# EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)
## Supporting information

**This guideline has been prepared with reference to the following:**

Global Initiative for Chronic Obstructive Lung Disease. Global strategy for prevention, diagnosis and management of COPD: 2023 Report. 2023. Global Initiative for Chronic Obstructive Lung Disease inc.

https://goldcopd.org/

NICE. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. 2019. NICE. London

https://www.nice.org.uk/guidance/ng115

NICE. Chronic obstructive pulmonary disease (acute exacerbation): antimicrobial prescribing. 2018. NICE. London

https://www.nice.org.uk/guidance/ng114

American Thoracic Society; European Respiratory Society. Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. 2017

http://www.thoracic.org/statements/resources/copd/mgmt-of-COPD-exacerbations.pdf

## Investigations

**Blood cultures should be taken from all patients?**
A retrospective observational study in 289 patients (Ramanujam, 2006) found that antibiotic regimens were rarely changed based on blood culture results and that potential savings from these changes were minimal.

Ramanujam P, Rathlev NK. Blood cultures do not change management in hospitalized patients with community-acquired pneumonia. Acad Emerg Med 2006;13:740-5
http://onlinelibrary.wiley.com/doi/10.1197/j.aem.2006.03.554/epdf

**Evidence Level: IV**

## Differential diagnosis

**Pulmonary embolism (PE) may be a cause of exacerbation of COPD?**
A systematic review of 7 studies found that the prevalence of PE in unexplained acute exacerbation of COPD was 16.1% (95% CI, 8.3%-25.8%) [Aleva, 2017]. The authors of this review concluded that "PE should receive increased awareness in patients with unexplained AE-COPD, especially when pleuritic chest pain and signs of cardiac failure are present, and no clear infectious origin can be identified". An editorial on this study further commented that there was insufficient evidence to support the widespread screening for PE in patients with AE-COPD (Ra, 2017). A 2021 systematic review of 16 studies (5035 patients) estimated the prevalence of PE in AE-COPD to be 12.9% (Wang, 2021). A 2021 RCT suggests that the addition of an active strategy for the diagnosis of pulmonary embolism to usual care in the setting of unexplained acute exacerbations of COPD does not benefit patients (Jimenez, 2021). The Significance of Pulmonary Embolism in COPD Exacerbations (SLICE) trial was a randomized, open-label clinical trial that compared the addition of an active strategy for the diagnosis of pulmonary embolism to usual care with usual care alone among patients hospitalized for an exacerbation of COPD. Eligible patients had a diagnosis of COPD and were hospitalized for an exacerbation. The strategy for the diagnosis of pulmonary embolism consisted of a D-dimer testing and, if positive (>500 ng/ml), a computed tomographic pulmonary angiography (CTPA). The primary outcome was the composite of nonfatal new or recurrent symptomatic VTE, readmission for COPD, or death within 90 days after randomization. The primary outcome occurred in 110 patients (29.7%) in the intervention group and 107 patients (29.2%) in the control group (absolute risk difference, 0.5% [95% CI, -6.2 to 7.3]; relative risk, 1.0 [95% CI, 0.8 to 1.3]).

Aleva FE, Voets LWLM, Simons SO et al. Prevalence and Localization of Pulmonary Embolism in Unexplained Acute Exacerbations of COPD: A Systematic Review and Meta-analysis. Chest. 2017;151:544-54

Jimenez D, Agustí A, Tabernero E, et al., SLICE Trial Group. Effect of a pulmonary embolism diagnostic strategy on clinical outcomes in patients hospitalized for COPD exacerbation: a randomized clinical trial. JAMA 2021;326: 1277–85
https://pmc.ncbi.nlm.nih.gov/articles/PMC8493436/

Ra SW, Sin DD. Should We Screen for Pulmonary Embolism in Severe COPD Exacerbations? Not Just Yet, Primum Non Nocere. Chest. 2017;151:523-4

Wang J, Ding YM. Prevalence and risk factors of pulmonary embolism in acute exacerbation of chronic obstructive pulmonary disease and its impact on outcomes: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci. 2021;25:2604-16
https://www.europeanreview.org/article/25424

**Evidence Level: I**

## Immediate treatment

### Antibiotics improve the recovery rate of patients with exacerbation of COPD?

A 2018 systematic review of RCTs (19 trials with 2663 participants) concluded that antibiotics have some effect on patients, but these effects are small, and they are inconsistent for some outcomes (treatment failure) and absent for other outcomes (mortality, length of hospital stay) [Vollenweider, 2018]. Analyses show a strong beneficial effect of antibiotics among ICU patients. Trials do not show that currently used antibiotics statistically significantly reduced the risk of treatment failure among inpatients with severe exacerbations (i.e. for inpatients excluding ICU patients) (RR 0.65, 95% CI 0.38 to 1.12).
A systematic review of 13 trials in 1557 patients (Puhan, 2007) concluded that antibiotics were most appropriate for those patients who were moderately or severely ill, with increased cough and purulent sputum.

Puhan MA, Vollenweider D, Latshang T, et al. Exacerbations of chronic obstructive pulmonary disease: when are antibiotics indicated? A systematic review. Respir Res 2007;8:30
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1853091/

Vollenweider DJ, Frei A, Steurer-Stey CA et al. Antibiotics for exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2018 Oct 29;10:CD010257
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010257.pub2/full

**Evidence Level: I**

### Usual causative organisms are *Strep. pneumoniae* and *H. influenzae?*

*H. influenzae* has been described as “the most commonly isolated bacterium” in exacerbations of COPD (Leanord, 2002).
An audit report on 167 patients from a Liverpool hospital (Davies, 2001) found bacterial pathogens in 34 of 101 sputum samples (31%). *H. influenzae* was isolated from 16 (47%) and *Strep. pneumoniae* from 6 (17%). Identical results were obtained in another audit report from a Manchester hospital (Smith, 1999).
A study on bacterial species recovered from sputa in 103 acute COPD cases (Chodosh, 1987) revealed that 41% were *H. influenzae* and 19.9% were *Strep. pneumoniae;* the authors commented that these figures tend to be remarkably similar worldwide.
Another study that included 29 patients with exacerbation of COPD (Monso, 1995) found *H. influenzae* in 10 (34%) and *Strep. pneumoniae* in 3 (10%).

Chodosh S. Acute bacterial exacerbations in bronchitis and asthma. Am J Med 1987;82(Suppl 4A):154-63

Davies L, Hadcroft J, Mutton K, et al. Antimicrobial management of acute exacerbation of chronic airflow limitation. Q J Med 001;94:373-8
http://qjmed.oxfordjournals.org/content/94/7/373.long

Leanord A, Williams C. Haemophilus influenzae in acute exacerbations of chronic obstructive pulmonary disease. Int J Antimicrob Agents 2002;19:371-5

Monso E, Ruiz J, Rosell A, et al. Bacterial infection in chronic obstructive pulmonary disease: a study of stable and exacerbated outpatients using the protected specimen brush. Am J Respir Crit Care Med 1995;152:1316-20

Smith JA, Redman P, Woodhead MA. Antibiotic use in patients admitted with acute exacerbations of chronic obstructive pulmonary disease. Eur Respir J 1999;13:835-8
http://www.ersj.org.uk/content/13/4/835.full.pdf

**Evidence Level: IV**

**Doxycycline 200 mg orally on first day, then 100 mg orally daily, is appropriate antibiotic treatment?**

A 2017 systematic review found dirithromycin, ofloxacin, ciprofloxacin, and trimethoprim-sulfamethoxazole are better antibiotic treatment options than doxycycline (Zhang, 2017). Doxycycline was recommended in Dutch guidelines (Van Kasteren, 1998) for its wide spectrum of activity, easy dosing and favourable price.

Van Kasteren M, Wijnands W, Stobberingh E et al. Optimizing antibiotic policy in the Netherlands. III. SWAB guidelines for antimicrobial treatment of adults with bronchitis in hospital. Ned Tijdschr Geneeskd 1998;142:2512-5

Zhang HL, Tan M, Qiu AM et al. Antibiotics for treatment of acute exacerbation of chronic obstructive pulmonary disease: a network meta-analysis. BMC Pulm Med. 2017;17:196
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5727987/

**Evidence Level: I**

**During influenza outbreaks, *S. aureus* is more likely to be responsible for exacerbations of COPD?**

*S. aureus* infections of the respiratory tract have long been known to be associated with influenza (Finland, 1942). More recently, influenza-associated *S. aureus* has been reported to cause toxic shock syndrome (Prechter, 1989; MacDonald, 1987).

Finland M, Peterson OL, Strauss E. Staphylococcic pneumonia during an epidemic of influenza. Arch Intern Med 1942;70:183-205

MacDonald KL, Osterholm MT, Hedberg CW, et al. Toxic shock syndrome: a newly recognized complication of influenza and influenzalike illness. JAMA 1987;257:1053-8

Prechter GC, Gerhard AK. Postinfluenza toxic shock syndrome. Chest 1989;95:1153-4
http://journal.publications.chestnet.org/data/Journals/CHEST/21593/1153.pdf

**Evidence Level: V**

**Flucloxacillin kills *Staph. aureus,*?**

Flucloxacillin is resistant to staphylococcal penicillinase, and is therefore active against both penicillinase-producing and non-penicillinase-producing staphylococci (Sweetman, 2002).

Sweetman SC (ed). Martindale: the complete drug reference, 33rd ed. London: Pharmaceutical Press, 2002. p.207

**Evidence Level: V**

**Salbutamol or terbutaline (beta2-agonists) are effective in improving the rate of recovery from an exacerbation of COPD?**

A Cochrane review (Smucny, 2004) found little to support the use of beta-agonists in acute bronchitis, other than weak evidence that symptoms (including cough) may be reduced in those patients with airflow obstruction.
Another Cochrane review (Appleton, 2006) found weak evidence that salmeterol 50 mcg improved lung function in COPD patients, but also a consistent trend towards fewer exacerbations. A more recent meta-analysis of 17 RCTs (Wang 2012) found that Salmeterol, formoterol and indacaterol significantly reduced COPD exacerbations compared with placebo.

A meta-analysis of 22 trials in 15,276 patients (Salpeter, 2006) found a 2-fold increased risk for severe exacerbations associated with beta-agonists compared with anticholinergics (RR 1.95; 95% CI 1.39-2.93).

Appleton S, Poole P, Smith B, et al. Long-acting beta2-agonists for poorly reversible chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2006;3
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001104.pub2/full

Salpeter SR, Buckley NS, Salpeter EE. Meta-analysis: anticholinergics, but not beta-agonists, reduce severe exacerbations and respiratory mortality in COPD. J Gen Intern Med 2006;21:1011-9
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1831628/

Becker L , Hom J, Villasis-Keever M et al. Beta2-agonists for acute bronchitis. Cochrane Database Syst Rev. 2011
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001726.pub4/full

Wang J, Nie B, Xiong W et al. Effect of Long-acting beta-antagonists on the frequency of COPD exacerbations: a meta-analysis. J Clin Phar Ther 2012; 37: 204-11.

**Evidence Level: I**

**Addition of ipratropium via nebuliser has a beneficial additional effect to that of beta-agonists?**
Of two Cochrane reviews on the subject, one (Brown, 2001) was inconclusive on the existence of an additional effect and the other (McCrory, 2002) found "no significant additional increase in change in FEV1 on adding ipratropium to beta2-agonist: Weighted Mean Difference (WMD) 0.02 liter (95% CI –0.08, 0.12). Long-term effects (24 hours) of the … combination were similar: WMD 0.05 liters (95% CI –0.14, 0.05)."
A small randomised double-blind trial in 55 patients (Shrestha, 1991) compared 30 patients given ipratropium in addition to beta-agonist therapy to 25 given beta-agonist alone. Those in the treatment group were discharged from the emergency department an average of 91 minutes sooner than the controls.

Brown CD, McCrory D, White J. Inhaled short-acting beta2-agonists versus ipratropium for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2001;1
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002984/full

McCrory DC, Brown CD. Anticholinergic bronchodilators versus beta2-sympathomimetic agents for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2002; 3
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003900/full

Shrestha M, O'Brien T, Haddox R, et al. Decreased duration of emergency department treatment of chronic obstructive pulmonary disease exacerbations with the addition of ipratropium bromide to beta-agonist therapy. Ann Emerg Med 1991;20:1206-9

**Evidence Level: I**

**IV aminophylline has an effect additive to that of ipratropium and a beta-agonist in improving recovery rate in exacerbation of COPD?**
A Cochrane review (Barr, 2003i) of 4 RCTs with a total of 172 patients concluded "There is no evidence to support the routine use of methyl-xanthines for COPD exacerbations. Methyl-xanthines do not appreciably improve FEV1 during COPD exacerbations and cause adverse effects; evidence of their effect on admissions is limited".
A later update (Barr, 2003ii) and a randomised, placebo-controlled trial in 80 patients (Duffy, 2005) reached the same conclusions, and these concur with the recommendations of a U.S. joint panel (Snow, 2001).

Barr RG, Rowe BH, Camargo CA. Methylxanthines for exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2003;2
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002168/full

Barr RG, Rowe BH, Camargo CA. Methylxanthines for exacerbations of chronic obstructive pulmonary disease: meta-analysis of randomised trials. BMJ 2003;327:643-6
http://www.bmj.com/content/327/7416/643

Duffy N, Walker P, Diamantea F, et al. Intravenous aminophylline in patients admitted to hospital with non-acidotic exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. Thorax 2005;60:713-7
http://thorax.bmj.com/content/early/2005/06/06/thx.2004.036046.full.pdf

Snow V, Lascher S, Mottur-Pilson C. Evidence base for management of acute exacerbations of chronic obstructive pulmonary disease. Joint Expert Panel on Chronic Obstructive Pulmonary Disease of the American College of Chest Physicians and the American College of Physicians-American Society of Internal Medicine. Ann Intern Med 2001;134:595-9

**Evidence Level: I**

**Corticosteroids (prednisolone or hydrocortisone) improve the rate of recovery from an exacerbation of COPD?**

A Cochrane review (Walters, 2014) concluded that systemic corticosteroids reduced the risk of treatment failure by over half compared with placebo in nine studies (n = 917) with median treatment duration 14 days, odds ratio (OR) 0.48 (95% confidence interval (CI) 0.35 to 0.67).

A 2024 systematic review of RCTs suggests potential noninferiority of inhaled to systemic corticosteroids in COPD exacerbations (Papadopoulou, 2024). Low-certainty evidence did not reveal significant differences between inhaled and systemic corticosteroids for treatment failure rate (relative risk 1.75, 95% CI 0.76 to 4.02, n=569 participants); breathlessness (mean change: standardised mean difference (SMD) -0.11, 95% CI -0.36 to 0.15, n=239; post-treatment scores: SMD -0.18, 95% CI -0.41 to 0.05, n=293); serious adverse events (relative risk 1.47, 95% CI 0.56 to 3.88, n=246); or any other efficacy outcomes. Moderate-certainty evidence implied a tendency for fewer adverse events with inhaled compared to systemic corticosteroids (relative risk 0.80, 95% CI 0.64 to 1.0, n=480).

Papadopoulou E, Safar SB, Khalil A et al. Inhaled versus systemic corticosteroids for acute exacerbations of COPD: a systematic review and meta-analysis. Eur Respir Rev. 2024;33:230151
https://pmc.ncbi.nlm.nih.gov/articles/pmid/38508668/

Walters J, Tan D, White C, et al. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2014
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001288.pub4/full

**Evidence Level: I**

**Physiotherapy aids the clearance of sputum but is not otherwise effective?**

Unfavourable results from three earlier randomised trials of chest physiotherapy in patients with chronic bronchitis led the authors of a position paper and guideline (Bach, 2001) to conclude that chest percussion was ineffective (or even detrimental) in acute exacerbations of COPD.

A systematic review of 13 RCTs (Tang, 2010) found moderate evidence that intermittent positive pressure ventilation and positive expiratory pressure were effective in improving sputum expectoration. In addition, there was moderate evidence that walking programmes led to benefits in arterial blood gases, lung function, dyspnoea and quality of life. No evidence was found supporting the use of any other chest physiotherapy techniques to change lung function, arterial blood gases, perceived level of dyspnoea or quality of life.

A randomised controlled trial in 372 patients (Cross, 2010) concluded that “In terms of longer-term quality of life the use of manual chest physiotherapy (MCP) did not appear to affect outcome. However, this does not mean that MCP is of no therapeutic value to patients with COPD in specific circumstances.”

Bach PB, Brown C, Gelfand SE, et al. Management of acute exacerbations of chronic obstructive pulmonary disease: a summary and appraisal of published evidence. Ann Intern Med 2001;600-20

Cross J, Elender F, Barton G. A randomised controlled equivalence trial to determine the effectiveness and cost-utility of manual chest physiotherapy techniques in the management of exacerbations of chronic obstructive pulmonary disease (MATREX). Health Technol Assess 2010;14:1-147

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;96:1-13

**Evidence Level: II**

**When is non-invasive ventilation (NIV) appropriate and what benefits does it provide?**
European Respiratory Society/American Thoracic Society guidelines strongly recommend NIV for patients with moderate-to-severe respiratory acidosis and distress to prevent endotracheal intubation and invasive mechanical ventilation (Rochwerg, 2017). Tables of evidence collecting data from 14 RCTs, show that NIV is indicated for hypercapnic (arterial carbon dioxide tension, $PaCO_2$ > 45 mmHg) and tachypneic acute exacerbations of COPD patients with a pH below 7.35, despite prior medical therapy.
A 2017 systematic review of RCTs concluded that there was strong evidence to show that NIV is beneficial as a first-line intervention in conjunction with usual care for reducing the likelihood of mortality and endotracheal intubation in patients admitted with acute hypercapnic respiratory failure secondary to an acute exacerbation of COPD (Osadnik, 2017). Use of NIV decreased the risk of mortality by 46% (risk ratio (RR) 0.54, 95% confidence interval (CI) 0.38 to 0.76; N = 12 studies; number needed to treat for an additional beneficial outcome (NNTB) 12, 95% CI 9 to 23) and decreased the risk of needing endotracheal intubation by 65% (RR 0.36, 95% CI 0.28 to 0.46; N = 17 studies; NNTB 5, 95% CI 5 to 6).

Osadnik CR, Tee VS, Carson-Chahhoud KV et al. Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2017 Jul 13;7:CD004104
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004104.pub4/full

Rochwerg B, Brochard L, Elliott MW et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017;50:1602426
https://publications.ersnet.org/lookup/pmid/28860265

**Evidence Level: I**

## Subsequent management

**For how long should antibiotics be continued?**
A randomised, double-blind comparison in 532 patients of 5 vs 7 days of oral levofloxacin (Masterson, 2001) found identical clinical success rates at 7-10 days post-treatment. Another trial, in 295 patients (McCarty, 2001) found no statistically significant difference in clinical cure rate between 5 days of cefprozil and 10 days of clarithromycin.

McCarty JM, Pierce PF. Five days of cefprozil versus 10 days of clarithromycin in the treatment of an acute exacerbation of chronic bronchitis. Ann Allergy Asthma Immunol 2001;87:327-34

Masterson RG, Burley CJ. Randomized, double-blind study comparing 5- and 7-day regimens of oral levofloxacin in patients with acute exacerbation of chronic bronchitis. Int J Antimicrob Agents 2001;18:503-12

**Evidence Level: IV**

**For how long should prednisolone (corticosteroids) be continued?**
A 2018 systematic review of RCTs concluded that five days of oral corticosteroids is likely to be sufficient for treatment of adults with acute exacerbations of COPD. This review found there was no difference in risk of treatment failure between short-duration (7 days or fewer) and longer-duration (more than 7 days) systemic corticosteroid treatment (n = 457; odds ratio (OR) 0.72, 95% confidence interval (CI) 0.36 to 1.46). No difference in risk of relapse (a new event) was observed between short-duration and longer-duration systemic corticosteroid treatment (n = 457; OR 1.04, 95% CI 0.70 to 1.56). No difference in the likelihood of an adverse event was found between short-duration and longer-duration systemic corticosteroid treatment (n = 503; OR 0.89, 95% CI 0.46 to 1.69). Length of hospital stay (n = 421; mean difference (MD) -0.61 days, 95% CI -1.51 to 0.28) and lung function at the end of treatment (n = 185; MD FEV1 -0.04 L; 95% CI -0.19 to 0.10) did not differ between short-duration and longer-duration treatment.

Walters JA, Tan DJ, White CJ et al. Different durations of corticosteroid therapy for exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2018 Mar 19;3:CD006897
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006897.pub4/full

**Evidence Level: I**

## Discharge and follow-up

**Influenza vaccination helps to prevent exacerbations of COPD?**
A Cochrane review (Kopsaftis, 2018) found that inactivated vaccine in COPD patients resulted in a significant reduction in the total number of exacerbations per vaccinated subject compared with those who received placebo (weighted mean difference (WMD) -0.37, 95% confidence interval -0.64 to -0.11, P = 0.006). This was due to the reduction in "late" exacerbations occurring after three or four weeks (WMD -0.39, 95% CI -0.61 to -0.18, P = 0.0004). There was a significant increase in the occurrence of local adverse reactions in vaccines, but the effects were generally mild and transient. There was no evidence of an effect of intranasal live attenuated virus when this was added to inactivated intramuscular vaccination. The studies are too small to have detected any effect on mortality.

Kopsaftis Z, Wood-Baker R, Poole P. Influenza vaccine for chronic obstructive pulmonary disease (COPD). Cochrane Database Syst Rev. 2018 Jun 26;6:CD002733
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD002733.pub3/full

**Evidence Level: I**

**Domiciliary oxygen in patients with COPD and a $P_aO_2$ < 7.3 kPa prolongs life and helps to prevent exacerbations?**
A Cochrane review (Cranston, 2005) has concluded that long-term home oxygen therapy improved survival in a selected group of COPD patients with severe hypoxaemia (arterial $PaO_2$ less than 55 mm Hg (8.0 kPa)). Home oxygen therapy did not appear to improve survival in patients with mild to moderate hypoxaemia or in those with only arterial desaturation at night.
A 2023 systematic review concluded that long-tern oxygen therapy at home was associated with a significantly lower risk of hospital readmission (Sami, 2023). Seven studies were included in the analysis and the pooled analysis showed that the relative risk for readmission reduced 1.54 [95% CI 1.28 to 1.85], and 1.69 [95% CI 1.65 to 1.74] for patients with length of long-tern oxygen therapy treatment under and above 8 months, respectively.
2020 guidance from the American Thoracic Society stated there was “moderate-quality evidence” to support the prescribing of long-term oxygen therapy (LTOT) for at least 15 hours per day to COPD patients with severe hypoxemia. On the basis of this evidence the guideline panel “strongly recommended” LTOT (Jacobs, 2020).

Cranston JM, Crockett AJ, Moss JR, et al. Domiciliary oxygen for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2005; 4
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001744.pub2/full

Jacobs SS, Krishnan JA, Lederer DJ et al. Home Oxygen Therapy for Adults with Chronic Lung Disease. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2020; 202:e121–e141
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7667898/

Sami R, Savari MA, Mansourian M et al. Effect of Long-Term Oxygen Therapy on Reducing Rehospitalization of Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. Pulm Ther. 2023;9:255-70
https://pmc.ncbi.nlm.nih.gov/articles/pmid/37093408/

**Evidence Level: I**

**Smoking cessation in patients with severe COPD prolongs life and helps to prevent exacerbations?**
Smoking cessation “is the most important intervention in the management of patients with COPD” (Sherk, 2000).
Mean FEV1 has been shown to decline from 2.7 L to 2.4 L over 5 years in continuing smokers vs almost no decline from 2.8 L in sustained quitters (Anthonisen, 1994). A follow-up to this study after 11 years (Anthonisen, 2002) found that men who had quit at the beginning of the study declined at the rate of 30.2 ml/year vs 66.1 ml/year in men that continued to smoke.
There is no evidence that exacerbations are prevented by smoking cessation.

Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline in $FEV_1$: the Lung Health Study. JAMA 1994;272:1497-1505 http://www.phillycopd.com/PDF/EC03_Lung_health_study.pdf

Anthonisen NR, Connett JE, Murray RP. Smoking and lung function of Lung Health Study participants after 11 years. Am J Respir Crit Care Med 2002;166:675-9

**Evidence Level: III**

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