation of COPD includes a medical history, physical examination and supported by investigations.[108]

The diagnosis of an exacerbation is made clinically and does not depend on the results of investigations.[107]

In certain situations, investigations may assist in ensuring appropriate treatment is given. Different investigation strategies are required for patients in hospital (who will tend to have more severe exacerbations) and those in the community.[107]

KEY RECOMMENDATION

C In all patients with an exacerbation referred to hospital, a chest radiograph should be obtained and is useful in excluding alternative diagnoses.[15, 107, 108]

Grade C, Level 2+

D Sending sputum samples for culture in primary care is not recommended.[12]

Grade D, Level 4

B Measuring arterial blood gas tensions should be considered and the inspired oxygen concentration should be recorded.[15]

Grade B, Level 2++

D Theophylline level should be measured in patients on theophylline therapy at admission to rule out toxicity.[107]

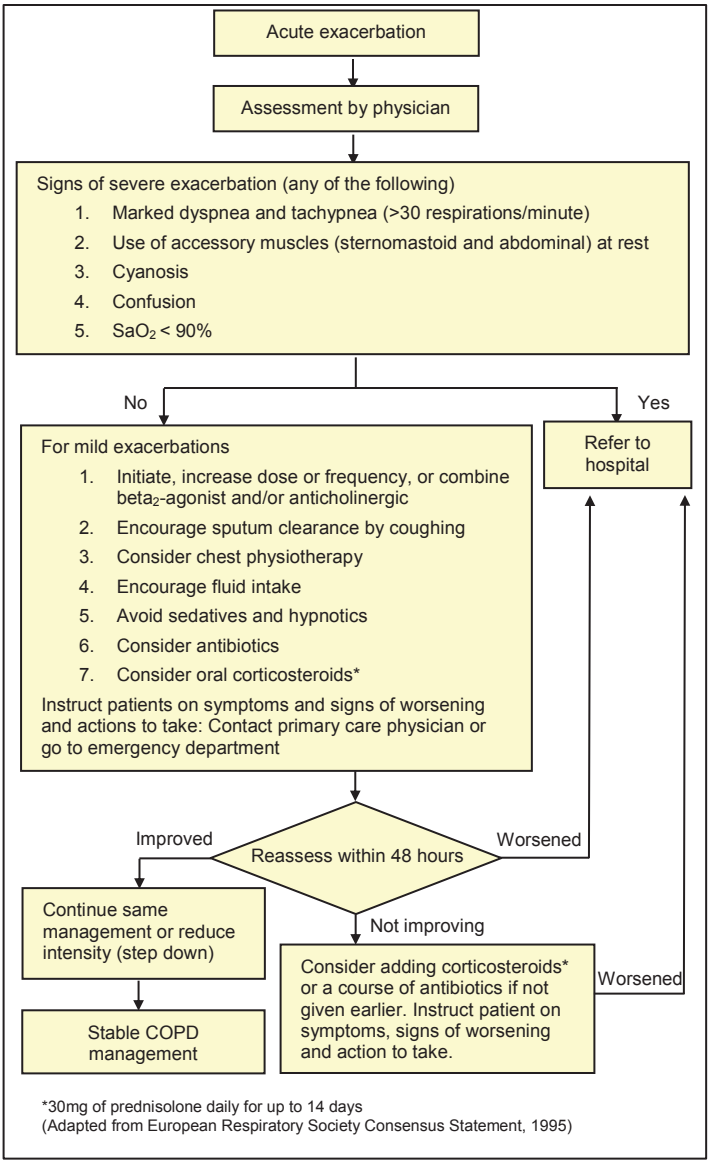
Grade D, Level 4

D Spirometric tests are not recommended during an exacerbation of COPD.[15, 107]

Grade D, Level 4

The management algorithm for an acute exacerbation is described in Figure 3.

Figure 3 Algorithm for the acute management of an acute exacerbation



8.2 Pharmacological management of an acute exacerbation

Increased breathlessness is a common feature of an exacerbation of COPD. This is usually managed by taking increased doses of short-acting bronchodilators.[107]

8.2.1 Bronchodilators

C Inhaled SABA with or without inhaled SAMA are the preferred bronchodilators for treatment of an exacerbation of COPD. [15, 107, 108]

Grade C, Level 2+

8.2.1.1 *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.[15, 107, 109]

Grade A, Level 1+

D Patients should be changed to hand-held inhalers as soon as their condition has stabilised.[107]

Grade D, Level 4

A If a patient is hypercapnic or acidotic the nebuliser should be driven by compressed air, not oxygen (to avoid worsening hypercapnia).[100] If oxygen therapy is needed it should be administered simultaneously by nasal cannulae.[107, 108]

Grade A, Level 1+

8.2.2 Systemic corticosteroids

Systemic corticosteroids shorten recovery time, improve lung function (FEV_1) and arterial hypoxemia (PaO_2), and reduce the risks of early relapse, treatment failure, and length of hospital stay.[15, 108]

A Systemic corticosteroids should be used, in conjunction with other therapies, in all patients admitted to hospital with an exacerbation of COPD.[107]

Grade A, Level 1+

A In the absence of significant contraindications, oral corticosteroids should be considered in patients in the community who have an exacerbation with a significant increase in breathlessness which interferes with daily activities. [15, 107, 108]

Grade A, Level 1+

A For COPD patients with acute exacerbation, prednisolone 30 mg orally should be administered for 5-10 days. There is no added clinical benefit of duration of systemic corticosteroids beyond 14 days.[107, 108]

Grade A, Level 1+

8.2.3 Antibiotics

Only selected patients will benefit from antibiotic treatment of COPD exacerbations.

A Antibiotics should be used to treat exacerbations of COPD associated with a history of more purulent sputum.[15, 107, 108]

Grade A, Level 1+

A Antibiotics should be given in exacerbations of COPD if the patient requires mechanical ventilation (invasive or noninvasive).[15]

Grade A, Level 1+

Initial empirical treatment should be a single agent preferably by oral route, using a beta-lactam antibiotic or a macrolide. When initiating empirical antibiotic treatment prescribers should always take into account of any guidance issued by their local microbiologists.

A The length of antibiotic therapy need not exceed 5 days for mild to moderate exacerbations of COPD.[110, 111]

Grade A, Level 1+

A For moderate to severe exacerbations of COPD, a 7 to 10 day course of antibiotics is recommended.[15, 108]

Grade A, Level 1+

8.2.4 Referrals to the Emergency Department

The majority of patients with COPD exacerbations can be successfully managed as outpatients with pharmacological treatment. The indications for hospital assessment and factors which determine site of care are listed in Table 4.

GPP Table 4 Indications for hospital assessment or admission

No.	Indications
1	Marked increase in intensity of symptoms, such as sudden development of resting dyspnea
2	Severe underlying COPD
3	Onset of new physical signs (e.g., cyanosis, peripheral edema)
4	Failure of an exacerbation to respond to initial medical management
5	Presence of serious comorbidities (e.g., heart failure or newly occurring arrhythmias)
6	Frequent exacerbations
7	Older age
8	Insufficient home support

GPP

8.3 Non-pharmacological therapy

8.3.1 Controlled oxygen therapy

The oxygen saturation should be measured in patients with an exacerbation of COPD.

KEY RECOMMENDATION

A For COPD patients with acute exacerbation, controlled oxygen should be given to keep the blood oxygen saturation, SaO_2 within a target saturation of 88 – 92%.[15, 107, 112]

Grade A, Level 1+

Patients with severe exacerbations who fail to respond to oxygen and pharmacotherapy may need ventilator support which may be invasive or non-invasive. Mechanical ventilation should be performed in a setting with local expertise such as an intensive care unit (ICU). The indications for admission to ICU are listed in Table 5.

D **Table 5 Indications for ICU admissions[12]**

No.	Indications
1	Severe dyspnoea that responds inadequately to initial emergency therapy
2	Changes in mental status (confusion, lethargy, coma)
3	Persistent or worsening hypoxaemia (PaO_2< 40 mm Hg) and/or severe worsening respiratory acidosis (pH <7.25) despite supplemental oxygen and non-invasive ventilation
4	Need for invasive mechanical ventilation
5	Haemodynamically unstable COPD patients who need vasopressors

Grade D, Level 4

8.3.2 Non-invasive ventilation (NIV)

KEY RECOMMENDATION

A Non-invasive ventilation should be used as the treatment of choice for persistent hypercapnic ventilatory failure during exacerbations of COPD despite optimal medical therapy.[15, 107, 108]

Grade A, Level 1++

KEY RECOMMENDATION

D When patients are started on non-invasive ventilation, there should be a clear plan covering what to do in the event of deterioration and ceilings of therapy should be agreed.[107]

Grade D, Level 4

The indications for non-invasive ventilation are listed in Table 6. The non-invasive ventilation should be delivered in a dedicated, structured setting with staff who have been trained in its application, who are experienced in its use, who are aware of its limitations and engaged in safety and quality improvement.

KEY RECOMMENDATION

A **Table 6 Indications for non-invasive mechanical ventilations[15]**

No.	Indications (at least 1 of the following)
1	Respiratory acidosis (arterial pH < 7.35 and/or $PaCO_2$ > 45 mm Hg)
2	Severe dyspnea

Grade A, Level 1++

8.3.3 Invasive ventilation

The indications for invasive mechanical ventilations are listed in Table 7.

D **Table 7 Indications for invasive mechanical ventilations[15]**

No.	Indications
1	Unable to tolerate non-invasive ventilation or non-invasive ventilation failure
2	Respiratory or cardiac arrest
3	Respiratory pauses with loss of consciousness or gasping for air
4	Diminished consciousness, psychomotor agitation inadequately controlled by sedation
5	Massive aspiration
6	Persistent inability to remove respiratory secretions
7	Heart rate < 50/min with loss of alertness
8	Severe hemodynamic instability without response to fluids and vasoactive drugs
9	Severe ventricular arrhythmias
10	Life-threatening hypoxemia in patients unable to tolerate non-invasive ventilation

Grade D, Level 4

A Non-invasive ventilation should be used to facilitate liberation from invasive ventilation in patients recovering from an exacerbation of COPD but who fail spontaneous breathing trials.[107, 108]

Grade A, Level 1+

During liberation from invasive ventilation, in selected patients, elective extubation to non-invasive ventilation reduces ventilator days, infective complications and mortality.

8.4 Discharge from hospitalisation for exacerbations

D Patients should be re-established on their optimal maintenance bronchodilator therapy before discharge.[107]

Grade D, Level 4

D Patients who have had an episode of respiratory failure should have satisfactory oximetry or arterial blood gas results before discharge.[107] If peripheral saturation is <92% arterial blood gases should be assessed.[113]

Grade D, Level 4

D All aspects of the routine care that patients receive (including appropriateness and risk of side effects) should be assessed before discharge.[107]

Grade D, Level 4

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.[107]

Grade D, Level 4

D Arrangements for follow-up and home care (such as visiting nurse, oxygen delivery, referral for other support) should be made before discharge.[107]

Grade D, Level 4

8.4.1 Clearance of secretions

Patients who regularly expectorate sputum or those with tenacious sputum may benefit from airway clearance techniques during an exacerbation. In individuals with copious secretions, mechanical vibration and positive expiratory therapy (PEP) increased sputum expectoration.[107, 108, 114, 115]

8.4.2 Home management of exacerbations

A Hospital-at-home and assisted-discharge schemes are safe and effective and should be used as an alternative way of caring for patients with exacerbations of COPD who would otherwise need to be admitted or stay in hospital.[107]

Grade A, Level 1+

The multi-professional team required to operate these schemes should include allied health professionals with experience in managing COPD, and may include nurses, physiotherapists, occupational therapists and generic health workers.[107, 119, 120]

Current evidence is insufficient to make firm recommendations about which patients with an exacerbation are suitable for hospital-at-home or early discharge. This depends on the resources available, absence of poor prognostic factors and patients' preferences about site of treatment.[107]

9 Palliative care

Palliative care aims to prevent and relieve suffering by controlling symptoms and supporting patients especially those suffering from advanced COPD or life-threatening exacerbations and their families so that the best possible quality of life may be achieved.

It is a philosophy of delivering care which expands traditional disease-focused medical treatments to include goals of optimising function and living as actively as possible until death, while integrating psychological and spiritual aspects and helping with medical decision making in advanced progressive illnesses. As such it can be delivered concurrently with life-prolonging care.[116]

The COPD patient‘s disease trajectory is often unpredictable, making the optimal point of transition to palliative care difficult to pinpoint. A palliative care approach should be available to all COPD patients based on the needs and preferences of the patient and the patient’s family.[117]

KEY RECOMMENDATION

D Clinicians who care for patients with chronic or advanced respiratory diseases should be trained in, and be capable of providing basic palliative care to prevent and relieve suffering by controlling symptoms.[117]

Grade D, Level 4

These include the ability to communicate with empathy and compassion, to provide medical information and prognosis skilfully, to identify values, life goals and preferences regarding end of life care, to establish an overall medical plan including palliative care elements.

D Clinicians should consult with palliative care specialists as appropriate for managing palliative care situations beyond their level of competence.[117]

Grade D, Level 4

9.1 Advance Care Planning

KEY RECOMMENDATION

D COPD patients with two or more of the following criteria are candidates for end-of-life discussion and advance care planning:[119-121]

- FEV_1 30% or less;
- Starting on long term oxygen therapy;
- Repeated admissions for COPD exacerbation;
- Unintended progressive weight loss or cachexia;
- Functional decline;
- Development of significant comorbidities;
- A positive answer to the 'surprise' question: "Will you be surprised if your patient dies in the next 1 year?";
- Lack of additional treatment options.

Grade D, Level 4

Advance care planning (ACP) is an iterative communication[122] that includes 'knowing' the patient,[107] providing probabilities of treatment outcomes including palliative options[116] so as to elicit patient and family's values*, and goals of care[117] at the end of life and prepare surrogates for in-the-moment decision making at times of acute deterioration.[123-125]

In advanced care planning, a balanced approach of encouraging maximising living whilst also preparing for death - 'to hope for the best and prepare for the worst', open-ended questions such as 'Have you any concerns about the future?' and 'What are you hoping we can achieve?' has been found to be helpful. Unhelpful phrases that should be avoided include 'nothing more can be done', 'stopping treatment' and 'withdrawing care'.[122]

The healthcare provider most involved in patient's care can provide 'captaincy' in advanced care planning supported by trained, non-physician facilitators.[122]

It has been shown that end-of-life wishes of patients who received advance care planning were more likely to be known and followed.

* "family" is a patient defined concept in palliative care which may include non-blood ties.

Family members of patients who received advance care planning and passed away were less likely to suffer from stress or depression, and satisfaction among patients and family members who had undergone advanced care planning was higher.[126]

9.2 Symptom management

Regular assessment, non-pharmacological and pharmacological holistic management of psychological and physical components of refractory dyspnea can be helpful in its management.[117]

D Opioids (oral or parenteral) are effective therapy for the management of refractory dyspnea[127] and should be considered on an individual basis.[121, 128]

Grade D, Level 4

D Anxiety and depression accompany dyspnea and should be evaluated and treated accordingly.[129] Benzodiazepines, tricyclic anti-depressants and major tranquilizers may be useful in this context.[130]

Grade D, Level 4

B Oxygen and fans blowing air onto the face can relieve breathlessness.[131-133]

Grade B, Level 2++

D Fatigue can be improved by self-management education, pulmonary rehabilitation, and mind-body interventions.[134]

Grade A, Level 2++

10 Clinical quality improvement

The following clinical quality indicators are recommended based on the guidelines in this CPG. Healthcare providers may use these indicators to monitor their practice and to better gauge their quality of care.

Quality indicators	Recommended minimum frequency*	Examples of suggested measurable indicators
Smoking	Annual	Percentage of COPD patients whose smoking habits and desire to quit were assessed on 1 occasions in the past one year (except for those who have never smoked where smoking habits should be recorded once)
Inhaler technique	Annual	Percentage of COPD patients who have a record of inhaler technique assessment in the past one year
Influenza vaccination	Annual	Percentage of COPD patients who have a record of influenza vaccination being offered in the past one year

*Users may consider allowing an added margin of time (e.g. +3months) when assessing adherence to recommended annual frequencies.

11 Cost-effectiveness issues

COPD inflicts an enormous economic burden to the patient and the healthcare system.[135] The mean total cost of COPD in 2 public health clusters (NUHS and NHG) from 2005 to 2009 was $9.9 million per year. The cost is dominated by hospitalisation costs for acute exacerbations.[136] The best sources of evidence for cost and resource utilisation data for guideline development are systematic reviews of randomised controlled trials that report resource utilisation, with direct comparisons between the interventions of interest.[137] By this criteria, the cost effective interventions in COPD include smoking cessation[138], chronic disease management programs[139], non-invasive ventilation for severe acute exacerbations[140] and possibly, pharmacotherapy.[141-143]

References

1. Ministry of Health, Singapore. Statistics: Singapore health facts: principal causes of death. 2014 [cited 2015 19 Nov]. Available from: https://www.moh.gov.sg/content/moh_web/home/statistics/Health_Facts_Singapore/Principal_Causes_of_Death.html
2. Global Initiative for Chronic Obstructive Lung Disease: global Strategy for the diagnosis, management and prevention of chronic obstructive pulmonay disease (2006). 2006 [cited 2013 1 Oct]. Available from: http://www.who.int/respiratory/copd/GOLD_WR_06.pdf
3. Mannino DM, Gagnon RC, Petty TL, Lydick E. Obstructive lung disease and low lung function in adults in the United States: data from the National Health and Nutrition Examination Survey, 1988-1994. Arch Intern Med. 2000 Jun 12;160(11):1683-9.
4. National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health. 2012 NHLBI morbidity and mortality chart book. [cited 2013 7 May]. Available from: http://www.nhlbi.nih.gov/resources/docs/cht-book.htm
5. Sullivan S, Strassels S, Smith D. Characterization of the incidence and cost of COPD in the US. Eur Respir J 1996;9(S421).
6. Cao Z, Ong KC, Eng P, Tan WC, Ng TP. Frequent hospital readmissions for acute exacerbation of COPD and their associated factors. Respirology. 2006 Mar;11(2):188-95.
7. Ng TP, Niti M, Tan WC, Cao Z, Ong KC, Eng P. Depressive symptoms and chronic obstructive pulmonary disease: effect on mortality, hospital readmission, symptom burden, functional status, and quality of life. Arch Intern Med. 2007 Jan 8;167(1):60-7.
8. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J. 2009 May;33(5):1165-85.
9. Janson C, Marks G, Buist S, Gnatiuc L, Gislason T, McBurnie MA, et al. The impact of COPD on health status: findings from the BOLD study. Eur Respir J. 2013 Dec;42(6):1472-83.
10. Chong J, Poole P, Leung B, Black PN, Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2011(5):CD002309
11. Ng TP, Niti M, Fones C, Yap KB, Tan WC. Co-morbid association of depression and COPD: a population-based study. Respir Med. 2009 Jun;103(6):895-901.

12. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD. 2015 [cited 2015 15 June]. Available from: http://www.goldcopd.org/
13. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009 Sep;34(3):648-54.
14. Jimenez-Ruiz CA, Andreas S, Lewis KE, Tonnesen P, van Schayck CP, Hajek P, et al. Statement on smoking cessation in COPD and other pulmonary diseases and in smokers with comorbidities who find it difficult to quit. Eur Respir J. 2015 Jul;46(1):61-79.
15. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013 Feb 15;187(4):347-65.
16. Nannini L, Cates CJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2007(4):CD003794.
17. Virchow JC, Crompton GK, Dal Negro R, Pedersen S, Magnan A, Seidenberg J, et al. Importance of inhaler devices in the management of airway disease. Respir Med. 2008 Jan;102(1):10-9.
18. Sestini P, Renzoni E, Robinson S, Poole P, Ram FS. Short-acting beta 2 agonists for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2002(4):CD001495.
19. Appleton S, Jones T, Poole P, Pilotto L, Adams R, Lasserson TJ, et al. Ipratropium bromide versus long-acting beta-2 agonists for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2006(3):CD006101.
20. Wang J, Nie B, Xiong W, Xu Y. Effect of long-acting beta-agonists on the frequency of COPD exacerbations: a meta-analysis. J Clin Pharm Ther. 2012 Apr;37(2):204-11.
21. Kerwin EM, Gotfried MH, Lawrence D, Lassen C, Kramer B. Efficacy and tolerability of indacaterol 75 mug once daily in patients aged >40 years with chronic obstructive pulmonary disease: results from 2 double-blind, placebo-controlled 12-week studies. Clin Ther. 2011 Dec;33(12):1974-84.
22. Dong YH, Lin HH, Shau WY, Wu YC, Chang CH, Lai MS. Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed

treatment comparison meta-analysis of randomised controlled trials. Thorax. 2013 Jan;68(1):48-56.
23. Casaburi R, Kukafka D, Cooper CB, Witek TJ, Jr., Kesten S. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. Chest. 2005 Mar;127(3):809-17.
24. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med. 2008 Oct 9;359(15):1543-54.
25. Vogelmeier C, Hederer B, Glaab T, Schmidt H, Rutten-van Molken MP, Beeh KM, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. N Engl J Med. 2011 Mar 24;364(12):1093-103.
26. Cole JM, Sheehan AH, Jordan JK. Concomitant use of ipratropium and tiotropium in chronic obstructive pulmonary disease. Ann Pharmacother. 2012 Dec;46(12):1717-21.
27. Cooper CB, Barjaktarevic I. A new algorithm for the management of COPD. The Lancet Respiratory medicine. 2015 Apr;3(4):266-8.
28. Wedzicha JA, Banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT, et al. Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. N Engl J Med. 2016 Jun 9;374(23):2222-34.
29. Tashkin DP, Pearle J, Iezzoni D, Varghese ST. Formoterol and tiotropium compared with tiotropium alone for treatment of COPD. COPD. 2009 Feb;6(1):17-25.
30. van Noord JA, Aumann JL, Janssens E, Smeets JJ, Verhaert J, Disse B, et al. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. Eur Respir J. 2005 Aug;26(2):214-22.
31. Decramer M, Anzueto A, Kerwin E, Kaelin T, Richard N, Crater G, et al. Efficacy and safety of umeclidinium plus vilanterol versus tiotropium, vilanterol, or umeclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease: results from two multicentre, blinded, randomised controlled trials. The Lancet Respiratory medicine. 2014 Jun;2(6):472-86.
32. Bateman ED, Ferguson GT, Barnes N, Gallagher N, Green Y, Henley M, et al. Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. Eur Respir J. 2013 Dec;42(6):1484-94.
33. Buhl R, Maltais F, Abrahams R, Bjermer L, Derom E, Ferguson G, et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2-4). Eur Respir J. 2015 Apr;45(4):969-79.

34. Frith PA, Thompson PJ, Ratnavadivel R, Chang CL, Bremner P, Day P, et al. Glycopyrronium once-daily significantly improves lung function and health status when combined with salmeterol/fluticasone in patients with COPD: the GLISTEN study-a randomised controlled trial. Thorax. 2015 Jun;70(6):519-27.
35. Welte T, Miravitlles M, Hernandez P, Eriksson G, Peterson S, Polanowski T, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009 Oct 15;180(8):741-50.
36. Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med. 2007 Apr 17;146(8):545-55.
37. Magnussen H, Disse B, Rodriguez-Roisin R, Kirsten A, Watz H, Tetzlaff K, et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. N Engl J Med. 2014 Oct 2;371(14):1285-94.
38. Yang IA, Clarke MS, Sim EH, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2012;7:CD002991.
39. Spencer S, Karner C, Cates CJ, Evans DJ. Inhaled corticosteroids versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2011(12):CD007033.
40. Loke YK, Cavallazzi R, Singh S. Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomised controlled trials and observational studies. Thorax. 2011 Aug;66(8):699-708.
41. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007 Feb 22;356(8):775-89.
42. Walters JA, Walters EH, Wood-Baker R. Oral corticosteroids for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2005(3):CD005374.
43. Schols AM, Wesseling G, Kester AD, de Vries G, Mostert R, Slangen J, et al. Dose dependent increased mortality risk in COPD patients treated with oral glucocorticoids. Eur Respir J. 2001 Mar;17(3):337-42.

44. Zhou Y, Wang X, Zeng X, Qiu R, Xie J, Liu S, et al. Positive benefits of theophylline in a randomized, double-blind, parallel-group, placebo-controlled study of low-dose, slow-release theophylline in the treatment of COPD for 1 year. Respirology. 2006 Sep;11(5):603-10.
45. Barnes PJ. Theophylline. Am J Respir Crit Care Med. 2013 Oct 15;188(8):901-6.
46. Ram FS, Jones PW, Castro AA, De Brito JA, Atallah AN, Lacasse Y, et al. Oral theophylline for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2002(4):CD003902.\
47. Martinez JM, Calverly PMA, Goehring UM, Brose M, Fabbri LM et al Effect of rofumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multicentre randomised trial. Lancet 2015 385: 857-66
48. Berghe B, Rabe KF, Fabbri LM Phosphodiesterase4-inhibitor therapy for lung diseases.. Am J Respir Crit Care Med 2013 Vol 188:271-278
49. Global Report for the Diagnosis, Management, and Prevention of COPD (2017 Report)
50. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA, Jr., Criner GJ, et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med. 2011 Aug 25;365(8):689-98.
51. 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 Crit Care Med. 2008 Dec 1;178(11):1139-47.
52. Donath E, Chaudhry A, Hernandez-Aya LF, Lit L. A meta-analysis on the prophylactic use of macrolide antibiotics for the prevention of disease exacerbations in patients with Chronic Obstructive Pulmonary Disease. Respiratory medicine. 2013;107(9):1385-92.
53. Yao GY, Ma YL, Zhang MQ, Gao ZC. Macrolide therapy decreases chronic obstructive pulmonary disease exacerbation: a meta-analysis. Respiration. 2013;86(3):254-60.
54. Zheng JP, Kang J, Huang SG, Chen P, Yao WZ, Yang L, et al. Effect of carbocisteine on acute exacerbation of chronic obstructive pulmonary disease (PEACE Study): a randomised placebo-controlled study. Lancet. 2008 Jun 14;371(9629):2013-8.
55. Zheng JP, Wen FQ, Bai CX, Wan HY, Kang J, Chen P, et al. Twice daily N-acetylcysteine 600 mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON): a randomised,

double-blind placebo-controlled trial. The Lancet Respiratory medicine. 2014 Mar;2(3):187-94.
56. Tse HN, Raiteri L, Wong KY, Yee KS, Ng LY, Wai KY, et al. High-dose N-acetylcysteine in stable COPD: the 1-year, double-blind, randomized, placebo-controlled HIACE study. Chest. 2013 Jul;144(1):106-18.
57. Poole PJ, Chacko E, Wood-Baker RW, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2006(1):CD002733.
58. Pascoe S, Locantore N, Dransfield M, Barnes NC Pavord ID Blood eosinophil counts, exacerbations and response to the addition of inhaled fluticasone to vilaterol Lancet Respiraory Medicine 2015; 3(6):435-42
59. Siddiqui SH, Guasconi A, Vestbo J, et al. Blood Eosinophils: A Biomarker of Response to Extrafine Beclomethasone/formoterol in COPD. Am J Respir Crit Care Med 192(4):523-5.
60. Pavord ID, Lettis S, Locantore N, et al. Blood eosinophils and inhaled corticosteroid/long-acting beta-agonist efficacy in COPD Thorax 2016;71(2):118-25
61. Watz H, Tezlaff K, Wouters EF, et al. Blood eosinophil count and exacerbations in COPD: post oc analysis of the wisdom trial The Lancet Respiratory Medicine 2016 4 (5); 390 -8.
62. Cranston JM, Crockett AJ, Moss JR, Alpers JH. Domiciliary oxygen for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2005(4):CD001744.
63. Cooper JD, Trulock EP, Triantafillou AN, Patterson GA, Pohl MS, Deloney PA, et al. Bilateral pneumectomy (volume reduction) for chronic obstructive pulmonary disease. The Journal of thoracic and cardiovascular surgery. 1995 Jan;109(1):106-16; discussion 16-9.
64. Fessler HE, Permutt S. Lung volume reduction surgery and airflow limitation. American journal of respiratory and critical care medicine. 1998 Mar;157(3 Pt 1):715-22.
65. Krishnamohan P, Shen KR, Wigle DA, Allen MS, Nichols FC, 3rd, Cassivi SD, et al. Bullectomy for symptomatic or complicated giant lung bullae. The Annals of thoracic surgery. 2014 Feb;97(2):425-31.
66. Schipper PH, Meyers BF, Battafarano RJ, Guthrie TJ, Patterson GA, Cooper JD. Outcomes after resection of giant emphysematous bullae. The Annals of thoracic surgery. 2004 Sep;78(3):976-82; discussion -82.
67. Davey C, Zoumot Z, Jordan S, McNulty WH, Carr DH, Hind MD, et al. Bronchoscopic lung volume reduction with endobronchial

valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi study): a randomised controlled trial. Lancet. 2015 Sep 12;386(9998):1066-73.
68. Sciurba FC, Ernst A, Herth FJ, Strange C, Criner GJ, Marquette CH, et al. A randomized study of endobronchial valves for advanced emphysema. N Engl J Med. 2010 Sep 23;363(13):1233-44.
69. Choi M, Lee WS, Lee M, Jeon K, Sheen S, Jheon S, et al. Effectiveness of bronchoscopic lung volume reduction using unilateral endobronchial valve: a systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis. 2015;10:703-10.
70. Aziz F, Penupolu S, Xu X, He J. Lung transplant in end-staged chronic obstructive pulmonary disease (COPD) patients: a concise review. J Thorac Dis. 2010 Jun;2(2):111-6.
71. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2013;1:Cd000422.
72. Bonten MJ, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. 2015 Mar 19;372(12):1114-25.
73. Alfageme I, Vazquez R, Reyes N, Munoz J, Fernandez A, Hernandez M, et al. Clinical efficacy of anti-pneumococcal vaccination in patients with COPD. Thorax. 2006 Mar;61(3):189-95.
74. Tomczyk S, Bennett NM, Stoecker C, Gierke R, Moore MR, Whitney CG, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged >/=65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morbidity and mortality weekly report. 2014 Sep 19;63(37):822-5.
75. Advisory Committee on Immunization Practices (ACIP) recommended immunization schedule for adults aged 19 years and older – United States 2013. Morbidity and Mortality Weekly Report February 1, 2013/Vol62 1997 [cited 2013 1 Oct]. Available from: http://www.cdc.gov/Mmwr/preview/mmwrhtml/00047135.htm
76. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). Morbidity and Mortality Weekly Report 46(RR-08);1-24 1997 [cited 2013 1 Oct]. Available from: http://www.cdc.gov/Mmwr/preview/mmwrhtml/00047135.htm

77. Fisman DN, Abrutyn E, Spaude KA, Kim A, Kirchner C, Daley J. Prior pneumococcal vaccination is associated with reduced death, complications, and length of stay among hospitalized adults with community-acquired pneumonia. Clin Infect Dis. 2006 Apr 15;42(8):1093-101.
78. Jackson LA, Neuzil KM, Yu O, Benson P, Barlow WE, Adams AL, et al. Effectiveness of pneumococcal polysaccharide vaccine in older adults. N Engl J Med. 2003 May 1;348(18):1747-55.
79. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med. 2013 Oct 15;188(8):e13-64.
80. Global strategy for the diagnosis, management and prevention of COPD: updated 2013. 2013 [cited 2013 1 Oct]. Available from: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2013_Feb20.pdf
81. Dales RE, Vandemheen KL, Clinch J, Aaron SD. Spirometry in the primary care setting: influence on clinical diagnosis and management of airflow obstruction. Chest. 2005 Oct;128(4):2443-7.
82. Enright P. Does screening for COPD by primary care physicians have the potential to cause more harm than good? Chest. 2006 Apr;129(4):833-5.
83. Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012 Jul 15;186(2):155-61.
84. American Association of Cardiovascular & Pulmonary Rehabilitation. Guidelines for pulmonary rehabilitation programs. 3rd ed. Champaign, IL Human Kinetics; 2004.
85. Bolton CE, Bevan-Smith EF, Blakey JD, Crowe P, Elkin SL, Garrod R, et al. British Thoracic Society guideline on pulmonary rehabilitation in adults. Thorax. 2013 Sep;68 Suppl 2:ii1-30.
86. 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.
87. Cambach W, Wagenaar RC, Koelman TW, van Keimpema AR, Kemper HC. The long-term effects of pulmonary rehabilitation in patients with asthma and chronic obstructive pulmonary disease: a

research synthesis. Arch Phys Med Rehabil. 1999 Jan;80(1):103-11.
88. Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shiels K, et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. Lancet. 2000 Jan 29;355(9201):362-8.
89. Troosters T, Gosselink R, Decramer M. Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. Am J Med. 2000 Aug 15;109(3):207-12.
90. Santus P, Bassi L, Radovanovic D, Airoldi A, Raccanelli R, Triscari F, et al. Pulmonary Rehabilitation in COPD: A Reappraisal (2008-2012). Pulm Med. 2013;2013:374283.
91. COPD Working Group. Pulmonary rehabilitation for patients with chronic pulmonary disease (COPD): an evidence-based analysis. Ontario Health Technology Assessment Series March 2012;12(6):1–75.
92. Bhandari NJ, Jain T, Marolda C, ZuWallack RL. Comprehensive pulmonary rehabilitation results in clinically meaningful improvements in anxiety and depression in patients with chronic obstructive pulmonary disease. J Cardiopulm Rehabil Prev. 2013 Mar-Apr;33(2):123-7.
93. Green RH, Singh SJ, Williams J, Morgan MD. A randomised controlled trial of four weeks versus seven weeks of pulmonary rehabilitation in chronic obstructive pulmonary disease. Thorax. 2001 Feb;56(2):143-5.
94. Reid WD, Yamabayashi C, Goodridge D, Chung F, Hunt MA, Marciniuk DD, et al. Exercise prescription for hospitalized people with chronic obstructive pulmonary disease and comorbidities: a synthesis of systematic reviews. Int J Chron Obstruct Pulmon Dis. 2012;7:297-320.
95. Alfarroba S, Rodrigues F, Papoila AL, Santos AF, Morais L. Pulmonary Rehabilitation in COPD According to Global Initiative for Chronic Obstructive Lung Disease Categories. Respiratory care. 2016 Jul 12.
96. Puhan MA, Spaar A, Frey M, Turk A, Brandli O, Ritscher D, et al. Early versus late pulmonary rehabilitation in chronic obstructive pulmonary disease patients with acute exacerbations: a randomized trial. Respiration. 2012;83(6):499-506.
97. Cote CG, Celli BR. Pulmonary rehabilitation and the BODE index in COPD. Eur Respir J. 2005 Oct;26(4):630-6.

98. Enfield K, Gammon S, Floyd J, Falt C, Patrie J, Platts-Mills TA, et al. Six-minute walk distance in patients with severe end-stage COPD: association with survival after inpatient pulmonary rehabilitation. J Cardiopulm Rehabil Prev. 2010 May-Jun;30(3):195-202.
99. Puhan MA, Scharplatz M, Troosters T, Steurer J. Respiratory rehabilitation after acute exacerbation of COPD may reduce risk for readmission and mortality -- a systematic review. Respir Res. 2005;6:54.
100. Barakat S, Michele G, George P, Nicole V, Guy A. Outpatient pulmonary rehabilitation in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2008;3(1):155-62.
101. Berry MJ, Rejeski WJ, Adair NE, Zaccaro D. Exercise rehabilitation and chronic obstructive pulmonary disease stage. Am J Respir Crit Care Med. 1999 Oct;160(4):1248-53.
102. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based guidelines. ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel. American College of Chest Physicians. American Association of Cardiovascular and Pulmonary Rehabilitation. Chest. 1997 Nov 5;112(5):1363-96.
103. Pulmonary rehabilitation-1999. American Thoracic Society. Am J Respir Crit Care Med. 1999 May;159(5 Pt 1):1666-82.
104. British Thoracic Society Standards of Care Subcommittee on Pulmonary Rehabilitation. Pulmonary rehabilitation. Thorax. 2001 Nov;56(11):827-34.
105. Nici L, ZuWallack R, Wouters E, Donner CF. On pulmonary rehabilitation and the flight of the bumblebee: the ATS/ERS Statement on Pulmonary Rehabilitation. Eur Respir J. 2006 Sep;28(3):461-2.
106. Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF, Mahler DA, et al. Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines. Chest. 2007 May;131(5 Suppl):4S-42S.
107. National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care: update guideline. 2010 [cited 2013 1 OCT]. Available from: http://www.nice.org.uk/nicemedia/live/13029/49425/49425.pdf
108. McKenzie DK, Abramson M, Crockett AJ, Dabscheck E, Glasgow N, Jenkins S, et al. The COPD X Plan: Australian and New Zealand Guidelines for the management of chronic obstructive pulmonary

disease V 2.30, 2011. 2011 [cited 2013 1 Oct].]. Available from: http://www.gpnsw.com.au/__data/assets/aboriginalhealth/201211_CCworkshop/TheCOPDXPlan.pdf
109. Turner MO, Patel A, Ginsburg S, FitzGerald JM. Bronchodilator delivery in acute airflow obstruction. A meta-analysis. Arch Intern Med. 1997 Aug 11-25;157(15):1736-44.
110. Falagas ME, Avgeri SG, Matthaiou DK, Dimopoulos G, Siempos, II. Short- versus long-duration antimicrobial treatment for exacerbations of chronic bronchitis: a meta-analysis. J Antimicrob Chemother. 2008 Sep;62(3):442-50.
111. El Moussaoui R, Roede BM, Speelman P, Bresser P, Prins JM, Bossuyt PM. Short-course antibiotic treatment in acute exacerbations of chronic bronchitis and COPD: a meta-analysis of double-blind studies. Thorax. 2008 May;63(5):415-22.
112. Austin MA, Wills KE, Blizzard L, Walters EH, Wood-Baker R. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial. BMJ. 2010;341:c5462.
113. Kelly AM, McAlpine R, Kyle E. How accurate are pulse oximeters in patients with acute exacerbations of chronic obstructive airways disease? Respiratory medicine. 2001 May;95(5):336-40.
114. Hill K, Patman S, Brooks D. Effect of airway clearance techniques in patients experiencing an acute exacerbation of chronic obstructive pulmonary disease: a systematic review. Chron Respir Dis. 2010;7(1):9-17.
115. Tang CY, Taylor NF, Blackstock FC. Chest physiotherapy for patients admitted to hospital with an acute exacerbation of chronic obstructive pulmonary disease (COPD): a systematic review. Physiotherapy. 2010 Mar;96(1):1-13.
116. National Consensus Project for Quality Palliative Care. Clinical Practice Guidelines for Quality Palliative Care. 2nd ed 2009.
117. Lanken PN, Terry PB, Delisser HM, Fahy BF, Hansen-Flaschen J, Heffner JE, et al. An official American Thoracic Society clinical policy statement: palliative care for patients with respiratory diseases and critical illnesses. Am J Respir Crit Care Med. 2008 Apr 15;177(8):912-27.
118. McKenzie DK, Abramson M, Crockett AJ, Dabscheck E, Glasgow N, Jenkins S, et al. The COPD-X Plan: Australian and New Zealand Guidelines for the management of chronic obstructive pulmonary disease. V2.34. 2012 Nov [cited 2013 1 Oct].]. Available from:

http://gpnsw.com.au/__data/assets/aboriginalhealth/201211_CCworkshop/TheCOPDXPlan.pdf
119. Curtis JR. Palliative and end-of-life care for patients with severe COPD. Eur Respir J. 2008 Sep;32(3):796-803.
120. Shuman AG, Montas SM, Barnosky AR, Smith LB, Fins JJ, McCabe MS. Clinical ethics consultation in oncology. J Oncol Pract. 2013 Sep 1;9(5):240-5.
121. Marciniuk DD, Goodridge D, Hernandez P, Rocker G, Balter M, Bailey P, et al. Managing dyspnea in patients with advanced chronic obstructive pulmonary disease: a Canadian Thoracic Society clinical practice guideline. Can Respir J. 2011 Mar-Apr;18(2):69-78.
122. Janssen DJ, Engelberg RA, Wouters EF, Curtis JR. Advance care planning for patients with COPD: past, present and future. Patient Educ Couns. 2012 Jan;86(1):19-24.
123. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J. 2004 Jun;23(6):932-46.
124. Patel K, Janssen DJ, Curtis JR. Advance care planning in COPD. Respirology. 2012 Jan;17(1):72-8.
125. Janssen DJ, Spruit MA, Schols JM, Wouters EF. Dynamic Preferences for Site of Death Among Patients With Advanced Chronic Obstructive Pulmonary Disease, Chronic Heart Failure, or Chronic Renal Failure. J Pain Symptom Manage. 2013 Apr 6.
126. Detering KM, Hancock AD, Reade MC, Silvester W. The impact of advance care planning on end of life care in elderly patients: randomised controlled trial. BMJ. 2010;340:c1345.
127. Foral PA, Malesker MA, Huerta G, Hilleman DE. Nebulized opioids use in COPD. Chest. 2004 Feb;125(2):691-4.
128. Qaseem A, Snow V, Shekelle P, Casey DE, Jr., Cross JT, Jr., Owens DK, et al. Evidence-based interventions to improve the palliative care of pain, dyspnea, and depression at the end of life: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2008 Jan 15;148(2):141-6.
129. Mahler DA, Selecky PA, Harrod CG, Benditt JO, Carrieri-Kohlman V, Curtis JR, et al. American College of Chest Physicians consensus statement on the management of dyspnea in patients with advanced lung or heart disease. Chest. 2010 Mar;137(3):674-91.
130. National Clinical Guideline Centre. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care. London: National Clinical

Guideline Centre. Available from: http://guidance.nice.org.uk/CG101/Guidance/pdf/English; 2010.
131. Abernethy A, McDonald C, Frith P, et al. Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial. Lancet. 2010;376:784–93.
132. Baltzan M, Alter A, Rotaple M, Kamel H, Wolkove N. Fan to palliative exercise-induced dyspnoea with severe COPD. Am J Respir Crit Care Med. 2000;161(3 Suppl):A59.
133. Bausewein C, Booth S, Gysels M, Kuhnbach R, Higginson I. Effectiveness of a hand-held fan for breathlessness: a randomised phase II trial. BMC Palliat Care. 2010;9:22.
134. Farver-Vestergaard I, Jacobsen D, Zachariae R, Efficacy of Psychosocial Interventions on Psychological and Physical Health Outcomes in Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. Psychother Psychosom 2015;84:37-50
135. D'Souza AO, Shah M, Dhamane AD, Dalal AA. Clinical and economic burden of COPD in a medicaid population. Copd. 2014 Apr;11(2):212-20.
136. Teo WS, Tan WS, Chong WF, Abisheganaden J, Lew YJ, Lim TK, et al. Economic burden of chronic obstructive pulmonary disease. Respirology (Carlton, Vic). 2012 Jan;17(1):120-6.
137. Hill SR, Olson LG, Falck-Ytter Y, Cruz AA, Atkins D, Baumann M, et al. Incorporating considerations of cost-effectiveness, affordability, and resource implications in guideline development: article 6 in Integrating and coordinating efforts in COPD guideline development. An official ATS/ERS workshop report. Proceedings of the American Thoracic Society. 2012 Dec;9(5):251-5.
138. Hoogendoorn M, Feenstra TL, Hoogenveen RT, Rutten-van Molken MP. Long-term effectiveness and cost-effectiveness of smoking cessation interventions in patients with COPD. Thorax. 2010 Aug;65(8):711-8.
139. Boland MR, Tsiachristas A, Kruis AL, Chavannes NH, Rutten-van Molken MP. The health economic impact of disease management programs for COPD: a systematic literature review and meta-analysis. BMC pulmonary medicine. 2013;13:40.
140. Keenan SP, Gregor J, Sibbald WJ, Cook D, Gafni A. Noninvasive positive pressure ventilation in the setting of severe, acute exacerbations of chronic obstructive pulmonary disease: more effective and less expensive. Critical care medicine. 2000 Jun;28(6):2094-102.

141. Dalal AA, St Charles M, Petersen HV, Roberts MH, Blanchette CM, Manavi-Zieverink K. Cost-effectiveness of combination fluticasone propionate-salmeterol 250/50 microg versus salmeterol in severe COPD patients. International journal of chronic obstructive pulmonary disease. 2010;5:179-87.
142. Hoogendoorn M, Kappelhoff BS, Overbeek JA, Wouters EF, Rutten-van Molken MP. Which long-acting bronchodilator is most cost-effective for the treatment of COPD? The Netherlands journal of medicine. 2012 Oct;70(8):357-64.
143. D'Souza AO, Smith MJ, Miller LA, Kavookjian J. An appraisal of pharmacoeconomic evidence of maintenance therapy for COPD. Chest. 2006 Jun;129(6):1693-708.

Self-assessment (MCQs)

After reading the Clinical Practice Guidelines, you can claim one CME point under Category 3A (Self-Study) of the SMC Online CME System. Alternatively, you can claim one CME point under Category 3B (Distance Learning – Verifiable Self-Assessment) if you answer at least 60% of the following MCQs correctly. You can submit your answers through the SMJ website at this link: http://sma.org.sg/publications/index.aspx?ID=26 (the link will only be available once the February 2018 issue of the SMJ becomes available). The answers will be published in the SMJ April 2018 issue and at the MOH webpage for these guidelines after the period for submitting the answers is over.

Instruction: Choose True or False for each statement.

		True	False
1.	Regarding pharmacotherapy for stable COPD:		
	A) Tiotropium should not be combined with inhaled corticosteroids.	☐	☐
	B) Combination therapy comprising a LABA and LAMA is a treatment option for patients with persistent breathlessness.	☐	☐
	C) When a patient is prescribed with Clarithromycin and Theophylline, closer monitoring of side effects of Theophylline is needed.	☐	☐
	D) Combination inhaled corticosteroids and long-acting bronchodilators are first choice treatment for GOLD A patients.	☐	☐
2.	The statements pertaining to non-pharmacological treatment of COPD are true or false?		
	A) Long-term oxygen therapy has been shown to improve survival in COPD patients with chronic respiratory failure.	☐	☐
	B) There is no evidence that lung volume reduction surgery improves quality of life and survival in patients with COPD.	☐	☐
	C) Annual influenza vaccination has been shown to significantly decrease COPD exacerbations due to influenza.	☐	☐
	D) Both the pneumococcal polysaccharide vaccine (PSV) and polysaccharide conjugate vaccine (PCV13) are effective in preventing invasive pneumococcal disease in adults.	☐	☐

		True	False
3.	With regards to pulmonary rehabilitation:		
	A) 23% of COPD patients take up pulmonary rehabilitation in Singapore.	☐	☐
	B) Pulmonary rehabilitation should commence once the patient is medically stable after acute exacerbation of COPD.	☐	☐
	C) Pulmonary rehabilitation is ineffective in reducing anxiety, depression and psychological well-being.	☐	☐
	D) Pulmonary rehabilitation improves maximal exercise capacity and endurance, but has no impact on reducing acute exacerbation and hospitalisation.	☐	☐
4.	With regards to co-morbidities:		
	A) When treating COPD patients for Hypertension, they have a higher Blood Pressure target as compared to non-COPD patients.	☐	☐
	B) Recurrent exacerbations in COPD patients could result in worsening diabetic control.	☐	☐
	C) COPD patients should undergo routine cardiovascular screening as part of their follow-up.	☐	☐
	D) COPD patients with diabetes have similar targets for control as patients without COPD.	☐	☐
5.	For patients with Stage D with persistent breathlessness:		
	A) Advanced Care Planning should be initiated.	☐	☐
	B) Eliciting both patient's and family's values, preferences and goals of care at the end of life is important.	☐	☐
	C) Opioids should not be used in patients suffering from refractory dyspnoea in advanced COPD as they may further increase $PaCO_2$.	☐	☐
	D) Management of the physical component of refractory dyspnoea takes precedence over management of the psychological aspect.	☐	☐

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