

COPD-X Summary of Changes V2.58, June 2019

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 March and June 2019 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.

C. Confirm diagnosis and assess severity

C1 Aetiology and natural history

Pathak et al (Pathak 2019) conducted a systematic review and meta-analysis of the risk of COPD due to indoor air pollution from biomass cooking fuel. A total of 35 studies with 73,122 participants were included and the pooled analysis showed that exposure to indoor air pollution due to solid biomass fuels increased the risk of COPD.

C3 Assessing the severity of COPD

Amendments made to **Box 1: Classification of severity of COPD:**

- "Cough and sputum production" moved from MODERATE to MILD column
- "Recurrent chest infections" moved from MILD to MODERATE column
- Removal of "experiencing regular sputum production" and "chronic cough" from SEVERE column

O. Optimise Function

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

In a systematic review of seven trials (Ni 2018), the aclidinium/formoterol fixed dose combination (FDC) was found to improve dyspnoea and lung function compared to the monocomponents or placebo. Quality of life was better with the combination compared to formoterol or placebo. There was no difference between the FDC and monotherapy or placebo for hospital admissions, mortality, and non-fatal adverse events. A lower risk of moderate exacerbations was observed with the FDC compared to formoterol but not with the FDC compared with aclidinium [evidence level I].

A meta-analysis and systematic review of 8,641 participants in 22 double-blinded randomised controlled trials comparing a once-daily LAMA/LABA combination with placebo demonstrated similar clinically and statistically significant differences with each of the inhalers with respect to quality of life and improvement in FEV₁. Of the four once-daily LAMA/LABA combinations studied, only the combination of umeclidinium/vilanterol was evaluated with respect to the outcome of exacerbation rate, with an overall pooled rate reduction of 47% in three studies (Maqsood 2019) [evidence level I].

A network meta-analysis was undertaken for dual combination inhalers compared with single-agent long-acting bronchodilators (Oba 2018) [evidence level I]. In the network meta-analysis, LAMA/LABA inhalers decreased the rate of moderate to severe exacerbations compared to ICS/LABA, and LABA in frequent exacerbators, with LABA being the least beneficial. However, the evidence was not statistically significant in some of the pairwise meta-analyses between treatments.

O4.2 Inhaled corticosteroids and long-acting beta2-agonists and long-acting antimuscarinics in combination (ICS/LABA/LAMA)

- Addition of new data on the use of the singler inhaler triple therapy, *budesonide/formoterol/glycopyrronium*:

In patients with severe COPD and frequent exacerbations, ICS/LABA/LAMA may be more beneficial than dual therapies ICS/LABA and LAMA/LABA. In the 24-week KRONOS study, triple therapy (ICS/LABA/LAMA - budesonide/formoterol/glycopyrronium MDI) was compared with dual therapies (ICS/LABA - budesonide/formoterol as MDI or DPI, and LAMA/LABA MDI - glycopyrrolate/formoterol) (Ferguson 2018) [evidence level II]. Triple therapy improved lung function compared to budesonide/formoterol and glycopyrrolate/formoterol. The rate of moderate or severe exacerbations was lower in the triple therapy group. The combinations of beclometasone/formoterol/glycopyrronium and budesonide/formoterol/glycopyrronium are not currently available in Australia.

- Addition of wording discussing comparative studies of fixed and separate inhaled triple therapy versus dual therapy:

A number of systematic reviews of randomised controlled trials have assessed the effects of fixed and separate inhaled triple therapy versus dual therapy (of LABA and LAMA, LABA and ICS, or LAMA and ICS) or monotherapy (LAMA, LABA, or ICS) (Cazzola 2018, Zheng 2018)). In a meta-analysis of 13 randomised controlled trials including 15,519 patients with COPD (Calzetta 2019) [evidence level I], triple therapy was significantly more effective than the ICS/LABA combination in improving trough FEV₁, health related quality of life (HRQoL) and dyspnoea, and protecting against the risk of moderate or severe exacerbations, without compromising cardiovascular safety. The NNT for a ≥100-mL increase from baseline in trough FEV₁ of ICS/LABA/LAMA combination versus ICS/LABA combination was 3.97 (95% CI, 3.25-5.13) and for protection against the risk of a COPD exacerbation was 26.07 (95% CI, 16.79-152.70).

A network meta-analysis of 14 trials found that ICS/LABA/LAMA combination therapy significantly ($p < 0.001$) reduced the risk of moderate or severe COPD exacerbation compared to LABA/LAMA combination therapy and single long-acting bronchodilator therapy (Cazzola 2018). No significant difference was found for the risk of pneumonia when comparing ICS/LABA/LAMA combination therapy with LABA/LAMA combination therapy and single long-acting bronchodilator therapy. Females with COPD seemed to be at higher risk of pneumonia and the risk of pneumonia was greater when the value of FEV₁ was high at enrolment.

In a meta-analysis of 21 trials, triple therapy reduced moderate or severe exacerbations compared to LAMA/LABA or ICS/LABA (Zheng 2018) [evidence level I]. A meta-analysis of two trials (Bremner 2018, Vestbo 2017) directly comparing fixed triple therapy with separate triple therapy found no statistically significant associations for all the outcomes,

including exacerbations of COPD, lung function, adverse events and HRQoL (Zheng 2018).

In summary, triple therapy results in a lower rate of moderate or severe COPD exacerbations, and better lung function and HRQoL than dual therapies. However, triple therapy did not improve patients' survival, and could increase the risk of pneumonia, when compared with dual bronchodilator therapy. Therefore, triple therapy should be limited to patients with exacerbations and more severe COPD symptoms that cannot be adequately managed by dual therapy, and to patients with COPD phenotypes most likely to respond to the triple therapy. In patients with COPD already on ICS/LABA combination, the therapy can be improved without increase of cardiovascular adverse events when a LAMA is added to the combination. Triple therapy delivered in a single inhaler is convenient for patients and may improve adherence, but it is non-inferior to the use of multiple inhalers in terms of clinical efficacy.

In Australia, for initiation of triple therapy (ICS/LABA/LAMA) 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.

O6.10 Nutrition

A meta-analysis of individual patient data from three randomised controlled trials of 468 patients (Jolliffe 2019) reported that vitamin D supplementation did not reduce overall moderate or severe exacerbations. There were however, protective effects of vitamin D supplementation in patients considered deficient, than in those with a baseline 25-hydroxyvitamin D level of <25 nmol/l, but not in those with baseline 25-hydroxyvitamin D levels ≥25 nmol/l [evidence level I]. In COPD patients, vitamin D deficiency should be considered and supplementation is recommended in deficient patients., particularly those with a 25-hydroxyvitamin D levels <25 nmol/l.

O7.2 Cardiac disease

Post hoc analysis of the SUMMIT cohort data (Kunisaki 2018) confirms a significantly increased risk of cardiovascular disease (CVD) events, especially within 30 days following a COPD exacerbation. The study population was selected for CVD or CVD risk factors but does not represent the "real patients" seen in clinical practice. The authors make a good case for heightened vigilance for CVD events in the immediate post exacerbation period.

O7.2.1 Heart failure

A study by Labaki et al found levels of the natriuretic peptide, NT-proBNP to be an independent risk factor for COPD exacerbations (Labaki 2018).

O7.5 Falls in COPD

In a large 4-year follow-up cohort study, the incidence rate of fall in patients aged ≥35 years with a new diagnosis of COPD was higher compared with a matched cohort of non-COPD patients in primary care. Patients with COPD were 55% more likely to have a fall compared to people without COPD (Hakamy 2018). When adjusting for smoking status, use of antidepressants and diuretics, patients with COPD were 47% more likely to have a fall than non-COPD patients (Hakamy 2018).

O7.11 Combined Pulmonary Fibrosis and Emphysema (CPFE)

New section added discussing **Combined Pulmonary Fibrosis and Emphysema (CPFE)** which is suspected based on the presence of upper zone emphysema and lower zone fibrosis. It includes discussion of the characteristics, risk factors, mortality and diagnosis of CPFE (Cottin 2017, Jankowich 2012, Papaioannou 2016, Ash 2018).

Currently, no specific treatment exists for CPFE. Post-hoc data from nintedanib trials in IPF (Richeldi 2014, Crestani 2019) which included patients with concurrent emphysema, showed attenuation of rate of decline in forced vital capacity (FVC) in IPF with emphysema, similar to IPF without emphysema. An observational cohort study of real-world patients who were commenced on pirfenidone also showed similar rate of progression between CPFE and IPF without emphysema (Oltmanns 2014). Hence, antifibrotic therapy can be considered in CPFE, where presence of IPF is confirmed. Early referral for lung transplantation should be considered in patients with rapidly declining lung function.

O10. Palliative and supportive care

A Belgian population cohort study (Faes 2018) identified that during the last six months of life, patients with COPD used resources which focused on preservation of life, with less use of resources or medications to alleviate symptoms or address end-of-life care needs.

In the randomised controlled trial by Higginson et al, patients with advanced lung disease (including COPD) who received integrated palliative care together with care from a respiratory medicine team had improved disease mastery and survival, but no change in quality of life, when compared with patients who received standard care alone. Similarly, Duenk et al (Duenk 2017) identified in another randomised controlled trial that "early" palliative care offered to COPD patients with a poor prognosis did not lead to improved quality of life (albeit it did lead to improved advance care planning completion), when compared with patients in the control group. However, in Duenk's trial there were methodological issues related to incomplete data and it is not clear what the exact nature of the palliative care intervention was or how often it was actually delivered. Therefore, further research is needed to evaluate new models of integrated care.

Pharmacological management of breathlessness – opioids and benzodiazepines

Addition of a sentence stating that morphine sulfate pentahydrate (modified release) capsules are approved by the Therapeutic Goods Administration (TGA) for use in people with severe chronic breathlessness, despite optimal treatment of all the underlying causes contributing to dyspnoea. This is not currently PBS-funded for this indication.

P: Prevent deterioration

P10 Oxygen therapy

It has been demonstrated in several studies that patients frequently do not fulfil the criteria for long term oxygen therapy (LTOT) at subsequent follow up (Eaton 2004, Levin 2018). In the latter study 54% of patients no longer required LTOT at review 1-2 months after discharge.

D: Develop a plan of care

A cluster randomised controlled trial conducted in Canadian primary care of an integrated disease management intervention aimed at patients with frequent and/or severe exacerbations and comprising on-site spirometry, case management, education, and skills training including self-management education by a certified respiratory educator resulted in improved disease-related quality of life, improved disease knowledge and FEV₁ and fewer exacerbations and unplanned service use compared to usual care (Ferrone 2019) [evidence level II].

D1.1 General Practitioner

A cluster randomised controlled trial of an interdisciplinary COPD intervention in 43 Australian primary care clinics coordinated by general practitioners (GPs) and involving smoking cessation support, home medicines review by a consultant pharmacist and home-based pulmonary rehabilitation delivered by a specially trained physiotherapist did not improve health related quality of life (HRQoL), symptom severity or lung function in a cohort of patients with predominantly mild COPD (Liang 2019) [evidence level II]. Uptake of the intended intervention components by both GPs and patients was suboptimal. Exploratory analyses of the 31% who received the intended full intervention showed statistically and clinically significant differences in HRQoL over usual care at 6 months.

D4. Telehealth

PROMETE II was a randomised control trial of a telehealth package offered to 229 subjects, recruited from across 5 centres, over 12 months, with a comprehensive range of outcomes (Soriano 2018) [evidence level II]. The intervention included an educational home visit, and provision of home oximeter, blood pressure gauge, spirometer, and oxygen therapy compliance monitor. It was rated as highly satisfactory with most subjects as well as clinicians, and followed on from the earlier single site, 7-month, 30 subject 'PROMETE' study, which had demonstrated a reduction in acute exacerbations. Despite the earlier study's promising positive finding, the larger PROMETE II study failed to demonstrate any such benefit in any of the diverse range of outcomes, including costs. This calls into question the generalisability of a single site positive finding (Segrelles Calvo 2014), where a very small number of highly motivated staff may be able to achieve extraordinary positive results, but which may prove difficult to replicate elsewhere.

D5. Treat anxiety and depression

A 2018 Cochrane systematic review conducted to assess the effectiveness and safety of pharmacological interventions for the treatment of depression in patients with COPD showed insufficient evidence relating to efficacy and safety to make recommendations on the use of selective serotonin reuptake inhibitors (SSRIs) for treating patients with COPD and depression (Pollok 2018) [evidence level I]. In a meta-analysis involving two randomised controlled trials of 148 participants there was no difference in the primary outcome of change in depressive symptoms post-intervention. Due to the risk of bias and high level of heterogeneity in depression levels, as well as in the types of medication and doses used, these results should be interpreted with caution (Pollok 2018).

X: Manage eXacerbations

X2.2.1 Inhaled bronchodilators for treatment of exacerbations

People with COPD often have cardiac co-morbidities, although these may be undiagnosed at the time of presentation with a COPD exacerbation. Such patients may be susceptible to adverse events from high dose, frequent short acting beta agonists. A review by Kopsaftis (Kopsaftis 2018) identified 10 relevant randomised or controlled trials and demonstrated that higher (5mg versus 2.5mg) doses of salbutamol were associated with increased risk of tremors, elevated heart rate, palpitations and lower blood pressure, but without evidence of any additional benefit. Given that elevated cardiac stress markers during COPD exacerbations are predictive of 30 day mortality (Chang 2011), the review authors recommend **caution in prescribing frequent high doses of short-acting beta agonists**, such as doses of salbutamol exceeding 2.5mg, when treating exacerbations of COPD [evidence level I].

X3.6 Pulmonary rehabilitation

A systematic review by Ryrso (Ryrso 2018) showed early supervised pulmonary rehabilitation (initiated within four weeks after a COPD exacerbation) reduced mortality after the end of treatment. There was no effect of early supervised pulmonary rehabilitation on mortality over the longer-term, most likely due to the small sample (three trials, 127 participants) [evidence level I]. The review also reported a decrease in the number of COPD-related hospital admissions in the three to 12 months following early supervised pulmonary rehabilitation programs initiated after discharge, and no difference in the drop-out rate between early supervised pulmonary rehabilitation and usual care. Given the personal and health-system benefits of pulmonary rehabilitation commenced shortly after an exacerbation, it is important to have appropriate screening and referral processes to increase participation in early pulmonary rehabilitation.

X4. Uptake and impact of guidelines for exacerbations

An audit of 801 breathless COPD patients who presented to 66 European and 46 Australasian participating emergency departments (ED) demonstrated a low adherence to COPD-X and GOLD guideline management recommendations with respect to the use of systemic corticosteroids and antibiotics, especially in the European sites (Kelly 2019). Use of non-invasive ventilation when indicated was equally low in both regions. The authors propose novel use of care bundles and supportive clinical support systems in EDs to reduce the evidence-practice gap.

A tertiary hospital in Israel introduced an electronic clinical decision support tool for use in COPD patient discharge and reported a very significant increase in adherence to guidelines with respect to prescription of appropriate inhalers, recommendations regarding vaccination and smoking cessation as well as follow up in outpatient clinics (Epstein 2019).

Appendix 1. Use and doses of long-term inhaled bronchodilator and corticosteroids determined in response trials

Updated to include doses for salbutamol 200-400mcg; indacaterol; tiotropium 2.5mcg; glycopyrronium 50mcg and fluticasone propionate 250-500mcg and 100mcg.

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

Abbreviations for health status and symptom measures and exacerbations amended for consistency.

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