COPD-X Summary of Changes V2.48 December2016

Implications for Clinical Practice

The following changes have been identified as being the most significant and likely to have an impact on clinical practice:

Executive Summary

Bullet point in Section O, "Pulmonary rehabilitation reduces hospitalisation for exacerbations and has been shown to be cost-effective" has been split into two separate points:

- Pulmonary rehabilitation reduces hospitalisation for exacerbations of COPD
- Pulmonary rehabilitation is cost effective

Change to bullet point in Section P to reflect text in main body of the document which recommends the use of long term oxygen therapy at 18 hours/day:

- Long-term oxygen therapy, ideally at least 18h/day, prolongs life in hypoxaemic patients (PaO_2<55mmHg, or 7.3kPa)

All Changes

Note: The use of the term acute exacerbation of COPD or AECOPD has been removed throughout COPD-X and is now referred to as "an exacerbation of COPD".

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C: Confirm diagnosis and assess severity

C1 Aetiology and natural history

Inclusion of a sentence based on evidence from a study by Elbehairy 2016 acknowledging that smokers who do not meet spirometric criteria for COPD may have respiratory symptoms and reduced physical activity, as well as other subtle abnormalities of lung function [1].

C2.3 Spirometry

Inclusion of a sentence stating there is evidence of both underdiagnosis and misdiagnosis of COPD in the community.

O: Optimise Function

O1.2.1 Long-acting muscarinic antagonists (LAMA)

Addition of level II evidence from a study by Feldman comparing once daily umeclidinium plus placebo, or tiotropium plus placebo in patients with symptomatic moderate-to-severe COPD. In this 12-week, multicentre, randomized, blinded, double-dummy, parallel-group, non-inferiority study, the least squares (LS) mean change from baseline in trough FEV_1 at day 85 was greater with umeclidinium. Both treatments showed clinically meaningful improvements, but there were no significant differences between groups for TDI, SGRQ, and CAT scores. Tolerability and safety profiles were also similar [2].

O3.2 Inhaled corticosteroids (ICS)

Inclusion of a paragraph discussing pneumonia risks in patients taking ICS based on two studies. The first, a meta-analysis of 38 studies (including 29 RCTs and nine observational studies) of ICS use reported by Festic et al [3], demonstrated similar increases in pneumonia risk, without associated

increases in pneumonia-associated mortality or overall mortality. A post-hoc meta-analysis by Pavord [4] gave a small signal suggesting that patients with eosinophil counts <2% were at marginally increased risk of pneumonia events whether or not they were receiving ICS. This may be the group who also derive least benefit from inhaled corticosteroids. Further prospective studies are awaited.

O4.2 Inhaled corticosteroids and long-acting beta2-agonists and long-acting antimuscarinics in combination

Inclusion of new wording around "triple" therapy from two studies. The first study was a Cochrane systematic review of six studies [5] comprising 1,902 participants that compared tiotropium plus LABA/ICS combination therapy versus tiotropium alone. The study found that "triple" therapy decreased hospital admissions in comparison with tiotropium alone. Health-related quality of life showed a statistically significant but not clinically significant improvement in total scores with the use of tiotropium plus LABA/ICS compared with tiotropium alone. Although statistically significant changes in FEV_1 with tiotropium plus LABA/ICS compared with tiotropium plus placebo were observed, the difference in treatment effect on FEV_1 did not reach the MCID. Compared with tiotropium alone, tiotropium plus LABA/ICS-based therapy did not seem to increase adverse effects. Evidence was insufficient to support the benefit of "triple" therapy for mortality or exacerbations. Not all patients included in these studies had COPD that was severe enough to be recommended "triple" therapy according to current guidelines [evidence level I].

The second study by Singh et al discussed escalation to ICS/LABA/LAMA (beclometasone/formoterol/glycopyrronium) in a single inhaler, in patients already taking ICS/LABA (beclometasone/formoterol). This intervention was tested in a 52 week RCT of 1,368 COPD patients who had FEV_1 <50% predicted, one or more exacerbations in the last 12 months, and significant dyspnoea and impact of COPD [6] [evidence level II]. Compared to ICS/LABA, ICS/LABA/LAMA in a single MDI improved pre-dose FEV_1, with no difference in dyspnoea score. At week 52, treatment with the "triple" therapy inhaler was associated with a reduced rate of moderate-severe exacerbations and increased proportion of patients having a beneficial improvement in SGRQ. In patients with severe COPD and frequent exacerbations, ICS/LABA/LAMA in a single inhaler may be more beneficial than ICS/LABA. The combination of beclometasone/formoterol/glycopyrronium is not currently available in Australia.

O6.1 Pulmonary rehabilitation

Inclusion of level I evidence that pulmonary rehabilitation reduces hospitalisation for exacerbations of COPD. A systematic review of 21 studies [7] reported the effects of pulmonary rehabilitation on subsequent hospitalisation for exacerbations of COPD. The meta-analysis included 18 studies (10 RCTs, five observational before and after studies, and three cohort studies), of which five were carried out in Australia or New Zealand. Data from the RCTs and from the five observational studies that compared hospital admissions in the 12 months before and following pulmonary rehabilitation favoured rehabilitation; however, the results of the cohort studies did not support this finding. Pooled analysis of the three cohort studies showed a higher rate of hospitalisation in the PR group compared to the reference group; however this finding was influenced predominantly by the results from one study.

O8.1 Treatment (Hypoxaemia and pulmonary hypertension)

Addition of a new paragraph based on a meta-analysis of 21 RCTs of domiciliary NIV trials [8]. The authors concluded that domiciliary NIV did not reduce mortality in patients with stable COPD or in

patients post admission for an exacerbation of COPD. Significant differences in patient populations and trial designs were noted.

O9.4 Pre-operative work-up for surgery

Inclusion of a new section discussing the increased risk of post-operative pulmonary complications in COPD patients after any thoracic or non-thoracic surgery. A US database analysis showed that COPD was associated with increased post-operative mortality and morbidity with major surgical procedures [9], including abdominal operations [10]. Careful pre-operative work-up of patients with COPD minimises post-operative complications. As no specific thresholds of lung function are mandated for non-thoracic surgery, the risk/benefit ratio for individual patients needs to be estimated for elective and urgent surgery. For lung resection to treat lung cancer, spirometry and diffusing capacity should be measured to estimate predicted post-operative lung function, and if required, exercise tests should be performed [11]. COPD management should be optimised in the pre-operative period, including smoking cessation, inhaled bronchodilators and pulmonary rehabilitation. Specific peri- and post-operative management strategies have been suggested for patients with severe COPD. These strategies include early mobilisation and, where appropriate, minimising medications leading to respiratory depression, regional anaesthesia and controlled oxygen delivery in the post-operative period [12, 13].

P: Prevent deterioration

P1.1 Smoking cessation

Addition of a paragraph based on the 2016 update of the van Eerd Cochrane Review [14] on smoking cessation for people with COPD. The review included 16 studies involving 13,123 participants; however, only two studies were rated as high quality. The review found high-quality evidence from a meta-analysis of four (1,540 participants) of the 16 studies that a combination of behavioural treatment and pharmacotherapy is effective in helping smokers with COPD to quit smoking.

P10. Oxygen therapy

Inclusion of new sub-section, “Oxygen in patients with moderate hypoxaemia” with discussion of the Long-Term Oxygen Treatment Trial [15]. This large study of patients with moderate hypoxaemia was powered originally to determine whether continuous oxygen therapy improved mortality. Subsequently, inclusion criteria were altered to include those who desaturated with exertion but were minimally hypoxaemic at rest. The study demonstrated no difference between groups in the composite outcome of mortality or time to first hospitalisation, nor in any other outcome including quality of life. Limitations to the study included an absence of blinding, no placebo arm, and lack of clarity as to whether the study was adequately powered for the modified composite primary outcome. The findings are consistent with clinical practice guidelines on adult domiciliary oxygen provided by the Thoracic Society of Australia and New Zealand which recommend provision of long term continuous oxygen therapy only in those who are significantly hypoxaemic and recommend use of ambulatory oxygen only in the few patients who demonstrate benefit in a blinded test.

D: Develop a plan of care

D3. Self-management

Addition of a new paragraph stating that there have been a number of systematic reviews evaluating the effect of self-management in COPD. Although it has consistently resulted in improvements to

quality of life, there have been conflicting findings in terms of its effect on healthcare utilisation. [16-20]

Inclusion of wording from a systematic review on COPD self-management by Jolly 2016 that included single and multi–component interventions [16]. There was no impact on hospital admissions, but there were improvements in health-related quality of life. The authors were not able to describe the package that led to the most significant improvements due to the degree of heterogeneity within the interventions and study designs.

Discussion of a study by Jonkman et al [18] who performed an individual patient meta-analysis of 3,282 subjects from 14 RCTs of self-management in COPD patients, with subgroup analyses to appraise if particular subjects were most likely to benefit. While several health service and patient centred benefits were demonstrated in this study, including a 20% reduction in all-cause hospitalisations, there was no consistent pattern of benefits across the health service and patient centred outcomes in any particular subgroup. Jonkman et al [17] also used this meta-analysis to evaluate whether certain self-management program characteristics were more likely to be associated with better outcomes. This evaluation demonstrated that duration of the intervention program, whatever it comprised, was most associated with reduction in all cause hospitalisations in COPD patients, but that other program characteristics were not consistently associated with positive effects across outcomes measured. There is no particular type of patient who should be omitted from these initiatives and the greatest benefits were from enduring interventions.

D5. Treat anxiety and depression

Inclusion of a study by Alexopoulos 2016 [21] to reference the sentence "Case management to support adherence to antidepressant medication in conjunction with attending pulmonary rehabilitation has been associated with improvements in both depression and dyspnoea-related disability" which builds on an earlier study by Alexopoulos published in 2014.

X: Manage eXacerbations

X2.2 Optimise treatment

Inclusion of a sentence stating a lack of evidence in favour of one mode of delivery over another for bronchodilators during exacerbations. In a Cochrane Review by van Geffen, [22] there were no differences between nebulisers and pressured metered dose inhalers plus spacer regarding the primary outcomes of FEV_1 at one hour and serious adverse events.

Appendix 5. Table of Minimum Clinically Important Differences (MCID)

Table included in new Appendix.

New References Included in V2.48

1. Elbehairy, A.F., et al., *Mechanisms of exertional dyspnoea in symptomatic smokers without COPD.* Eur Respir J, 2016. **48**(3): p. 694-705.
2. Feldman, G., et al., *A randomized, blinded study to evaluate the efficacy and safety of umeclidinium 62.5 mug compared with tiotropium 18 mug in patients with COPD.* Int J Chron Obstruct Pulmon Dis, 2016. **11**: p. 719-30.
3. Festic, E., et al., *Association of Inhaled Corticosteroids with Incident Pneumonia and Mortality in COPD Patients; Systematic Review and Meta-Analysis.* COPD, 2016. **13**(3): p. 312-26.
4. Pavord, I.D., et al., *Blood eosinophil count and pneumonia risk in patients with chronic obstructive pulmonary disease: a patient-level meta-analysis.* Lancet Respir Med, 2016. **4**(9): p. 731-41.
5. Rojas-Reyes, M.X., et al., *Combination inhaled steroid and long-acting beta(2)-agonist in addition to tiotropium versus tiotropium or combination alone for chronic obstructive pulmonary disease.* Cochrane Database Syst Rev, 2016(6): p. Cd008532.
6. Singh, D., et al., *Single inhaler triple therapy versus inhaled corticosteroid plus long-acting beta2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial.* Lancet, 2016. **388**(10048): p. 963-73.
7. Moore, E., et al., *Pulmonary Rehabilitation as a Mechanism to Reduce Hospitalizations for Acute Exacerbations of COPD: A Systematic Review and Meta-Analysis.* Chest, 2016. **150**(4): p. 837-859.
8. Dretzke, J., et al., *The effect of domiciliary noninvasive ventilation on clinical outcomes in stable and recently hospitalized patients with COPD: a systematic review and meta-analysis.* Int J Chron Obstruct Pulmon Dis, 2016. **11**: p. 2269-2286.
9. Gupta, H., et al., *Impact of COPD on postoperative outcomes: results from a national database.* Chest, 2013. **143**(6): p. 1599-606.
10. Fields, A.C. and C.M. Divino, *Surgical outcomes in patients with chronic obstructive pulmonary disease undergoing abdominal operations: An analysis of 331,425 patients.* Surgery, 2016. **159**(4): p. 1210-1216.
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12. Diaz-Fuentes, G., H.R. Hashmi, and S. Venkatram, *Perioperative Evaluation of Patients with Pulmonary Conditions Undergoing Non-Cardiothoracic Surgery.* Health Serv Insights, 2016. **9**(Suppl 1): p. 9-23.
13. Lakshminarasimhachar, A. and G.W. Smetana, *Preoperative Evaluation: Estimation of Pulmonary Risk.* Anesthesiol Clin, 2016. **34**(1): p. 71-88.
14. van Eerd, E.A., et al., *Smoking cessation for people with chronic obstructive pulmonary disease.* Cochrane Database Syst Rev, 2016(8): p. Cd010744.
15. Long-Term Oxygen Treatment Trial Research, G., *A Randomized Trial of Long-Term Oxygen for COPD with Moderate Desaturation.* N Engl J Med, 2016. **375**(17): p. 1617-1627.
16. Jolly, K., et al., *Self-management of health care behaviors for COPD: a systematic review and meta-analysis.* Int J Chron Obstruct Pulmon Dis, 2016. **11**: p. 305-26.
17. Jonkman, N.H., et al., *Characteristics of effective self-management interventions in patients with COPD: individual patient data meta-analysis.* Eur Respir J, 2016. **48**(1): p. 55-68.
18. Jonkman, N.H., et al., *Do self-management interventions in COPD patients work and which patients benefit most? An individual patient data meta-analysis.* Int J Chron Obstruct Pulmon Dis, 2016. **11**: p. 2063-74.

19. Majothi, S., et al., *Supported self-management for patients with COPD who have recently been discharged from hospital: a systematic review and meta-analysis.* Int J Chron Obstruct Pulmon Dis, 2015. **10**: p. 853-67.
20. Zwerink, M., et al., *(Cost-)effectiveness of self-treatment of exacerbations in patients with COPD: 2 years follow-up of a RCT.* Respirology, 2016. **21**(3): p. 497-503.
21. Alexopoulos, G.S., et al., *Two Behavioral Interventions for Patients with Major Depression and Severe COPD.* Am J Geriatr Psychiatry, 2016. **24**(11): p. 964-974.
22. van Geffen, W.H., et al., *Bronchodilators delivered by nebuliser versus pMDI with spacer or DPI for exacerbations of COPD.* Cochrane Database Syst Rev, 2016(8): p. Cd011826.