COPD-X Summary of Changes V2 72

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Snapshot of the evidence review cycle for V2 72 - Oct 2023

The latest update of the COPD-X Plan has been provided by Lung Foundation Australia following the October 2023 meeting of the COPD-X Guidelines Committee. There are **10** changes outlined in this summary.

- 4 = Case finding and confirm diagnosis
- 3 = Optimise function
- 1 = Prevent deterioration
- 2 = Develop a plan of care
- 1 = Manage eXacerbations

2 out of **10**

changes are significant and may impact clinical practice.

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: Case finding and confirm diagnosis

Section Item #	Change	Type of change	Related key Recommendation	Page
C1 Aetiology and natural history				
#1	**New paragraph:** Exposure to second hand smoke (SHS) is also associated with increased risk of developing COPD. Chen et al in a meta-analysis 15 studies (6 cross-sectional studies, 6 case-control studies, and 3 cohort studies) with 25,592 participants found that SHS exposure was associated with an increased risk of COPD (OR 2.25; 95% CI 1.40 to 3.62, $p < 0.01$, $I^2 = 98\%$, for heterogeneity based on a random-effects analysis model). The risk was higher in those with exposure of more than 5 years (OR 4.38; 95% CI 1.28 to 15.00, $p < 0.01$, $I^2 = 89\%$ for heterogeneity based on a random effects analysis model) (**Chen 2023**) [evidence level I].	New citation and paragraph added discussing results of a meta-analysis.	**Smoking is the most important risk factor in COPD development** [evidence level I, strong recommendation]	20
C1.1 Natural history				
#2	**New paragraph:** The Tasmanian Longitudinal Health Study investigated spirometry patterns in a cohort of 2422 subjects at ages 7, 13, 18, 45, 50, and 53 years (n=2422) (**Dharmage 2023**) [evidence level III-2]. The finding of obstructive and mixed pattern phenotypes may contribute to early detection of individuals who are at risk of developing COPD, while a restrictive phenotype predicted a high prevalence of comorbidities (obesity, diabetes, cardiovascular conditions, hypertension, and obstructive sleep apnoea). These findings could assist with targeted early management (Dharmage 2023). Five asthma phenotypes have also been identified in this study, four of which were strongly associated with developing COPD by age 53 years old (**Tan 2023**) [evidence level III-2].	Two new citations and paragraph added discussing results of a longitudinal cohort study. New citations were (**Dharmage 2023**) and (**Tan 2023**).	**Not directly related to a key recommendation.**	24

#3	**New paragraph:** A report from the multicentre, observational, prospective COPDGene study indicated that the presence of mucous plugs on CT chest was associated with higher all-cause mortality in the 4363 subjects who had smoked >10 pack years and in whom mucous plug scores had been measured (**Diaz 2023**) [evidence level III-2]. However, the CT methods used submillimetric slice thickness, which might not be routinely acquired in clinical practice. Also, as this was an observational study it cannot be concluded that mucous plugs cause death.	New citation and paragraph added discussing results of an observational study.	**Not directly related to a key recommendation.**	24

O: Optimise function

Section Item #	Change	Type of change	Related key Recommendation	Page
O1.2.3 Long-acting bronchodilator combinations (LAMA/LABA)				
#4	**New paragraph:** A Cochrane systematic review of 19 studies (22,354 participants) found that LAMA/LABA and LABA+ICS had similar odds of having an exacerbation (OR 0.91, 95% CI 0.78 to 1.06; I^2 = 61%; 13 studies, 20,960 participants; moderate-certainty evidence) or a serious adverse event (OR 1.02, 95% CI 0.91 to 1.15; I^2 = 20%; 18 studies, 23,183 participants; high-certainty evidence) (**Fukada 2023**) [evidence level I]. Improvements in SGRQ and the odds of achieving a minimal clinically important difference of four or more points on the SGRQ were similar between groups (MD -0.57, 95% CI -1.36 to 0.21; I^2 = 78%; 9 studies, 14,437 participants; moderate-certainty evidence) and (OR 1.06, 95% CI0.90 to 1.25; I^2 = 77%; 4 studies, 13,614 participants). However, participants receiving LAMA/LABA showed a greater improvement in trough FEV_1 (MD 0.07, 95% CI 0.05 to 0.08; I^2 = 73%; 12 studies, 14,681 participants; moderate-certainty evidence). LAMA/LABA decreased the odds of pneumonia compared with LABA+ICS from 5% to 3% (OR 0.61, 95% CI 0.52 to 0.72; I^2 = 0%; 14 studies, 21,829 participants; high-certainty evidence) but increased the odds of all-cause death from 1% to 1.4% (OR 1.35, 95% CI 1.05 to 1.75; I^2 = 0%; 15 studies, 21,510 participants) [evidence level I]. Combined LAMA/LABA inhalers hold similar benefits to LABA/ICS inhalers for exacerbations and quality of life for people with moderate to severe COPD but offer a larger improvement in FEV_1 and a lower risk of pneumonia. LAMA/LABA demonstrated statistically significant advantage over LABA/ICS for avoiding pneumonia and improving FEV_1 (though the clinical significance on FEV_1 remains uncertain). Other outcomes were similar. The choice between LAMA/LABA and LABA/ICS should be based on the individual's condition, including blood eosinophil count, history of pneumonia, and recent exacerbations.	Updated Cochrane Review results. New citation (**Fukuda 2023**) replacing existing citation (**Horita 2017**).	**Optimise pharmacotherapy using a stepwise approach.** [evidence level I, strong recommendation].	43

	Removed paragraph: *A Cochrane systematic review analysed 11 RCTs (9,839 patients) studying LAMA/LABA versus. ICS/LABA therapy (Horita 2017). Compared to ICS/LABA, LAMA/LABA resulted in a small reduction in the rate of exacerbations (OR 0.82, 95% CI 0.70 to 0.96), no significant change in mean SGRQ score (although there was a higher proportion achieving the MCID) and a small improvement in FEV_1 (mean difference 0.08 L, 95% CI 0.06 to 0.09). Pneumonia rates were lower, and there was no change in mortality. The studies were heterogeneous in study design and of relatively short duration, and the evidence was of low to moderate quality. Even with these limitations, this systematic review supports the use of LAMA/LABA fixed dose combinations over ICS/LABA inhalers, when initiating long-acting inhaled medicines. Further RCTs of ICS/LABA/LAMA in a single inhaler are awaited, to clarify their efficacy compared to LAMA/LABA.*			
O4.3 Biologic therapies				
#5	**New paragraph:** Dupilumab is a monoclonal antibody which blocks the interleukin-4 receptor α for interleukin-4 and interleukin-13, inhibiting type 2 inflammation. In a multicentre, double-blind RCT (BOREAS trial), 939 patients with COPD with chronic bronchitis for at least 3 months and at least 2 moderate exacerbations or one severe exacerbation in the year prior to screening, blood eosinophil count >300 per µl, and using ICS/LABA/LAMA therapy were randomised to dupilumab 300 mg subcutaneous every 2 weeks for 52 weeks vs placebo. Patients with a clinical diagnosis of asthma were excluded. Mean FEV_1 was 51% predicted. Dupilumab reduced the rate of moderate or severe COPD exacerbations (rate ratio 0.70, 95% CI 0.58 to 0.86), improved prebronchodilator FEV_1 (mean difference 83 ml, 95% CI 42 to 125) and improved HRQL (SGRQ improvement exceeding the MCID, odds ratio 1.4, 95% CI 1.1 to 1.9) (**Bhatt 2023**) [evidence level II]. Adverse effects were similar. Although biologic therapy with dupilumab targeting type 2 inflammation has potentially beneficial effects in a select group of people with COPD and increased blood eosinophils, dupilumab is not indicated in Australia for COPD at this time, and cost-effectiveness has not been evaluated.	New citation and paragraph added discussing results of a randomised control trial.	**Not directly related to a key recommendation.**	57

O6.11				
#6	**New paragraph:** A meta-analysis of 28 RCTs that included 2130 stable COPD patients using acupuncture therapy (AT) alone or combined with other treatments found that the AT group compared to the control group had significant improvements in FVC (WMD = 0.29 L, 95% CI: 0.22–0.36, P < .001), FEV1 (WMD = 0.33 L, 95% CI: 0.23–0.43, P < .001), FEV1% (WMD = 3.30%, 95% CI: 3.30–4.64, P < .001), FEV1/FVC (WMD = 5.45%, 95% CI: 4.41–6.49, P < .001), 6MWD (WMD = 45.48 m, 95% CI: 28.21–62.16, P < .001) and SGRQ (WMD = −7.79, 95% CI: −12.34 to −3.24, P < .001) (**Fan 2023**) [evidence level I]. However, subgroup analyses stratified by comparison model (AT combined with other treatments vs other treatments, AT alone vs sham AT) and treatment duration (≥8 weeks, <8 weeks) showed little between-subgroup differences. Small sample sizes, high risk of bias and unclear definitions of COPD used in individual studies are threats to external validity of the above findings and applications of these to Australian populations should be with caution.	New citation and paragraph added discussing results of a meta-analysis.	**Not directly related to a key recommendation.**	75 to 76

O7.3 Osteoporosis				
#7	**New paragraph:** A large systematic review and meta-analysis to determine the fracture risk of people with COPD who were using ICS (**Peng 2023**) [evidence level I]. Included in the review were 44 RCTs involving 87,594 patients. Meta-analysis showed that there was a significantly increased risk of fracture risk in people with inhalers containing ICS compared to inhalers without ICS (RR, 1.19; 95% CI 1.04 to 1.37; p = 0.010), and the risk was great in people using dual bronchodilator/ICS inhalers (RR 1.30; 95% CI 1.10 to 1.53; p = 0.002) and triple therapy (RR 1.49; 95% CI, 1.03 to 2.17; p = 0.04). Other factors that were associated with increased risk, identified in subgroup analyses were treatment duration ≥ 12 months, budesonide therapy, fluticasone furoate therapy, older age, and disease severity (**Peng 2023**) [evidence level I]. Being aware of these findings in addition to a patient's other risk factors for osteoporosis should underpin clinical decision-making relating to bone mineral density screening. **Removed paragraph:** *There are contradictory findings of a small but deleterious effect of inhaled corticosteroids at conventional doses on fracture risk. Triamcinolone was associated with reduced BMD in the Lung Health Study (Lung Health Study Research Group 2000) [evidence level II]. However, a separate study by Ferguson et al (Ferguson 2009) demonstrated that the combination of salmeterol and fluticasone 1000 micrograms daily had no increase in decline in bone mineral density over three years in compared with placebo in the subgroup of patients whose bone density was measured [evidence level II].*	New citation and paragraph added discussing results of a meta-analysis. Replaced paragraph with lower certainty evidence. Lung Health Study Research Group 2000 was removed from the reference list; Ferguson 2009 is cited elsewhere in COPD-X	**Comorbid conditions are common in patients with COPD** [evidence level III-2, strong recommendation]	83

P: Prevent deterioration

P3. Immunomodulatory agents				
#8	**New paragraph:** A Cochrane review of 36 studies published between 1981 and 2015 and involved 6192 participants with chronic bronchitis or COPD treated with either immunostimulants or placebo over a mean treatment period of 6 months (**Fraser 2022**) [evidence level I]. Participants treated with immunostimulants were slightly more likely to be free of exacerbations during the treatment period (OR 1.48, 95% CI 1.15 to 1.90; 15 RCTs, n=2961; I2 = 53%). Based on a mean estimate of baseline risk of 52%, 11 (95% CI 7 to 29) participants required treatment with an immunostimulant agent for one to be exacerbation-free. Compared to placebo, fewer participants receiving immunostimulants required antibiotics during treatment (OR 0.34, 95% CI 0.18 to 0.63; 542 participants). The odds of experiencing an adverse event were similar between immunostimulant and placebo groups (OR 1.01, 95% CI 0.84 to 1.21; 20 RCTs, 3780 participants). Because there were so few events, the effect of immunostimulants on all-cause and respiratory-related mortality was unclear. The evidence assessed in this Cochrane review has several limitations. The agents used across studies were diverse, and detail about their purity and composition was limited, though the majority are designed to stimulate an immune response from bacterial products. The external validity of the study findings are uncertain, as only two of the 15 included trials were published in the last 10 years, and they will not reflect the current standards of practice. Furthermore, the reviewed population may not represent people with COPD according to our current definition, as included participants with chronic bronchitis who did not necessarily have airflow limitation, making it less generalisable to COPD. In conclusion, it is uncertain whether immunostimulants improve quality of life, and whether they are associated with reduced exacerbation risk and duration of respiratory-related hospitalisations in people with COPD. Further trials are needed to determine efficacy along with current recommended treatments.	New citation and paragraph added discussing results of a meta-analysis.	**Not directly related to a key recommendation.**	110

P4. Macrolides				
#9	**New paragraph:** Since the publication of the above two systematic reviews, a further 12-month double-blind RCT comparing doxycycline 100mg daily to placebo has also demonstrated a lack of benefit of long-term doxycycline. The UK-based study recruited 222 patients with COPD and a history of exacerbations. Doxycycline did not reduce the exacerbation rate. Those receiving doxycycline experienced a deterioration in health status on the SGRQ by 5.2 points (95% CI 1.44 to 9, p=0.007) compared to the placebo group (**Allinson 2023**) [evidence level II].	New citation and paragraph added discussing results of a randomised control trial.	**Not directly related to a key recommendation.**	110 to 111

X: Manage eXacerbations

Section Item #	Change	Type of change	Related key Recommendation	Page
X2.2.3 Antibiotics for treatment of exacerbations				
#10	**New paragraph:** Nonetheless, sputum colour was shown to have limited value as a stand-alone test in diagnosing bacterial infection in a systematic review and meta-analysis of 13 studies by Spies et al (**Spies 2023**) [evidence level I).	New citation and wording/paragraph added based on systematic review and meta-analysis outcomes.	**Independent of the severity and practice setting, exacerbations with clinical features of infection (increased volume and change in colour of sputum and/or fever) benefit from antibiotic therapy** [evidence level I, strong recommendation].	147

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