COPD-X Summary of Changes V2.52, December 2017

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 December 2017 meeting 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.

Key Recommendations of the COPD-X Guidelines

Each of the key recommendations throughout the main body of the document now incorporates the GRADE strength of recommendation as well as the NHMRC level of evidence. The recommendations are clearly marked in ***bold and italics***.

C. Confirm diagnosis and assess severity

No changes made

O. Optimise Function

O1.2.1 Long-acting muscarinic antagonists (LAMA)

Rewrite of section with separate sub-sections for aclidinium, glycopyrronium, tiotropium and umeclidinium included. These discuss the benefits of each and the potential adverse effects. It is noted that there are few head to head comparisons of LAMAs available, so the choice of LAMA and inhaler device depends on patient and clinician preferences.

O1.2.2 Long-acting beta$_2$-agonists (LABA)

Addition of a paragraph stating that in a network meta-analysis of 33 double-blind, multicentre RCTs of LABA monotherapies, no clinically significant differences were noted at 12 or 24 weeks among the different LABAs (Donohue 2017).

Addition of a paragraph comparing LAMAs with LABAs. A meta-analysis of 16 randomised, double-blinded controlled trials which included 22,872 patients with moderate to severe or very severe COPD with a treatment period ranging from 12 to 52 weeks found that LAMAs were associated with a lower risk of acute exacerbations and lower incidence of adverse events compared with LABAs (Chen 2017). There were no significant differences between LAMAs and LABAs in terms of changes in lung function, symptom score, health status and serious adverse events. It is concluded that LAMAs may be preferable to LABAs in patients with stable COPD, especially in those at risk of frequent exacerbations.

O2.2 Phosphodiesterase type-4 inhibitors

Update of phosphodiesterase type-4 (PDE-4) inhibitors section based on a 2017 Cochrane Review which analysed results from RCTs of roflumilast (20 trials, 17,627 patients) and cilomilast (14 trials, 6,457 patients) (Chong 2017). Compared to placebo, PDE-4 inhibitors improved FEV_1 and reduced exacerbation rates, but had relatively small effects on quality of life and symptoms. Gastrointestinal adverse effects were more frequent with the PDE-4 inhibitors, and psychiatric adverse events such as insomnia and depressive mood symptoms were more frequent with roflumilast. These oral agents are not currently available in Australia.

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

Change to wording based on a 2016 Cochrane Review (Rojas-Reyes 2016) which compared tiotropium plus LABA/ICS combination therapy with tiotropium alone and found that "triple" therapy decreased all cause hospitalisation in comparison with tiotropium alone. Following a correction to the results contained within the paper, the findings changed such that there was no significant difference in risk of hospital admission with the use of tiotropium plus LABA/ICS compared with tiotropium alone. It is noted the quality of evidence for this outcome is low because of the risk of bias in included studies and imprecision of the estimates of effect.

Addition of a paragraph discussing the TRINITY study which compared the use of extra-fine beclometasone dipropionate (BDP), formoterol fumarate (FF) and glycopyrronium bromide (BDP/FF/GB; *fixed triple*) with tiotropium, and BDP/FF plus tiotropium (open triple)(Vestbo 2017). The rates of moderate to severe COPD exacerbations were 0·46 (0·41–0·51) per patient per year for *fixed triple*, 0·57 (0·52–0·63) for tiotropium, and 0·45 (0·39–0·52) for *open triple*. Extra-fine particle fixed triple was superior to tiotropium - the time to first severe exacerbation was prolonged with fixed triple compared with tiotropium, and was similar for fixed triple and open triple. The adjusted mean changes from baseline in pre-dose FEV_1 at week 52 were 0·082 L for fixed triple, 0·021 L for tiotropium and 0·085 L for open triple. The incidence of adverse events (55 to 58%), including serious adverse events (13 to 15%) and pneumonia (1 to 2%) were similar across the three groups.

Addition of a paragraph discussing a 24 week RCT of 1,810 patients with moderate to severe COPD in which once daily fluticasone furoate/umeclidinium/vilanterol in a single inhaler was compared to twice daily budesonide/formoterol (Lipson 2017). Fluticasone furoate/umeclidinium/vilanterol improved FEV_1 and St Georges Respiratory Questionnaire total score and reduced exacerbation rates supporting some benefits of single inhaler triple therapy. However, the combination of fluticasone furoate/umeclidinium/vilanterol is not currently available in Australia.

Addition of wording discussing the over-prescribing of inhaled corticosteroids (ICS)and referencing four studies in Australia and the UK. In Australia, ICS prescription was reviewed in 711 outpatients with spirometry-confirmed COPD at a tertiary hospital and it was found that 52.4% of patients were prescribed an ICS despite a post-bronchodilator FEV_1 ≥50% which is inconsistent with COPD-X recommendations (Harrison 2017). The study did not consider other guideline criteria such as recurrent exacerbations. Several UK GP database studies have

demonstrated overprescribing of ICS in COPD (Brusselle 2015, Price 2014, White 2013). Price et al examined inhaler use in primary care in the UK in over 3,000 patients with spirometry confirmed COPD. Over 50% of patients who did not qualify for ICS based on GOLD guidelines were inappropriately prescribed ICS (Price 2014). Under-treatment was reported in 17% of patients. A similar study, also in primary care in the UK reported over prescription of ICS in approximately 35% of patients (White 2013). Conversely, only 8% of patients were under-treated. These studies highlight the importance of commencing long-acting bronchodilators as initial pharmacological therapy for patients with symptomatic COPD, before considering adding inhaled steroids (as ICS/LABA inhalers) in patients who have both severe airflow obstruction (FEV_1 <50% predicted) AND frequent exacerbations (two or more in the past year) (current PBS criteria).

O4.3 Biologic therapies

Addition of a new section discussing studies which have highlighted blood eosinophil count as a potentially important biomarker of response to glucocorticoid treatment. Pavord and colleagues compared the interleukin-5 inhibitor, mepolizumab, with placebo in patients with COPD in two 12-month randomised, controlled, parallel-group trials (METREX and METREO) (Pavord 2017). The results indicate that an eosinophilic subgroup of patients with COPD may benefit from biologic therapies, although it is noted that although patients with current asthma were excluded, those with a past history of asthma or atopy were not. Further prospective studies are awaited.

O5.1 Inhaler technique

Inclusion of further supporting evidence that incorrect inhaler technique is common and is associated with worse outcomes. A systematic review of articles reporting direct observation of inhaler technique in COPD and asthma reported that the overall prevalence of optimal inhaler technique was only 31% and that this pattern had not improved over 40 years (Sanchis 2016). Common errors for the MDI and DPI are discussed. The data highlights the importance of inhalation technique education.

O6.1 Pulmonary rehabilitation

Inclusion of reference to the 2017 Australian and New Zealand Pulmonary Rehabilitation Guidelines) (Alison 2017) in support of pulmonary rehabilitation.

O6.5 Physical activity and sedentary behaviour

Addition of a paragraph from a systematic review and meta-analysis (Lahham 2016) supporting the use of physical activity counselling in addition to pulmonary rehabilitation which resulted in an increase in physical activity as measured by daily step count.

O6.10 Nutrition

Inclusion of level III evidence that malnutrition is an independent predictor of mortality and healthcare use in COPD patients (Hoong 2017).

O6.11 Complementary and alternative therapies

Addition of evidence from an RCT, including sham acupuncture, with blinding of all involved apart from the acupuncturists themselves, which demonstrated an 80 metre improvement in 6 minute walk distance as well as improvements in quality of life (Feng 2016). The effect of the lack of blinding of the acupuncturist is uncertain.

O7.2 Cardiac disease

High sensitivity troponin T levels in stable COPD were associated with increased mortality risk. Compared to the group with troponin T levels <5ng/L, adjusted Hazard Ratios (HR) were higher at 1.7 (0.8-3.9) and 2.9 (1.2-7.2), for the groups with troponin T levels 5.1-13.9 ng/L and ≥14 ng/L, respectively(Neukamm 2016).

O7.2.2 Safety of beta-blockers

Addition of evidence from an Australian study (Neef 2016) to support the statement that despite a paucity of evidence to suggest harm, beta-blockers are still under-utilised in COPD for guideline-based indications such as systolic heart failure.

O7.5 Sleep-related breathing disorders

Inclusion of a reference to support the statement that COPD patients with overlapping obstructive sleep apnoea (OSA) have higher mortality and more frequent exacerbations than COPD patients without OSA (Shawon 2017)

O7.12 Cognitive impairment

Inclusion of evidence from a systemic review of the effect of cognitive impairment on self-management in COPD which demonstrated high degrees of inhaler incompetency with cognitive impairment, although dry powder inhalers are easier to learn to use (Baird 2017).

O9.2 Lung volume reduction surgery and bronchoscopic interventions

Addition of a new reference (Kemp 2017), the first multicentre RCT examining endobronchial valves.

P: Prevent deterioration

P2.1 Influenza immunisation

Minor rewording of section with specific reference to the three strains of the vaccine removed and inclusion of additional information stating that in people with COPD, inactivated influenza vaccine reduces exacerbations due to influenza, especially in epidemic years and there is no increase in early exacerbations before immunity has developed.

P7. Mucolytic agents

Inclusion of wording based on a double blind RCT which found that the use of erdosteine reduced exacerbations, duration of exacerbation and decreased use of reliever; however it did not affect quality of life or time to first exacerbation (Dal Negro 2017).

P12 Alpha1-antitrypsin deficiency

Addition of two new paragraphs at the start of the section based on a Swedish study of individuals with alpha1-antitrypsin deficiency (AAD) (Piitulainen 2017) which followed up a cohort of PiZZ and PiSZ indivuduals and examined their smoking history. The study concluded that PiZZ current smokers may have symptoms of COPD at the age of 37–40 years, whereas the never-smoking PiZZ and PiSZ individuals have normal lung function. Tanash and colleagues also compared mortality rates in 1,585 Swedish individuals with severe AAT deficiency (Tanash 2017). Individuals with AAT deficiency had lower survival rates compared with controls; however, the survival rate of never-smoking individuals with severe AAT deficiency identified by screening (rather than identified after presenting with respiratory symptoms) is similar to the never-smokers in the Swedish general population. This highlights the importance of smoking prevention in individuals with AAT deficiency.

D: Develop a plan of care

Inclusion of a paragraph discussing an intensive, comprehensive health coaching intervention that included motivational interviewing delivered via telephone, a written action plan for exacerbations including the use of antibiotics and oral steroids, and an exercise prescription. This intervention decreased COPD-related hospitalisations at one, three and six months after hospital discharge, but not at one year after discharge. Disease-specific quality of life improved significantly in the health coaching group compared with the control group at 6 and 12 months, based on the Chronic Respiratory Disease Questionnaire emotional score and physical score. There were no differences between groups in measured physical activity at any time point (Benzo 2016). It should be noted that several of these individual components have been shown to be effective in isolation.

D3. Self management

Addition of a Cochrane Review (Lenferink 2017) of trials published between 1995 and 2016 which replaces the Zwerink 2014 Cochrane Review. This confirms a benefit for self-management interventions on health related quality of life and a 31% lower probability of respiratory-related hospitalisation but there was no effect on all-cause hospitalisation or all-cause mortality. Exploratory analysis showed a small but significantly increased respiratory-related mortality.

D5. Treat anxiety and depression

Addition of a new paragraph discussing the benefits of cognitive behaviour therapy (CBT). In a trial of 28 patients undergoing pulmonary rehabilitation with a three month follow up, CBT showed a short term improvement in fatigue, stress and depression and anxiety scores. However, as the follow up was short, it is unknown if the benefits are sustained (Luk 2017).

X: Manage eXacerbations

Inclusion of evidence from a prospective study which examined exacerbation rates in 1,105 patients with COPD over a three year period (Han 2017). The study found that individual exacerbation rates varied significantly from year to year, and very few patients experienced two or more exacerbations over successive years. It was also reported that IL-15 and IL-8 levels in blood as well as small airway abnormalities on CT chest predicted frequent exacerbations.

Retrospective data from an Australian tertiary hospital demonstrated that influenza virus and rhinovirus were the most common viral pathogens found in patients admitted to hospital with an exacerbation of COPD (Biancardi 2016).

X3.7 Discharge planning

Inclusion of a paragraph supporting the key recommendation that patients with COPD discharged from hospital following an exacerbation should receive comprehensive follow-up led by the primary healthcare team. A meta-analysis which included an appraisal of four RCTs across three countries and demonstrated that the use of COPD discharge bundles reduced hospital readmissions by 20% but showed no demonstrable benefit in terms of length of stay or mortality (Ospina 2017). Outpatient follow-up was found to be a core element to reduce re-admissions.

Appendix 6. Uptake and impact of guidelines for exacerbations

Movement of previously named section X4 into a standalone Appendix and addition of a new paragraph discussing an audit of COPD patients in the Outpatient respiratory clinics of 59 Spanish hospitals (Calle Rubio 2017). This demonstrated that clinical practice, at least as recorded in the case notes, fell well short of recommendations in GOLD and Spanish national guidelines for COPD.

Glossary of Terms

This is newly added for this version.

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