COPD-X Summary of Changes V2.62

June and October 2020

The latest update of The COPD-X Plan: Australian and New Zealand Guidelines for the Management of COPD has been provided by Lung Foundation Australia in conjunction with the Thoracic Society of Australia and New Zealand following the June 2020 and October 2020 meetings of the COPD-X Guidelines Committee.

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.

Current COPD Guidelines Committee

Assoc. Professor Eli Dabscheck, MBBS, M Clin Epi, FRACP, Respiratory and Sleep Physician, Department of Respiratory Medicine, The Alfred Hospital, Melbourne, VIC (Co-Chair)

Lung Foundation Australia Secretariat Support

Ms Juliet L Brown, BA(Hons), MLib, COPD Project and Guidelines Manager, Lung Foundation Australia, Brisbane; Adjunct Fellow, The University of Queensland, Brisbane

Ms Mearon O'Brien, BPubH, Guidelines Manager, Lung Foundation Australia, Brisbane

Website Updates: Ms Mearon O'Brien, Guidelines Manager, Lung Foundation Australia, Brisbane

C. Confirm diagnosis and assess severity

C2.5 COPD case finding

No changes

O. Optimise Function

O1.2.3 Long-acting bronchodilator combinations (LAMA/LABA) (p41)

A systematic review of 24 studies (n=45,441 participants) found statistically significant reductions in hospital admissions (risk ratio 0.89, 95% CI 0.82 to 0.97) and exacerbations (risk ratio 0.80, 95% CI 0.69 to 0.92) with LAMA/LABA combination therapy, compared with LAMA or LABA monotherapy (Mammen 2020) [evidence level I]. Reductions in dyspnoea and health-related quality of life did not reach MCID.

O4.2 Inhaled corticosteroids and long-acting beta$_2$-agonists and long-acting antimuscarinics in combination (ICS/LABA/LAMA) (p50)

ICS/LABA/LAMA – single inhaler triple therapy

Budesonide/formoterol/glycopyrronium

In patients with moderate-to-very-severe COPD who are at risk of exacerbations, triple therapy with a budesonide–glycopyrrolate–formoterol combination MDI (ETHOS Trial) showed significant benefits over dual therapy with a LAMA–LABA or an ICS–LABA combination with respect to the annual rate of moderate or severe COPD exacerbations (Rabe 2020). The rate was significantly lower with 320-µg–budesonide triple therapy than with glycopyrrolate–formoterol (24% lower: rate ratio, 0.76; 95% confidence interval [CI], 0.69 to 0.83; P<0.001) or budesonide–formoterol (13% lower: rate ratio, 0.87; 95% CI, 0.79 to 0.95; P = 0.003). The rate was significantly lower also with 160-µg–budesonide triple therapy than with glycopyrrolate–formoterol (25% lower: rate ratio, 0.75; 95% CI, 0.69 to 0.83; P<0.001) or budesonide–formoterol (14% lower: rate ratio, 0.86; 95% CI, 0.79 to 0.95; P = 0.002).

Triple therapy with a 320-µg dose of budesonide also resulted in a 46% lower all-cause mortality than glycopyrrolate–formoterol group [28 vs. 49 deaths; hazard ratio, 0.54; 95% CI, 0.34 to 0.87].

The incidence of any adverse event was similar across the treatment groups (range, 61.7 to 64.5%); the incidence of confirmed pneumonia was higher in the groups that included inhaled glucocorticoid (range 3.5 to 4.5%) than the glycopyrrolate–formoterol group (2.3%).

O5.1 Inhaler technique (June 2020 Meeting) (p55-56)

A systematic review that included 55 studies and evaluated health professionals performing 9,996 tests demonstrating their inhaler technique was only considered correct in 15.5% of health professionals (95% CI, 12 to 19.3) overall (Plaza 2018).

Due to the lack of long-term data, differences in outcome definitions and study designs, robust conclusions regarding the differences between single- and multiple inhaler users with regards to technique cannot be made (Zhang 2020) [evidence level I].

Pharmacist-led interventions comprising information provision, motivating patients and taught necessary behavioural skills significantly improved medication adherence (1.41 [1.24 to 1.61], P < .00001) and correct inhalation technique (Risk Ratio 1.85 [95% CI 1.57 to 2.17]), compared with the control group (Jia 2020) [evidence level I].

O6.1 Pulmonary rehabilitation (June 2020 Meeting) (p59)

Telerehabilitation may enable people with high symptom burden or travel restrictions to access pulmonary rehabilitation (see section **D4 Telehealth**).

O7.2 Cardiac disease (October 2020 Meeting) (p75)

High sensitivity troponin (hs-Tn) levels have now been associated with increased mortality in prospective cohort studies in stable COPD (Neukamm 2016, Waschki 2019) [evidence level III-2]. In a well characterised cohort of 2085 patients with COPD, Waschki and colleagues report baseline hs-Tn level to be independently associated with all-cause mortality at three years whether considered as a continuous variable [log hs-TnI, HR 1.28 (95%CI, 1.01 to 1.62)] or dichotomised at 6ng/L [HR 1.63 (95%CI, 1.10 to 2.42)] (as hs-TnI levels greater than 6ng/L identify individuals in the general population who are at high risk of death during follow-up) (Waschki 2019).

O7.3 Osteoporosis (October 2020 Meeting) (p79)

A systematic review of 58 studies of heterogeneous quality limited by largely cross-sectional designs (8,753 patients with COPD) found a mean prevalence of 38% (95% CI 34 to 43) for osteoporosis in patients with COPD, with increasing odds ratios for osteoporosis associated with lower BMI and sarcopenia (Chen 2019), indicating that people with COPD are at special risk of osteoporotic fracture. The overall OR for osteoporosis in COPD was 2.83 (95% CI: 2.00 to 4.03), with particular risk (OR 4.26: 95% CI: 1.07 to 16.99) for those with BMI of < 18.5 kg/m2.

O9.2 Surgical Lung Volume Reduction (October 2020 Meeting) (p91)

A retrospective analysis of 2,815 LVRS cases performed in America demonstrated an in-hospital mortality rate of 5.5% (Attaway 2019). Pulmonary hypertension was associated with an increased risk in mortality (adjusted OR, 4.4; 95% CI 1.7 to 1.5).

O10 Pharmacological management of breathlessness – opioids and benzodiazepines (October 2020 Meeting) (p95)

Low dose morphine SR, 10mg twice day, with up-titration after 1 week if required, in a double blind RCT with 111 patients, over 4 weeks, significantly improved health status as measured by the CAT score (-2.18, 95% CI -4.14 to -0.22). Overall there was no effect on breathlessness measures; however, in the subgroup of people with MMRC 3-4, there was a significant difference in change of worst breathlessness in the previous 24 hours between the treatment groups (-1.33, 95% CI -2.5 to 0.16; p=0.03). The only adverse effect demonstrated was constipation (Verberkt 2020) [evidence level-II].

P: Prevent deterioration

P8. Humidification and nasal high flow (NHF) therapy (October 2020 Meeting) (p109)

Several trials have shown that nasal high flow (NHF) humidified air in stable COPD patients reduces transcutaneous CO_2 ($PtCO_2$) and respiratory rate (Fraser 2016, Biselli 2017), (McKinstry 2018, **2019**).

P11 Non-invasive ventilation (October 2020 Meeting) (p113)

Section reworded.

A meta-analysis of 8 RCTs and 5 observational studies (Wilson 2020) concluded that home bilevel ventilation reduces mortality (22.31% vs. 28.57%; risk difference [RD], −5.53% (95% CI −10.29% to −0.76%); odds ratio [OR], 0.66 (95% CI,0.51 to 0.87); P = 0.003). 13 studies were included in this analysis with 1,423 patients. The authors rated strength of evidence for this finding as moderate. Note is made of significant differences in trial design and NIV pressures delivered. The use of home NIV was also associated with a reduction in all cause hospitalisation and no significant difference in quality of life. Smoking status was not reported. A sensitivity analysis found that the mortality benefit was only present if the home NIV was commenced in stable patients (pCO2 greater than 45mmHg at least two weeks after an exacerbation) rather than at the time of a COPD exacerbation. Although this meta-analysis did not evaluate NIV pressures, the recent trials with positive outcomes used inspiratory pressures above 20cm (Kohnlein 2014, Murphy 2017).

Long term NIV should be considered in suitable patients with severe stable COPD and hypercapnia. Such patients should be referred to a centre with expertise in home NIV.

D: Develop a plan of care

D3.2 Exacerbation prevention (October 2020 Meeting) (p126)

A commentary about appropriate person-centred language to improve response to COPD exacerbations has been included in the Exacerbation prevention section. It has been suggested that this is an area for future collaborative work among the respiratory community and patients.

D5. Treat anxiety and depression (October Meeting 2020) (p129-130)

Entire section updated with more contemporary references.

X: Manage eXacerbations

Introduction section

Link to COVID-19 Living Guidelines (p134):
Given the current COVID-19 pandemic, it is recommended that patients with COPD take adequate precautions to stay well (https://lungfoundation.com.au/lung-health/protecting-your-lungs/coronavirus-disease-covid-19/what-you-need-to-know/). Guidance for diagnosis and management of COVID-19 infection is highly relevant to patients with COPD. Living guidelines from the National COVID-19 Clinical Evidence Taskforce are available at https://covid19evidence.net.au/#living-guidelines.

X2.2.3 Antibiotics for treatment of exacerbations (October 2020 Meeting) (p144)

A meta-analysis of RCTs and observational studies investigating the impact of a procalcitonin-based protocol on antibiotic prescription and clinical outcomes in patients with COPD exacerbations, found that the use of procalcitonin-based protocols significantly reduced the length of antibiotic treatment in COPD exacerbation (MD = -2.01 days, 95% CI -3.89 to -0.1] days, p=0.04, moderate quality, and MD = -1.64 days, 95% CI -2.91 to -0.36 days, p=0.01, very low quality for RCTs and observational study, respectively), while no apparent effects were found on length of hospital stay, treatment failure and all-cause mortality. The effect of procalcitonin on antibiotic duration was no longer significant (MD = -1.88 days, 95% CI -3.95 to 0.19 days, p=0.08, and MD = -1.72 days, 95% CI -4.28 to 0.83 days, p=0.19, respectively), when studies with high risk of bias were excluded.

Procalcitonin has limited value in guiding antibiotic use in COPD exacerbation (Chen 2020) [evidence level I].

References added

BAFADHEL, M., CRINER, G., DRANSFIELD, M. T., JANSSENS, W., MCDONALD, V. M., VOGELMEIER, C. F., RUSSELL, R. E. & COLLIS, P. 2020. Exacerbations of chronic obstructive pulmonary disease: time to rename. *Lancet Respir Med,* 8**,** 133-135.

CHEN, K., PLEASANTS, K. A., PLEASANTS, R. A., BEIKO, T., WASHBURN, R. G., YU, Z., ZHAI, S. & DRUMMOND, M. B. 2020. Procalcitonin for Antibiotic Prescription in Chronic Obstructive Pulmonary Disease Exacerbations: Systematic Review, Meta-Analysis, and Clinical Perspective. *Pulm Ther*.

FITZGERALD, J. M. 2011. Targeting lung attacks. *Thorax,* 66**,** 365-6.

GARCÍA-SANZ, M. T., CÁNIVE-GÓMEZ, J. C., SENÍN-RIAL, L., ABOAL-VIÑAS, J., BARREIRO-GARCÍA, A., LÓPEZ-VAL, E. & GONZÁLEZ-BARCALA, F. J. 2017. One-year and long-term mortality in patients hospitalized for chronic obstructive pulmonary disease. *J Thorac Dis,* 9**,** 636-645.

HALPIN, D. 2008. Mortality in COPD: inevitable or preventable? Insights from the cardiovascular arena. *Copd,* 5**,** 187-200.

HOLVERDA, S., RUTGERS, M. R. & KERSTJENS, H. A. M. 2020. Time to rename COPD exacerbations: implementing the term lung attack. *Lancet Respir Med,* 8**,** e25.

JIA, X., ZHOU, S., LUO, D., ZHAO, X., ZHOU, Y. & CUI, Y. M. 2020. Effect of pharmacist-led interventions on medication adherence and inhalation technique in adult patients with asthma or COPD: A systematic review and meta-analysis. *J Clin Pharm Ther*.

JONES, K. A., GIBSON, P. G., YORKE, J., NIVEN, R., SMITH, A. & MCDONALD, V. M. 2019. Attack, flare-up, or exacerbation? The terminology preferences of patients with severe asthma. *J Asthma***,** 1-10.

KESSLER, R., STÅHL, E., VOGELMEIER, C., HAUGHNEY, J., TRUDEAU, E., LÖFDAHL, C. G. & PARTRIDGE, M. R. 2006. Patient understanding, detection, and experience of COPD exacerbations: an observational, interview-based study. *Chest,* 130**,** 133-42.

KHOR, Y. H., WONG, R. & MCDONALD, C. F. 2019. Post-Hospitalization Short-Term Oxygen Therapy: Use of a Clinical Management Pathway and Long-Term Follow-Up. *Respir Care,* 64**,** 272-278.

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.

MAMMEN, M. J., PAI, V., AARON, S. D., NICI, L., ALHAZZANI, W. & ALEXANDER, P. E. 2020. Dual LABA/LAMA Therapy versus LABA or LAMA Monotherapy for Chronic Obstructive Pulmonary Disease. A Systematic Review and Meta-analysis in Support of the American Thoracic Society Clinical Practice Guideline. Ann Am Thorac Soc,17,1133-1143.

MCDONALD, V. M., OSADNIK, C. R. & GIBSON, P. G. 2019. Treatable traits in acute exacerbations of chronic airway diseases. *Chron Respir Dis,* 16**,** 1479973119867954.

MCKINSTRY, S., SINGER, J., BAARSMA, J. P., WEATHERALL, M., BEASLEY, R. & FINGLETON, J. 2019. Nasal high-flow therapy compared with non-invasive ventilation in COPD patients with chronic respiratory failure: A randomized controlled cross-over trial. *Respirology,* 24**,** 1081-1087.

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., BEASLEY, R., AGUSTI, A., ANDERSON, G. P., BEL, E., BRUSSELLE, G., CULLINAN, P., CUSTOVIC, A., DUCHARME, F. M., FAHY, J. V., FREY, U., GIBSON, P., HEANEY, L. G., HOLT, P. G.,

HUMBERT, M., LLOYD, C. M., MARKS, G., MARTINEZ, F. D., SLY, P. D., VON MUTIUS, E., WENZEL, S., ZAR, H. J. & BUSH, A. 2018. After asthma: redefining airways diseases. *Lancet,* 391**,** 350-400.

PLAZA, V., GINER, J., RODRIGO, G. J., DOLOVICH, M. B. & SANCHIS, J. 2018. Errors in the Use of Inhalers by Health Care Professionals: A Systematic Review. *J Allergy Clin Immunol Pract,* 6**,** 987-995.

RABE, K. F., MARTINEZ, F. J., FERGUSON, G. T., WANG, C., SINGH, D., WEDZICHA, J. A., TRIVEDI, R., ST ROSE, E., BALLAL, S., MCLAREN, J., DARKEN, P., AURIVILLIUS, M., REISNER, C. & DORINSKY, P. 2020. Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD. *N Engl J Med,* 383**,** 35-48.

VERBERKT, C. A., VAN DEN BEUKEN-VAN EVERDINGEN, M. H. J., SCHOLS, J., HAMELEERS, N., WOUTERS, E. F. M. & JANSSEN, D. J. A. 2020. Effect of Sustained-Release Morphine for Refractory Breathlessness in Chronic Obstructive Pulmonary Disease on Health Status: A Randomized Clinical Trial. *JAMA Intern Med*.

WASCHKI, B., ALTER, P., ZELLER, T., MAGNUSSEN, C., NEUMANN, J. T., TWERENBOLD, R., SINNING, C., HERR, C., KAHNERT, K., FAHNDRICH, S., BLANKENBERG, S., RABE, K. F., WELTE, T., JORRES, R. A., VOGELMEIER, C. F., BALS, R. & WATZ, H. 2019. High-sensitivity troponin I and all-cause mortality in patients with stable COPD: An analysis of the COSYCONET study. *Eur Respir J*.

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.

ZHANG, S., KING, D., ROSEN, V. M. & ISMAILA, A. S. 2020. Impact of Single Combination Inhaler versus Multiple Inhalers to Deliver the Same Medications for Patients with Asthma or COPD: A Systematic Literature Review. *Int J Chron Obstruct Pulmon Dis,* 15**,** 417-438.

References removed

ALEXOPOULOS, G. S., KIOSSES, D. N., SIREY, J. A., KANELLOPOULOS, D., SEIRUP, J. K., NOVITCH, R. S., GHOSH, S., BANERJEE, S. & RAUE, P. J. 2014. Untangling therapeutic ingredients of a personalized intervention for patients with depression and severe COPD. *Am J Geriatr Psychiatry,* 22**,** 1316-24.

ARGYROPOULOU, P., PATAKAS, D., KOUKOU, A., VASILIADIS, P. & GEORGOPOULOS, D. 1993. Buspirone effect on breathlessness and exercise performance in patients with chronic obstructive pulmonary disease. *Respiration,* 60**,** 216-20

EISER, N., HARTE, R., SPIROS, K., PHILLIPS, C. & ISAAC, M. T. 2005. Effect of treating depression on quality-of-life and exercise tolerance in severe COPD. *COPD,* 2**,** 233-41.

EVANS, M., HAMMOND, M., WILSON, K., LYE, M. & COPELAND, J. 1997. Placebo-controlled treatment trial of depression in elderly physically ill patients. *Int J Geriatr Psychiatry,* 12**,** 817-24.

HE, Y., ZHENG, Y., XU, C., YANG, H., WANG, Z., ZHOU, L., WAN, Y., ZHENG, D. & ZHU, J. 2016. Sertraline hydrochloride treatment for patients with stable chronic obstructive pulmonary disease complicated with depression: a randomized controlled trial. *Clin Respir J,* 10**,** 318-25.

IYER, A. S., BHATT, S. P., GARNER, J. J., WELLS, J. M., TREVOR, J. L., PATEL, N. M., KIRKPATRICK, D., WILLIAMS, J. C. & DRANSFIELD, M. T. 2016. Depression Is Associated with Readmission for Acute Exacerbation of Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc,* 13**,** 197-203.

LACASSE, Y., BEAUDOIN, L., ROUSSEAU, L. & MALTAIS, F. 2004. Randomized trial of paroxetine in end-stage COPD. *Monaldi Arch Chest Dis,* 61**,** 140-7

MA, R. C., YIN, Y. Y., WANG, Y. Q., LIU, X. & XIE, J. 2019. Effectiveness of cognitive behavioural therapy for chronic obstructive pulmonary disease patients: A systematic review and meta-analysis. *Complement Ther Clin Pract,* 38**,** 101071.

OMACHI, T. A., KATZ, P. P., YELIN, E. H., GREGORICH, S. E., IRIBARREN, C., BLANC, P. D. & EISNER, M. D. 2009. Depression and health-related quality of life in chronic obstructive pulmonary disease. *Am J Med,* 122**,** 778 e9-15.