# COPD-X Summary of Changes V2.54, June 2018

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 2018 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.

## *C. Confirm diagnosis and assess severity*

No changes

## *O. Optimise Function*

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

Paragraph added discussing the once daily tiotropium/olodaterol combination. Patients taking the tiotropium/olodaterol combination had no significant differences in moderate and severe exacerbation rate and time to first moderate or severe event over a 52-week treatment period, compared to tiotropium alone (Calverley 2018) [evidence level II].

### O3.2 Inhaled corticosteroids (ICS)

Addition of wording discussing abrupt withdrawal of ICS from long-term triple therapy (tiotropium AND fluticasone/salmeterol administered via separate inhalers) to a LABA/LAMA combination (indacaterol/glycopyrronium administered via Breezhaler) in COPD patients (mean $FEV_1$ 57%) with no more than one moderate or severe exacerbation in the previous year (the 26 week SUNSET trial (Chapman 2018)).

- This led to a small but significant decrease in trough $FEV_1$ with no differences in the rates of COPD exacerbations or the time to first moderate or severe COPD exacerbation.
- Patients with high blood eosinophils at baseline showed greater differences in lung function and were at increased risk of exacerbations after ICS withdrawal.
- The incidence of adverse events was similar across both treatment arms.

It is concluded that In COPD patients without evidence of asthma and with infrequent exacerbations, ICS withdrawal could be considered. However, close follow up is recommended following cessation. Post hoc analysis suggests ICS withdrawal should be approached cautiously in patients with COPD and elevated eosinophil counts.

**O4.1 Inhaled corticosteroids and long-acting beta2-agonists in combination (ICS/LABA)**

Inclusion of wording from an RCT of 26 weeks discussing the benefits of an ICS/LABA combination (Ferguson 2017): Twice daily budesonide/formoterol resulted in a 24% reduction in exacerbation rates and a 22% reduction in time to first exacerbation compared with twice daily formoterol. The study did not show any important difference between the groups in their safety profile, including incidence of pneumonia.

Inclusion of additional reference discussing SUMMIT (Study to Understand Mortality and MorbITy in COPD) (Crim 2017) focusing on pneumonia risk with inhaled fluticasone furoate and vilanterol in COPD patients with moderate airflow limitation. It concluded that rates of pneumonia were similar between fluticasone and placebo groups.

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

Addition of wording discussing the IMPACT study, a large (n=10,355) 52 week trial comparing the ICS/LAMA/LABA triple therapy combination (fluticasone furoate, umeclidinium and vilanterol) with dual therapies using the same molecules (ICS/LABA and LAMA/LABA), all administered once-daily via a single-inhaler (Lipson 2018). The findings included:

- A significantly lower rate of moderate or severe COPD exacerbations with triple therapy compared with both dual comparators.
- Annual rate of severe exacerbations (resulting in hospitalisation) in the triple therapy group was lower compared with the umeclidinium–vilanterol group.
- Overall, the adverse-event profile of triple therapy was similar to that of the dual therapy comparators. Incidence of pneumonia was higher in the ICS groups than in the umeclidinium–vilanterol group, and the risk of clinician-diagnosed pneumonia was also significantly higher with triple therapy than with umeclidinium–vilanterol.
- The difference in the mean change in trough $FEV_1$ between the triple therapy and fluticasone furoate–vilanterol groups was 97 ml and the difference between the triple therapy and umeclidinium–vilanterol groups was 54 ml.
- There were significant differences between the triple therapy group and the dual therapy comparators in the mean change from baseline in the SGRQ total score and in the percentage of patients who had a response as defined by a decrease in the SGRQ total score of at least 4 points.
- ICS regimens also showed a possible signal toward lower all-cause mortality during treatment than umeclidinium–vilanterol.
- Pre-specified secondary analyses of patients with eosinophil levels either lower than or higher than 150 cells/μL indicated the annual rate of moderate or severe exacerbations was lower with triple therapy compared with both dual comparators.

In Australia, for initiation of triple therapy (LABA/LAMA/ICS) subsidised through the PBS, the patient must have a post-bronchodilator FEV1 <50% of predicted normal prior to therapy, AND must have a history of repeated exacerbations (2 or more) with significant symptoms despite regular bronchodilator therapy with a LAMA/LABA or an ICS/LABA OR the patient must have been stabilised on a combination of a LAMA, LABA and an ICS for COPD.

### O4.2.1 Eosinophil count and inhaled corticosteroids

Addition of new section on the use of blood eosinophil count as a prognostic marker and to guide the use of ICS in COPD.

- The FORWARD study compared 48 weeks of treatment with beclomethasone dipropionate plus formoterol fumarate (BDP/FF) versus formoterol fumarate (FF) in patients with severe COPD with a history of exacerbations. Patients with eosinophil counts ≥ 279.8 cells/μL experienced the highest exacerbation rate with FF and the greatest benefit from the BDP/FF combination (Siddiqui 2015).
- Analysis of data from the WISDOM study showed patients with higher blood eosinophil counts were more likely to develop exacerbations after withdrawal of inhaled corticosteroids, with a significant treatment-by-subgroup interaction above an eosinophil count ≥ 300 cells/μL (Watz 2016).
- An additional study examined data from RCTs of budesonide/formoterol in patients with COPD, a history of exacerbations and available eosinophil counts (Bafadhel 2018). They found a treatment effect interaction between the budesonide-formoterol combination and eosinophil count with respect to exacerbations, lung function and health status as compared with formoterol alone.
- Casanova et al examined the prevalence and stability of the finding of a blood eosinophil count ≥ 300 cells/μl and its relationship to outcomes over two years from the CHAIN (patients with COPD and smokers without COPD) and BODE (patients with COPD only) cohorts (Casanova 2017). 15.8% of COPD patients in CHAIN and 12.3% of those in BODE had persistently elevated eosinophils during the period of follow-up. A similar eosinophil blood pattern was observed in controls. Exacerbation rates did not differ in patients with and without eosinophilia. All-cause mortality was lower in patients with high eosinophils compared with those with values < 300 cells/μL–1.
- In the SPIROMICS database of patients with COPD, smokers without COPD and non smokers, blood eosinophil count alone was not a reliable biomarker for COPD severity or exacerbations (Hastie 2017). Although there was a statistically significant relationship between blood and sputum eosinophils, blood eosinophil count did not reliably predict level of sputum eosinophilia. Sputum eosinophils were available in a subset of just on 1,000 patients. The authors found that high sputum eosinophils, but not blood eosinophils, identified a subset of patients with more severe airflow obstruction, worse quality of life, more emphysema and gas trapping and more exacerbations. However there were no differences in CAT scores noted with either blood or sputum eosinophil stratification.

Prospective studies that randomise patients based on eosinophil count are required to confirm these associations and guide treatment decisions.

**O5.2 Inhaler adherence**

Addition of wording based on the findings of an observational study which showed that inhaler adherence and technique were suboptimal in patients using an ICS/LABA combination inhaler fitted with an electronic audio recording device. Impaired lung function and cognition, as well as cough, predicted suboptimal adherence and technique (Sulaiman 2017).

**O6. Non-pharmacological interventions**

Inclusion of a paragraph based on a large cohort study (Cheng 2018) which reported associations of total and type-specific physical activity with mortality in patients with COPD. The study found a dose-response association between physical activity and all-cause and cardiovascular mortality, with protective effects appearing at levels considerably lower than the general physical activity recommendations. Individuals who met the physical activity guidelines demonstrated the greatest reductions in all-cause and respiratory mortality risk. Dose response associations with mortality risk were found for walking and sport/exercise but not for domestic physical activity. These findings provide further support for encouraging walking and structured exercise in people with COPD with the aim of reducing mortality risk.

**O7.1 Increased risks from comorbidities in the presence of COPD**

Addition of evidence from a Spanish cohort study showing that COPD was associated with an increased number of comorbidities, occurring at an earlier age (on average 10 to 20 years earlier) compared to non-COPD controls suggesting accelerated ageing (Divo 2018).

**O7.2.3 Stroke**

Inclusion of evidence from a meta-analysis showing that patients with COPD had a significantly increased stroke risk compared to controls (Kim 2018).

**O7.6 Aspiration**

Addition of a paragraph stating that research characterising dysphagia in COPD has identified additional impairments in swallow physiology (Regan 2017).

**O10. Palliative and supportive care**

Addition of a paragraph outlining the need to improve patient and carer access to palliative care approaches generally and more specifically within the ICU (Brown 2016). A review of COPD patient deaths occurring in the ICU identified that patients with COPD were less likely to receive specialist palliative care input or have opportunities to discuss end of life care preferences related to resuscitation in the ICU, compared with cancer patients. This occurred despite COPD patients having longer hospital and ICU stays than cancer patients.

## *P: Prevent deterioration*

### P7. Mucolytic agents

Addition of a paragraph discussing the benefits of erdosteine. A meta-analysis of 10 RCTs which included the previously cited Dal Negro trial reported that compared to placebo, erdosteine improved the clinical condition of COPD, as measured by global overall clinical scores comprising a number of measures (Cazzola 2018). Erdosteine treatment also reduced the risk of COPD exacerbation and the risk of experiencing at least one exacerbation, compared to control.

## *D: Develop a plan of care*

### D1.3 GP practice nurse/ nurse practitioner/ respiratory educator/ respiratory nurse

Updated section discussing the role of nurses in the assessment and delivery of education and management for people living with COPD. Specific mention is made of the training, expert knowledge and skills of respiratory nurses which allow them to undertake multidimensional assessments and to work with patients to tailor specific therapeutic interventions and to co-ordinate the delivery of person centred care (McDonald 2018). Specific examples of COPD care provided by nurses are listed.

### D3. Self-management

Revision of section discussing the effects of self-management interventions. The section now includes a table of systematic reviews evaluating the effect of self-management in COPD. Comment is made that the high degree of heterogeneity within interventions and study designs limits the ability to analyse which characteristics of self-management programs are associated with the most significant improvements. However, a meta regression review of complex interventions identified that general education, exercise and relaxation therapy components contributed to reduced use of urgent healthcare (Dickens 2014) [evidence level I]. In addition, it has been demonstrated that intervention duration, regardless of composition, displayed the strongest associated with reduction in all cause hospitalisations in COPD patients (Jonkman 2016). An additional reference identified that interventions targeting mental health were the most effective in improving HRQoL and reducing ED visits (Newham (2017).

### D4. Telehealth

Addition of a paragraph discussing a study of telehealth with multiple components which failed to demonstrate a reduction in hospitalisation based on intention to treat analysis (Kessler 2018). It was noted there was reduced mortality as a safety/secondary outcome in the per-protocol analysis.

**D5. Treat anxiety and depression**

Inclusion of wording discussing the Patient Health Questionnaire (PHQ) used in screening for symptoms of the most commonly seen mental disorders in medical patients – depression, generalised anxiety, panic attacks, somatoform and eating disorders. It is noted that the PHQ has high statistical reliability and validity and is an easily administered measure that is available on the internet at no cost (Kroenke 2010).

## *X: Manage eXacerbations*

**X3.8 Support after discharge**

Addition of wording from a systematic review of structured, planned, post-discharge support which, although finding evidence for a reduction in readmissions at 30 days, was unable to identify a single intervention 'package' that could be recommended (Pedersen 2017). In addition, a study of supported self-management following discharge, which combined home visits to empower participants to manage their COPD independently and case management to facilitate prompt and appropriate access to care (not included in the above-mentioned systematic review), did not find any significant benefit on COPD admissions or death when compared to usual care (Bucknall 2012). It is noted that many of these studies have different outcomes and as many were conducted in Europe, their applicability to the Australasian setting is not known. Telephone follow-up may be a way of systematically extending support to patients and increasing their coping strategies at home, but the outcomes of this intervention have not been studied systematically.

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