COPD-X Summary of Changes V2 65

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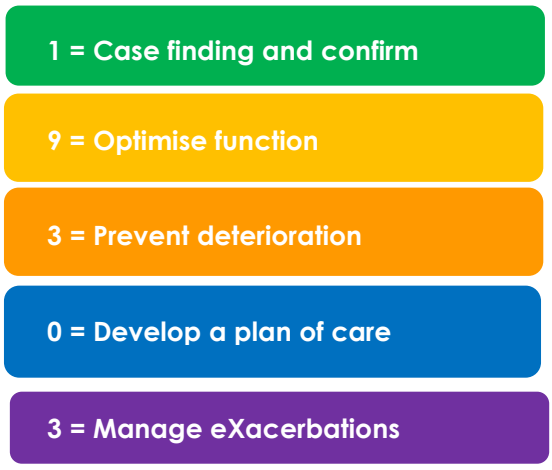
Snapshot of the evidence review cycle for V2 65 - Dec 2021

The latest update of The COPD-X Plan has been provided by Lung Foundation Australia following the December 2021 meeting of the COPD-X Guidelines Committee. There are **16** changes outlined in this summary.



Implications for Clinical Practice

All changes made to the document are outlined below and those highlighted in yellow are differentiated as the most significant and likely to have an impact on clinical practice.

C: Case finding and diagnosis

Change	Section	Type of change	If there is a relevant key recommendation, this is listed below for each change	Page number
C2.5 COPD case finding				
1	Schnieders et al (2021) published a systematic review and meta-analysis of the performance of micro-spirometers or two questionnaires compared to post-bronchodilator spirometry for detection of COPD. The meta-analysis included 17 studies. The overall area under the curve (AUC) of micro-spirometers was 0.84 (95% CI 0.80–0.89). For questionnaires the AUC for the COPD population screener (COPD-PS) questionnaire was 0.77 (95% CI 0.63–0.85) and the COPD diagnostic questionnaire (CDQ) was 0.72 (95% CI 0.64–0.78) (Schnieders 2021). *If spirometry is unavailable either a micro spirometer or questionnaire are useful tests for early detection.*	New citation and wording added to existing section describing tools for detection of COPD in a systematic review and meta-analysis study.	**A thorough history and examination is the first step in COPD diagnosis** [evidence level III-2, strong recommendation].	P29

O. Optimise function

Change	Section	Type of change	If there is a relevant key recommendation, this is listed below for each change	Page number
O2.1 Methylxanthines				
2	A meta-analysis of 4 RCTs and 3 cohort studies (n=47,556) examined the addition of theophylline to inhaled corticosteroids. Of the 7 studies reviewed, 4 used an ICS/LABA combination, 2 used ICS alone and 1 trial did not specify. Theophylline was associated with a higher hospitalization rate (HR 1.12, 95% CI 1.10-1.15, and mortality (HR 1.19, 95% CI 1.14-1.25) (Shuai 2021) [evidence level I]. Based on the available evidence, theophylline cannot be recommended for patients with COPD.	New citation and wording added to existing section to update use of Theophylline.	**Not directly related to a key recommendation.**	P43
O3.2 Inhaled corticosteroids (ICS)				
3	A comprehensive overview by Miravitlles et al (2021) of the risks associated with the use of ICS in patients with COPD found an increased risk of local disorders such as oral candidiasis and dysphonia and infectious adverse events such as pneumonia [evidence level I]. The pooled analysis of 16 RCTs with n=33,725 participants showed that exposure to ICSs almost tripled the risk of oral candidiasis (RR 2.89, 95% CI 2.36–3.55; p<0.00001). The pooled analysis of nine RCTs with 22 841 participants showed that exposure to ICS increased the risk of dysphonia by 277% (RR 3.77, 95% CI 2.81–5.05; p<0.00001; I^2=0%). The pooled analysis of 19 RCTs with 66 485 participants showed that exposure to ICSs for ⩾1 year increased the risk of pneumonia by 41% (RR 1.41, 95% CI 1.23–1.61; p<0.00001; I^2=55%). An interaction was found between the risk of pneumonia and the type of ICS used, with the highest risk being associated with fluticasone (10 studies with 45870 participants), whereas exposure to budesonide (six studies with 13 479 participants) was not associated with an increased risk of	New citation and wording added to existing section describing a more comprehensive systematic review, including updated information on long-term adverse effects of inhaled corticosteroid in the treatment of COPD. Some sections deleted and replaced with new information.	**Assessment is the first step to optimising function** [evidence level III-2, strong recommendation]. **Optimise function using a stepwise approach** [evidence level I, strong recommendation].	P45

	pneumonia (Miravitlles 2021). A dose–response relationship was observed, indicating that lower doses of ICS should be used in patients with COPD whenever possible. The risks of diabetes, osteoporosis, bone fractures and eye disorders are less clear.			
O4.2 Inhaled corticosteroids and` long-acting beta2-agonists and long-acting antimuscarinics in combination (ICS/LABA/LAMA)				
4	Different formulations of single inhaler triple therapy (ICS/LABA/LAMA) have similar efficacy for reducing exacerbations, as shown in two network meta-analyses (Bourdin 2021, Lee 2021) [evidence level I].	Additional citation and wording added to existing section noting the efficacy in two network meta-analyses.	**Optimise function using a stepwise approach** [evidence level I, strong recommendation].	P53
O5.2 Inhaler adherence				
5	Bhattarai et al (2020) conducted a systematic review of 38 studies published from 2003 to 2019 that examined rates of medication adherence and reported on barriers and enablers to adherence. Rates of non-adherence ranged from 22% to 93%. The majority of studies identified the presence of depression and subjects' concern about the harmful effects of the medicine as barriers to adherence (Bhattarai 2020).	New wording and citation added discussing medication adherence in a systematic review.	**Adherence and inhaler technique need to be checked on a regular basis** [evidence level I, strong recommendation].	P59

O6.1 Pulmonary Rehabilitation				
6	A Cochrane review of 21 studies comparing supervised maintenance pulmonary rehabilitation programs with usual care showed an improvement in health-related quality of life at 6-12 months (Chronic Respiratory Disease Questionnaire total score mean difference (MD) 0.54 points, 95% CI 0.04 - 1.03, 258 participants, four studies, which exceeds the minimal important difference of 0.5 points). It is uncertain whether supervised maintenance programs improve 6-minute walk distance (MD 26 meters, 95% CI -1.04 - 52.84, 639 participants, 10 studies) (Malaguti 2021). Whilst the optimal model for supervised maintenance exercise programs is still unclear, some form of regular exercise should be encouraged following completion of a pulmonary rehabilitation program to sustain the benefits gained (Alison 2017).	New citation describing Cochrane review included with additional wording. Relevant section changes made to reflect publication of Cochrane review.	**Non-pharmacological strategies (such as pulmonary rehabilitation and regular exercise) should be provided to all patients with COPD** [evidence level I, strong recommendation].	P62
O6.2 Exercise training				
7	Unsupervised exercise training using a formal prescription of frequency, intensity, time and type can significantly improve disease-specific quality of life in people with COPD, but not exercise capacity (Taylor 2021) [evidence level I]. Supervised exercise training is required to improve exercise capacity.	New citation and wording added to existing section regarding exercise training.	**Non-pharmacological strategies (such as pulmonary rehabilitation and regular exercise) should be provided to all patients with COPD** [evidence level I, strong recommendation].	P63

O7.3 Osteoporosis				
8	A meta-analysis by Kakoullis et al (2021) included 27 studies with a range of study designs, with 7662 participants and defined osteoporosis as a T-score of -2.5 SD where available. Participants with osteoporosis and or vertebral compression fractures were found to be older (3.17 years, 95% CI 2.14-4.19), lower BMI -3.15 (95% CI -4.41 to -1.88) and more likely to be female, which are recognised general population risk factors. These participants had a mortality OR of 2.40 (95% CI 1.24-4.64) and lower FEV1 -0.41L (95% CI -0.59 to -0.24) with a lower FEV1/FVC ratio. The authors note that it is likely that osteoporosis is a marker of severity of COPD or patient frailty, with surrogate associations with the outcomes demonstrated, rather than a direct cause of increased airflow obstruction or death (Kakoullis 2021) [evidence level I]. Pro-active screening and preventative treatment of osteoporosis are recommended	New citation and wording added to existing section describing a meta-analysis review.	**Comorbid conditions are common in patients with COPD** [evidence level III-2, strong recommendation].	P81
O7.5 Falls in COPD				
9	A systematic review (Oliveira 2021) has reported a falls incidence rate in COPD of 1.17 to 1.49 falls/person-year.	Updated citation reporting falls in COPD patients.	**Comorbid conditions are common in patients with COPD** [evidence level III-2, strong recommendation].	P83

Change	Section	Type of change	If there is a relevant key recommendation, this is listed below for each change	Page number
O9.2 Lung volume reduction surgery and bronchoscopic interventions ➢ *Endobronchial lung volume reduction*				
10	There was no difference in early mortality between valves/coils and control in this meta-analysis. However, a 2021 randomised controlled study of coils in patients with severe COPD (FEV1 15-45% predicted) was terminated early with only 120 of the > 200 planned participants recruited. There were 6 month follow up results available for 57 coil and 34 control participants, demonstrating clinically significant improvements in SGRQ of -10.6 (95%CI -15.9 - 5.4) and improvement in FEV1 +10.3% predicted (95% CI 4.7-16.0) in the coil arm. There were no deaths in the control arm, whilst there were 5 deaths in the coil arm. Also, the incidence of serious adverse events was higher in the coil arm (n=30 of the coil participants, n=3 of the control participants) (Klooster 2021). Overall, these results indicate mixed results for coils. There was concern regarding the lack of sham bronchoscopy and/or unclear status of blinding in some studies that may cause a risk of bias (van Agteren 2017). Endobronchial valves may be appropriate in highly selected patients with severe COPD and hyperinflation if collateral ventilation can be excluded (intact fissure on imaging and Chartis negative during bronchoscopy). Based on the data above the role of coils is unclear.	New citation and wording added (blue text) to existing section describing a meta-analysis. Additional statement regarding the role of coils (blue text.)	**Not directly related to a key recommendation.**	P93

P: Prevent deterioration

Change	Section	Type of change	If there is a relevant key recommendation, this is listed below for each change	Page number
P1 Risk factor reduction ➢ P1.2.5 Electronic cigarettes (e-cigarettes)				
11	In some cases, doctors may choose to prescribe nicotine e-cigarettes as a means of supporting smoking cessation. There is currently a lack of evidence of effectiveness and safety of nicotine e-cigarettes. TGA approved pharmacotherapy combined with behavioural support should be offered as first line therapy. Nicotine e-cigarettes are an unapproved product, meaning that unlike other forms of nicotine replacement therapy, they have not been assessed by the TGA for safety, quality and efficacy. From 1 October 2021, the Australian government introduced further restrictions aimed at reducing access to the use of nicotine e-cigarettes among adolescents and young adults while making them available for supporting smoking cessation. The arrangements include requiring a valid prescription to import nicotine e-cigarettes and liquids containing nicotine. A focussed update of the RACGP Smoking Cessation guidelines was undertaken to provide guidance about the rescheduling of nicotine e-liquids. Therapeutic Goods (Standard for Nicotine Vaping Products) (TGO 110) Order 2021 (TGO 110) came into effect on 1 October 2021. Refer to the following to access these guidelines: https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/supporting-smoking-cessation/pharmacotherapy-for-smoking-cessation Lung Foundation Australia has a position statement about electronic cigarettes: https://lungfoundation.com.au/lung-health/protecting-your-lungs/e-cigarettes-and-vaping/e-cigarettes-for-smoking-cessation/ https://lungfoundation.com.au/health-professionals/clinical-information/smoking-cessation/	Update to section to reflect change in availability of nicotine e-cigarettes.	**Smoking cessation is the most important intervention to prevent the worsening of COPD** [evidence level II, strong recommendation].	P105

Change	Section	Type of change	If there is a relevant key recommendation, this is listed below for each change	Page number
P4 Macrolides				
12	A Cochrane network meta-analysis by Janjua et al (2021) of various prophylactic antibiotics for patients with COPD (12 studies, n=3,405 patients) found beneficial effects of macrolides for reducing exacerbations (hazard ratio 0.67, 95% credible interval 0.60 - 0.75) compared to placebo and improving quality of life (mean difference in SGRQ of -2.30, 95% credible interval -3.61 - -0.99, although this difference did not reach the MCID) (Janjua 2021) [evidence level I]. No significant benefits were associated with use of long-term quinolones or tetracyclines, compared to placebo.	New citation and wording added to existing section describing results of a Cochrane network meta-analysis.	**Not directly related to a key recommendation.**	P108
P11 Long-term home non-invasive ventilation				
13	Raveling et al (2021) performed a meta-analysis of chronic non-invasive ventilation use in patients with COPD and hypercapnia compared to usual care. The analysis was separated into studies where NIV was commenced in a stable phase and studies where NIV was commenced after an exacerbation. Data was included from 13 stable COPD studies (n= 778) and 3 post exacerbation studies (n =364). There is a high risk of bias due to lack of blinding. Note is made of significant differences in trial design and NIV pressures delivered. Smoking status was not reported. Most studies excluded people with obstructive sleep apnoea. For the outcomes of quality of life and mortality sub-group analyses based on NIV pressures and baseline PaCO2 were not performed. In the stable COPD group, quality of life scores improved with NIV, after three months (SMD 0.39, 95% CI 0.15-0.62; 5 studies, 259 participants); however, the improvement in quality of life was not sustained to 12 months. There was no effect of NIV on exercise capacity. The risk for all-cause mortality is reduced by NIV (adjusted hazard ratio 0.75, 95% CI 0.58- 0.97; 3 studies, 405 participants; moderate-certainty evidence).	New meta-analysis discussed, with resulting changes to existing section to reflect this study.	**Not directly related to a key recommendation.**	P115-116

	In the group where NIV was commenced after an exacerbation there was no improvement in quality of life or mortality however, NIV did lead to an improvement in admission-free survival (adjusted hazard ratio 95% CI 0.54-0.94; 2 studies, 317 participants) (Raveling 2021). There was no effect of NIV on lung function in either group. Long term NIV can be considered in patients with severe stable COPD and hypercapnia. Such patients should be referred to a centre with expertise in home NIV.			

X: Manage eXacerbations

Change	Section	Type of change	If there is a relevant key recommendation, this is listed below for each change	Page number
X2.2 Optimise treatment ➢ *X2.2.3 Antibiotics for treatment of exacerbations*				
14	A retrospective cohort study from the Danish registry of COPD by Bagge et al (2021) examined outcomes following patients redeeming prescriptions for amoxycillin (AMX) or amoxycillin-clavulanic acid (AMC) for presumed community exacerbations of COPD. They found pneumonia hospitalisation or death by all cause after 30 days was decreased with AMX compared to AMC (adjusted HR 0.6, 95% CI 0.5-0.7, p<.0001). This was also observed for all cause hospitalisation or death (aHR 0.8, 95% CI 0.8-0.9, p<0.0001). Although confounding by severity is not excluded, the findings of this study support the recommendation broad - spectrum antibiotics such as AMC should not be the drug of first choice for outpatient exacerbations of COPD (Bagge 2021) [evidence level III-2].	Updated citation and wording added to an existing section describing a retrospective cohort study.	**Independent of the severity and practice setting, exacerbations with clinical features of infection (increased volume and change in colour of sputum and/or fever) benefit from antibiotic therapy** [evidence level I, strong recommendation].	P146

Change	Section	Type of change	If there is a relevant key recommendation, this is listed below for each change	Page number
X3.2 Non-invasive ventilation				
15	These findings were replicated in a similar but retrospective study based in a teaching hospital in China (Hong 2020).	Additional sentence added describing international data from China.	**Non-invasive ventilation (NIV) is effective for patients with rising paCO2 levels** [evidence level I, strong recommendation]. **Non-invasive ventilation (NIV) should be strongly considered in patients with an exacerbation of COPD who present with hypercapnic respiratory failure as defined on an arterial blood gas with a PaCO2 above 45mmHg and a pH less than 7.35** (Osadnik 2017) [evidence level I].	P150
X4. Uptake and impact of guidelines for exacerbations				
16	A retrospective study of 134 patients admitted with an exacerbation of COPD at an Australian tertiary hospital demonstrated poor adherence to COPD-X recommendation for management of exacerbations. Controlled oxygen therapy to achieve SpO2 88-92% was provided in 42% of cases and referral to pulmonary rehabilitation was made in only 17.9% of cases. Furthermore, smoking cessation counselling was provided to 40% of patients and a review of immunisation status only occurred in 2% of cases (Sha 2020).	New citiation and wording added to an existing section describing a retrospective study in the Australian setting.	**A COPD exacerbation is characterised by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset and may warrant a change in regular medication or hospital admission** [evidence level III-2, strong recommendation].	P158

New studies cited (listed in alphabetical order)

BAGGE, K., SIVAPALAN, P., EKLÖF, J., HERTZ, F. B., ANDERSEN, C., HANSEN, E. F., JARLØV, J. O. & JENSEN, J. S. 2021. Antibiotic treatment in acute exacerbation of COPD: patient outcomes with amoxicillin vs. amoxicillin/clavulanic acid-data from 43,636 outpatients. *Respir Res,* 22**,** 11.

BHATTARAI, B., WALPOLA, R., MEY, A., ANOOPKUMAR-DUKIE, S. & KHAN, S. 2020. Barriers and Strategies for Improving Medication Adherence Among People Living With COPD: A Systematic Review. *Respir Care,* 65**,** 1738-1750.

HONG, Y., LIU, Q., BAI, L., JIANG, L., HAN, X., HUANG, S., HU, W., DUAN, J. & LIU, C. 2020. Head-To-Head Comparison of Treatment Failure and Costs among COPD Patients Who Used Noninvasive Ventilation in the Ward versus in the ICU: A Propensity-Matched Cohort Study. *Can Respir J,* 2020**,** 6682589.

JANJUA, S., MATHIOUDAKIS, A. G., FORTESCUE, R., WALKER, R. A., SHARIF, S., THREAPLETON, C. J. & DIAS, S. 2021. Prophylactic antibiotics for adults with chronic obstructive pulmonary disease: a network meta-analysis. *Cochrane Database Syst Rev,* 1**,** Cd013198.

KAKOULLIS, L., SAMPSONAS, F., KARAMOUZOS, V., KYRIAKOU, G., PARPERIS, K., PAPACHRISTODOULOU, E., CHRISTOPHI, C., LYKOURAS, D., KALOGEROPOULOU, C., DAOUSSIS, D., PANOS, G., VELISSARIS, D., KARKOULIAS, K. & SPIROPOULOS, K. 2021. The impact of osteoporosis and vertebral compression fractures on mortality and association with pulmonary function in COPD: A meta-analysis. *Joint Bone Spine,* 89**,** 105249.

KLOOSTER, K., VALIPOUR, A., MARQUETTE, C. H., BOUTROS, J., MAL, H., MARCEAU, A., SHAH, P. L., CONWAY, F., DESLÉE, G., BOURDIN, A., PISON, C., GRAH, C., HETZEL, M., SCHUMANN, C., KESSLER, R., HUEBNER, R. H., SKOWASCH, D., DARWICHE, K., HAMMERL, P., STANZEL, F., BEZZI, M., DUTAU, H., HERTH, F. J. F. & SLEBOS, D. J. 2021. Endobronchial Coil System versus Standard-of-Care Medical Management in the Treatment of Subjects with Severe Emphysema. *Respiration,* 100**,** 804-810.

LEE, H. W., KIM, H. J., JANG, E. J. & LEE, C. H. 2021. Comparisons of Efficacy and Safety between Triple (Inhaled Corticosteroid/Long-Acting Muscarinic Antagonist/Long-Acting Beta-Agonist) Therapies in Chronic Obstructive Pulmonary Disease: Systematic Review and Bayesian Network Meta-Analysis. *Respiration,* 100**,** 631-643.

MALAGUTI, C., DAL CORSO, S., JANJUA, S. & HOLLAND, A. E. 2021. Supervised maintenance programmes following pulmonary rehabilitation compared to usual care for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev,* 8**,** Cd013569.

MIRAVITLLES, M., AULADELL-RISPAU, A., MONTEAGUDO, M., VÁZQUEZ-NIEBLA, J. C., MOHAMMED, J., NUÑEZ, A. & URRÚTIA, G. 2021. Systematic review on long-term adverse effects of inhaled corticosteroids in the treatment of COPD. *Eur Respir Rev,* 30.

OLIVEIRA, C. C., ANNONI, R., LEE, A. L., MCGINLEY, J., IRVING, L. B. & DENEHY, L. 2021. Falls prevalence and risk factors in people with chronic obstructive pulmonary disease: A systematic review. *Respir Med,* 176**,** 106284.

RAVELING, T., VONK, J., STRUIK, F. M., GOLDSTEIN, R., KERSTJENS, H. A., WIJKSTRA, P. J. & DUIVERMAN, M. L. 2021. Chronic non-invasive ventilation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev,* 8**,** Cd002878.

SCHNIEDERS, E., ÜNAL, E., WINKLER, V., DAMBACH, P., LOUIS, V. R., HORSTICK, O., NEUHANN, F. & DECKERT, A. 2021. Performance of alternative COPD case-finding tools: a systematic review and meta-analysis. *Eur Respir Rev,* 30.

SHA, J., WORSNOP, C. J., LEAVER, B. A., VAGIAS, C., KINSELLA, P., RAHMAN, M. A. & MCDONALD, C. F. 2020. Hospitalised exacerbations of chronic obstructive pulmonary disease: adherence to guideline recommendations in an Australian teaching hospital. *Intern Med J,* 50**,** 453-459.

SHUAI, T., ZHANG, C., ZHANG, M., WANG, Y., XIONG, H., HUANG, Q. & LIU, J. 2021. Low-dose theophylline in addition to ICS therapy in COPD patients: A systematic review and meta-analysis. *PLoS One,* 16**,** e0251348.

TAYLOR, D., JENKINS, A. R., PARROTT, K., BENHAM, A., TARGETT, S. & JONES, A. W. 2021. Efficacy of unsupervised exercise in adults with obstructive lung disease: a systematic review and meta-analysis. *Thorax,* 76**,** 591-600.

Citations removed (listed in alphabetical order)

FESTIC, E., BANSAL, V., GUPTA, E. & SCANLON, P. D. 2016. Association of Inhaled Corticosteroids with Incident Pneumonia and Mortality in COPD Patients; Systematic Review and Meta-Analysis. *COPD,* 13**,** 312-26.

GUELL, M. R., CEJUDO, P., ORTEGA, F., PUY, M. C., RODRIGUEZ-TRIGO, G., PIJOAN, J. I., MARTINEZ-INDART, L., GOROSTIZA, A., BDEIR, K., CELLI, B. & GALDIZ, J. B. 2017. Benefits of Long-Term Pulmonary Rehabilitation Maintenance Program in Patients with Severe Chronic Obstructive Pulmonary Disease. Three-Year Follow-up. *Am J Respir Crit Care Med,* 195**,** 622-629.

JENKINS, A. R., GOWLER, H., CURTIS, F., HOLDEN, N. S., BRIDLE, C. & JONES, A. W. 2018. Efficacy of supervised maintenance exercise following pulmonary rehabilitation on health care use: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis,* 13**,** 257-273.

KEW, K. M. & SENIUKOVICH, A. 2014b. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev,* 3**,** CD010115

KOHNLEIN, T., WINDISCH, W., KOHLER, D., DRABIK, A., GEISELER, J., HARTL, S., KARG, O., LAIER-GROENEVELD, G., NAVA, S., SCHONHOFER, B., SCHUCHER, B., WEGSCHEIDER, K., CRIEE, C. P. & WELTE, T. 2014. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *Lancet Respir Med,* 2**,** 698-705.

MURPHY, P. B., REHAL, S., ARBANE, G., BOURKE, S., CALVERLEY, P. M. A., CROOK, A. M., DOWSON, L., DUFFY, N., GIBSON, G. J., HUGHES, P. D., HURST, J. R., LEWIS, K. E., MUKHERJEE, R., NICKOL, A., OSCROFT, N., PATOUT, M., PEPPERELL, J., SMITH, I., STRADLING, J. R., WEDZICHA, J. A., POLKEY, M. I., ELLIOTT, M. W. & HART, N. 2017. Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation: A Randomized Clinical Trial. *Jama,* 317**,** 2177-2186.

PAVORD, I. D., LETTIS, S., ANZUETO, A. & BARNES, N. 2016. Blood eosinophil count and pneumonia risk in patients with chronic obstructive pulmonary disease: a patient-level meta-analysis. *Lancet Respir Med,* 4**,** 731-741.

WILSON, M. E., DOBLER, C. C., MORROW, A. S., BEUSCHEL, B., ALSAWAS, M., BENKHADRA, R., SEISA, M., MITTAL, A., SANCHEZ, M., DARAZ, L., HOLETS, S., MURAD, M. H. & WANG, Z. 2020. Association of Home Noninvasive Positive Pressure Ventilation With Clinical Outcomes in Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-analysis. *Jama,* 323**,** 455-465.