GLOBAL STRATEGY FOR DIAGNOSIS, MANAGEMENT AND PREVENTION OF COPD 2020 UPDATE

SUMMARY OF KEY CHANGES MADE

[please note this list is not exhaustive and focuses on the main changes only]

All figures and tables have been enlarged to improve clarity and readability. New figures/tables have been created for:

- Factors to Consider When Initiating ICS Treatment **(Figure 3.1)**
- Management of COPD **(Figure 4.1)**
- Follow-up of Non-Pharmacological Treatment **(Table 4.9)**
- Differential Diagnosis of COPD Exacerbation **(Table 5.1)**

Minor edits have been made to other tables and figures.

Chapter 1

The definition of COPD has been updated as follows:

Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous disease/syndrome that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development. Significant comorbidities may have an impact on morbidity and mortality.

There may be significant lung pathology (e.g., emphysema) in the absence of airflow limitation that needs further evaluation (**Figure 1.1**).

Other changes include:

In a large observational study *Pseudomonas aeruginosa* colonization independently predicted an increased risk of hospitalization for exacerbation and all-cause mortality. (Eklof *et al.* 2019)

Switching to cleaner fuels or reducing exposure can reduce the risk of non-smokers developing COPD. (Chan *et al.* 2019)

Cross-sectional analyses have shown an association between ambient levels of particulate matter (PM2.5/10) and COPD prevalence. (Liu *et al.* 2017; Doiron *et al.* 2019)

Chapter 2

The sections on 'Differential diagnoses' and 'Biomarkers' have been updated as follows:

Differential diagnoses. In some patients with chronic asthma, a clear distinction from COPD is difficult using current imaging and physiological testing techniques, since the two conditions share common traits and clinical expressions. Most other potential differential diagnoses are easier to distinguish from COPD (**Table 2.7**).

Biomarkers. There is rapidly increasing interest in the use of biomarkers in COPD. Biomarkers are 'characteristics that are objectively measured and evaluated as an indicator of normal biological or pathogenic processes or pharmacological responses to therapeutic interventions'. In general such data has proven difficult to interpret, largely as a result of weak associations and lack of reproducibility between large patient cohorts (Stockley *et al.* 2019) which was further confirmed in the recent SUMMIT study.(Celli *et al.* 2019). Recent studies (see **Chapter 5** - Exacerbations) have indicated the use of C-reactive protein (CRP) and procalcitonin in restricting antibiotic usage during exacerbations, although the observed sputum colour remains highly sensitive and specific for a high bacterial load during such episodes.

At present the assessment of eosinophils provides the best guidance to the use of corticosteroids (Stockley *et al.* 2019) especially in the prevention of some exacerbations (see **Chapter 3** - Inhaled Corticosteroids).

Continued cautious and realistic interpretation of the role of biomarkers in the management of identified clinical traits is required.

Chapter 3

The section on 'Nicotine replacement products' has been updated as follows:

E-cigarettes were originally promoted as a form of nicotine replacement therapy to aid in smoking cessation, although the efficacy to aid smoking cessation remains controversial.(Bullen *et al.* 2013; Hajek *et al.* 2019) Tetrahydrocannabinol (THC), cannabinoid (CBD) oils, Vitamin E and other flavoring substances and additives have been added to nicotine and promoted to previously non-smoking adolescents and young adults (also known as vaping). Severe acute lung injury, eosinophilic pneumonia, alveolar hemorrhage, respiratory bronchiolitis and other forms of lung abnormalities have been reportedly linked to E-cigarette use. (He *et al.* 2017; Henry *et al.* 2019; Layden *et al.* 2019; CDC website)

Recently, the U.S. Centers for Disease Control (CDC), the U.S. Food and Drug Administration (FDA), state and other clinical and public health partners are investigating outbreaks of lung disease associated with e-cigarette product (devices, liquids, refill pods, and/or cartridges) use. As of 15 October 2019, 1,479 cases of lung illness have been associated with using e-cigarette products and 33 deaths have been associated with using e-cigarette products. (CDC website) All patients had reported a history of using e-cigarette, or vaping products and most reported a history of using THC-containing products. These latest findings suggest that products containing THC, particularly those obtained off the street or from unofficial sources (e.g., friends, family members, illicit dealers), are linked to most of the cases in the outbreak. (CDC website) In a case cohort analysis, no evidence of infection was found, lung inflammation and injury was evident. (CDC website) Patients were reported to have had

clinical improvement with systemic glucocorticoid therapy and the majority received prolonged courses; specific clinical recommendations are not available at this time.(Layden *et al.* 2019)

Added to 'Methylxanthines' section:
A study that investigated the effectiveness of adding low-dose theophylline to ICS in COPD patients at increased risk of exacerbation showed no difference compared with placebo in the number of COPD exacerbations over a one-year period. (Devereux *et al.* 2018)

Added to 'Combination bronchodilator therapy' section:
A large observational pharmaco-epidemiological study found similar effectiveness of LABA/LAMA and ICS/LABA but a significantly higher risk of pneumonia in those treated with ICS/LABA. (Suissa et al. 2019)

Added to 'Blood eosinophil count' section:
These thresholds of < 100 cells/µL and > 300 cells/µL should be regarded as estimates, rather than precise cut-off values, that can predict different probabilities of treatment benefit.
and
Factors to consider when initiating ICS treatment in combination with one or two long-acting bronchodilators are shown in **Figure 3.1.** (Agusti et al. 2018)

Added to 'Triple inhaled therapy' section:
The search for a mortality benefit with inhaled respiratory medications in patients with COPD has been elusive. Prior large, prospective and randomized trials with mortality as the primary endpoint failed to show a statistically significant survival benefit with salmeterol/fluticasone propionate or vilanterol/fluticasone furoate compared to the mono-components and placebo. (Calverly et al. 2007; Vestbo et al. 2016) Recently, trials utilizing triple combinations of LABA/LAMA/ICS in comparison to LAMA, LABA/LAMA or LABA/ICS have reported reduced mortality with triple therapy. (Lipson et al. 2018; Vestbo et al. 2018) Unlike previous trials, the recent studies target patient populations that are enriched increased respiratory symptoms and a prior history of frequent and/or severe exacerbations with the majority receiving background treatment with triple or LABA/ICS based therapy before study enrollment. The largest of these trials (n=10,355) compared single inhaler triple therapy versus ICS/LABA or LABA/LAMA dual therapy (Lipson et al. 2018); there was a statistically significant 42.1% reduction in the risk of on-treatment all-cause mortality and a 28.6% reduction in the risk of all-cause mortality including off-treatment data, comparing triple therapy with LABA/LAMA.(Lipson et al. 2019) Independently adjudicated findings reported reduced cardiovascular and respiratory deaths, and deaths associated with COPD. A post-hoc pooled analysis of triple therapy clinical trials conducted in severe COPD patients with a history of exacerbations showed a trend for lower mortality with use of triple inhaled therapy compared to non-ICS based treatments, but the differences were not statistically significant.(Vestbo et al. 2018) It should be noted that none of the recent studies reporting a reduction in mortality with triple inhaled therapy had survival as the primary endpoint. (Lipson et al. 2018, Papi et al. 2018; Vestbo et al. 2017) These effects are most likely to be seen in patients with COPD who are severely symptomatic, have moderate to very severe airflow obstruction and a history of frequent and/or severe exacerbations.

Additionally, if de-escalating ICS is considered after respiratory stability is achieved in this patient group, it should be done with caution.

Added to 'Other drugs with anti-inflammatory potential' section:
More recently four large phase 3 studies have investigated the efficacy of the anti-IL-5 monoclonal antibody mepolizumab (Pavord et al. 2017) and the anti-IL-5 receptor-α antibody benralizumab (Criner et al. 2019) in patients with severe COPD, recurrent exacerbations and peripheral blood evidence of eosinophilic inflammation despite high intensity inhaled therapy. The studies showed a 15-20% reduction in the rate of severe exacerbations but the effect was not always statistically significant, and it was variable between studies and doses. There was no effect on FEV_1 or quality of life scores and no consistent relationship between the response to treatment and the peripheral blood eosinophil count. A post-hoc analysis of the mepolizumab trial showed greater benefit and more clear evidence of a blood eosinophil related treatment effect against oral corticosteroid treated exacerbations raising the possibility that this treatment might find a role in a highly selected subgroup of patients with eosinophilic COPD and frequent requirement for oral corticosteroids. Further studies are required to investigate this possibility.

and

In a recent meta-analysis vitamin D supplementation reduced exacerbation rates in patients with low baseline vitamin D levels (<10ng/mL or <25nM). (Jolliffe et al. 2019)

Added to the 'Pulmonary rehabilitation' section:
Supervised exercise training at least twice weekly is recommended, and this can include any regimen from endurance training, interval training, resistance/strength training; upper and lower limbs ideally should be included as well as walking exercise; flexibility, inspiratory muscle training and neuromuscular electrical stimulation can also be incorporated. In all cases the rehabilitation intervention (content, scope, frequency, and intensity) should be individualized to maximize personal functional gains. (Alison et al. 2017) When the intervention includes ongoing feedback (telephone calls, biofeedback provided via pedometer and progressive goal setting) but without supervision, change in physical activity is similar to a walking program without feedback. (Wootton et al. 2019) The importance of behavior change to facilitate physical functionality and reduce the psychological impact of COPD should be emphasized to the patient.

and

Pulmonary rehabilitation can be conducted at a range of sites. (Spruit et al. 2013) Community-based and home-based programs have been shown to be as effective as hospital-based programs in randomized controlled trials,(Holland et al. 2017; Maltais et al. 2008) as long as the frequency and intensity are equivalent.(Bourne et al. 2017) There is also evidence that standardized home-based pulmonary rehabilitation programs improve dyspnea in COPD patients.(Horton et al. 2018) However, in real life, traditional pulmonary rehabilitation with supervision remains the standard of care and first-line option, with home-based exercise likely to be a less effective alternative for patients with COPD who are unable to attend pulmonary rehabilitation.(Nolan et al. 2019) Another challenge is that

the benefits of rehabilitation tend to wane over time. There is insufficient evidence, with conflicting research findings in the 11 available RCTs, to recommend continuation of lower intensity or lower frequency exercise programs with the aim of maintaining benefit long-term. However, if such programs are available they should target health behavior taking into account the patient's own preferences, needs and personal goals.(Guell et al. 2017; Alison et al. 2017) Pulmonary rehabilitation may help reduce anxiety and depression symptoms.(Gordon et al. 2019)

Added to 'Education, self-management and integrative care' section:

There remain problems with heterogeneity among interventions, consistency of their application, specifics of the intervention, patient populations, follow-up times and outcome measures that make generalization difficult in real life. It is also challenging to formulate clear recommendations regarding the most effective form and content of a self-management intervention in COPD given the range of heterogeneity across studies, and lack of precise definitions of self-management components (e.g., skills taught) and fidelity measures. The recent conceptual definition should help redress these deficiencies. For example, in the definition it is mentioned that: "The process requires iterative interactions between patients and healthcare professionals who are competent in delivering self-management interventions." Having proper health coaching is important to improve self-management abilities. In patients with COPD admitted for an exacerbation, a study has reported the positive effect of health coaching, commencing at the time of hospital discharge, on reducing risk of re-hospitalization and emergency department visits.(Benzo et al. 2016) Furthermore, this randomized study indicated that health coaching delivered by a respiratory therapist or nurse may improve self-management abilities as demonstrated by meaningful improvements in Chronic Respiratory Disease Questionnaire mastery scores.(Benzo and McEvoy 2019)

Added to 'Supportive, palliative, end-of-life & hospice care' section:

Nutritional support. Low BMI and particularly low fat free mass is associated with worse outcomes in people with COPD.(Guo et al. 2016) In malnourished patients with COPD, nutritional supplementation promotes significant weight gain and leads to significant improvements in respiratory muscle strength and overall health-related quality of life.(Ferreira et al. 2012) Nutritional antioxidant supplementation (vitamin C and E, zinc, and selenium) has been shown to improve antioxidant deficits, quadriceps strength, and serum total protein, without further improvement in quadriceps endurance. Only in malnourished patients has nutritional supplementation demonstrated significant improvements for 6-minute walk test, respiratory muscle strength and health status.(Gouzi et al. 2019) A 12-month nutritional intervention in muscle wasted patients had no effect on physical capacity but physical activity was significantly higher.(van Beers et al. 2019)

Added to 'Bronchoscopic interventions to reduce hyperinflation in severe emphysema' section:

A large multicenter, prospective, RCT of endobronchial valve treatment in patients with heterogeneous emphysema distribution and little to no collateral ventilation, demonstrated significant clinically meaningful benefits over current standard care in lung function, dyspnea, exercise capacity, and quality of life out to at least 12-months post-procedure.(Criner et al. 2018) Pneumothorax was seen in 26.6% of subjects treated with the endobronchial valve usually within the first 72 hours of the procedure (76%).(Kemp et al. 2017; Valipour et al. 2016; Criner et al. 2018) Another large multicenter prospective RCT using a different type of endobronchial valve in patients

selected for targeted lobe treatment based on fissure integrity assessed by high resolution chest CT showed a significant between-group increase in mean FEV_1 from baseline (0.101L) and a 25.7% between-group difference in FEV_1 responder rates (improvement ≥15%). (Criner et al. 2019) These results persisted at 12 months. The endobronchial valve treated group also had significant reductions in hyperinflation and dyspnea. Improved health status and quality of life was also observed. Consistent with prior studies, pneumothorax occurred in 25.5% of endobronchial valve treated patients; the majority occurred in the first three days following the procedure during the period of average hospitalization. Early-onset pneumothorax in the endobronchial valve treatment group likely results from lung conformation changes due to acute volume reduction in the emphysematous targeted lobe by valve therapy that triggers rapid ipsilateral non-targeted lobe expansion, a recognized indicator of successful target lobe occlusion in patients with intact fissures or absence of collateral ventilation. The occurrence of pneumothorax highlights the need for physicians performing this procedure to have expertise in the management of procedural complications. After the post-procedural period however, patients treated with the endobronchial valve compared to usual care tend to have a lower number of exacerbations and episodes of respiratory failure. A comparison of treatment benefits and complications associated with endobronchial valve placement compared to LVRS show comparable benefits with endobronchial valve treatment but with fewer complications.(Criner et al. 2018) Endobronchial valve therapy is now clinically available and approved for treatment in many countries in the treatment of patients who have intact fissures or lack of collateral ventilation.(Criner et al. 2018; Naunheim et al. 2006; DeCamp et al. 2006)

Other bronchoscopic lung volume reduction techniques do not depend upon the presence of intact fissures or absence of collateral ventilation. In a prospective RCT, targeted thermal vapour ablation of more diseased segments resulted in clinically meaningful and statistically significant improvements in lung function and health status at 6 months. COPD exacerbation was the most common serious adverse event. Durability of these changes was subsequently reported at 12 months follow-up. (Shah et al. 2016; Herth et al. 2016) This therapy has limited clinical availability.

Two multicenter trials have examined nitinol coils implanted into the lung compared to usual care on changes in 6-minute walk distance, lung function and health status in patients with advanced homogenous and heterogeneous emphysema. Both studies reported an increase in 6-minute walk distance with coil treatment compared to control and smaller improvements in FEV_1, and quality of life measured by St George's Respiratory Questionnaire.(Deslee et al. 2016; Sciurba et al. 2016) Major complications included pneumonia, pneumothorax, hemoptysis and COPD exacerbations occurring more frequently in the coil group.(Sciurba et al. 2016) This therapy has limited clinical availability.

Additional data are needed to define the optimal bronchoscopic lung volume technique to produce bronchoscopic lung volume reduction in patients who lack fissure integrity, or exhibit collateral ventilation, and to refine the procedure to reduce complications and improve longer term clinical outcomes. (Sciurba et al. 2016)

Key points for interventional therapy in stable COPD are summarized in **Table 3.11**.

The Introduction was changed as follows:
COPD patients should have an assessment of the severity of their airflow obstruction, symptoms, history of exacerbations, exposure to risk factors and comorbidities (**Figure 4.1**) to guide management. The assessment is summarized in **Chapter 2**.

We propose a tailored approach to initiate treatment based on the level of symptoms and risk for exacerbations. Treatment can be escalated/de-escalated based on the presence of the predominant symptoms of breathlessness and exercise limitation, and the continued occurrence of exacerbations whilst on maintenance therapy. The basis for these recommendations, which propose an organized approach to treatment, was partly derived from evidence generated from randomized controlled trials. However, as these recommendations are intended to support clinician decision-making, they also incorporate expert advice based on clinical experience.

It is crucial for people with COPD to understand the nature of the disease, risk factors for its progression, and the role that they and their healthcare workers must play in order to achieve optimal management and health outcomes.

Following the assessment, initial management should address reducing exposure to risk factors including smoking cessation. Vaccination should be offered, and patients should receive general advice on healthy living, including diet, and that physical exercise is safe and encouraged for people with COPD. Initial pharmacotherapy should be based on the patient's GOLD group (**Figure 4.2**). Patients should be offered guidance on self-management of breathlessness, energy conservation and stress management, and they should be given a written action plan. Comorbidities should also be managed (**Figure 4.1**).

Patients should be reviewed after a suitable interval and their current level of symptoms (using either the CAT or mMRC scores) and exacerbation frequency assessed. The effect of treatment and possible adverse effects should be evaluated, and comorbidities reassessed.

Inhaler technique; adherence to prescribed therapy (both pharmacological and non-pharmacological); smoking status and continued exposure to risk factors should be checked. Physical activity should be encouraged and pulmonary rehabilitation should be considered. The need for oxygen therapy, ventilatory support, lung volume reduction and palliative approaches should be reviewed. The action plan should be updated. Spirometry should be repeated at least annually.

Pharmacological and non-pharmacological therapy should be adjusted as necessary (see below) and further reviews undertaken (**Figure 4.1**).

The aim of management is to reduce both current symptoms and future risks of exacerbations (**Table 4.1**).

Added to the 'Treatment of stable COPD: Non-pharmacological treatment' section:
Non-pharmacological treatment is complementary to pharmacological treatment and should form part of the comprehensive management of COPD.

After receiving a diagnosis of COPD, a patient should be given further information about the condition. Physicians should emphasize the importance of a smoke free environment, prescribe vaccinations, empower adherence to prescribed medication, ensure proper inhaler technique, promote physical activity and refer patients (GOLD B - GOLD D) to pulmonary rehabilitation.

Some relevant non-pharmacological measures based on the GOLD group **AT DIAGNOSIS** are summarized in **Table 4.8**.

Recommendations for **FOLLOW UP** non-pharmacological treatments are based on patient's treatable traits e.g., symptoms and exacerbations (**Table 4.9**).

Added to the 'Education and self-management' section:
Physicians and healthcare providers need to go beyond pure education/advice-giving (didactic) approaches to help patients learn and adopt sustainable self-management skills. The basis of enabling patients to become active partners in their ongoing care is to build knowledge and skills. It is important to recognize that patient education alone does not itself change behavior, motivate patients, or positively impact exercise performance or lung function,(Ashikaga, Vacek, and Lewis 1980; Janelli, Scherer, and Schmieder 1991) but it can play a role in improving skills, ability to cope with illness, and health status.(Spruit et al. 2013)

Patients may have individual and/or group education sessions. During group sessions, patients engage in active, participatory-based learning of program content. During one-on-one interactions, a motivational communication style should be used. This approach empowers patients to take greater responsibility for their health and well-being; physicians and other healthcare professionals serve as guides in the behavior change process.

Topics considered appropriate for an education program include: smoking cessation; basic information about COPD; general approach to therapy and specific aspects of medical treatment (respiratory medications and inhalation devices); strategies to help minimize dyspnea; advice on when to seek help; decision-making during exacerbations; and advance directives and end-of-life issues. The intensity and content of these educational messages will vary depending on the severity of the patient's disease, although the specific contributions of education to the improvements seen after pulmonary rehabilitation remain unclear.(Blackstock et al. 2014) Implicit in this description is the provision of "self-management support/coaching", which refers to the strategies, techniques and skills used by healthcare providers to arm patients with the knowledge, confidence and skills required to self-manage their disease effectively.

Added to the 'Physical activity' section:
Technology-based interventions have the potential to provide convenient and accessible means to enhance exercise self-efficacy, and to educate and motivate people in their efforts to make healthy lifestyle changes. The use of an internet-mediated intervention may benefit patients with COPD with low baseline self-efficacy to increase physical activity. (Robinson et al. 2019)

Added to the 'Pulmonary rehabilitation programs' section:

The World Health Organization (WHO) "Rehabilitation 2030: a call for action" (Gimigliano and Negrini 2017) makes the case for accessible and affordable rehabilitation as an essential component of health services, stating that this is crucial to achieve Sustainable Development Goal 3: 'good health and wellbeing'. Although there is clear potential for pulmonary rehabilitation to improve health, wellbeing and economic productivity, research is necessary to develop culturally appropriate pulmonary rehabilitation in low- and middle-income countries; programs are likely to be different across cultures and countries. (Singh et al. 2019)

Added to the 'Interventional bronchoscopy and surgery' section:

In patients with fissure integrity or lack of interlobar collateral ventilation based on physiologic assessment, endobronchial valve, lung coil treatment, vapor ablation therapy or LVRS could all be useful. In patients with lack of fissure integrity or interlobar collateral ventilation, vapor ablation, lung coil therapy or LVRS may be performed but endobronchial valve therapy is not useful. Patients with heterogeneous upper lobe predominant emphysema may be candidates for either LVRS or bronchoscopic lung reduction approaches. The presence of interlobar collateral ventilation would exclude the use of endobronchial valve therapy but lung coil or vapor ablation therapies could be considered along with LVRS. Patients with homogenous emphysema are not routinely considered candidates for LVRS at most centers, however, bronchoscopic lung reduction can be successful using endobronchial valve, vapor ablation or coil therapies. Again, the presence of interlobar collateral ventilation is important in selecting endobronchial valve as the intervention of choice. An algorithm depicting an overview of various interventions is shown in **Figure 4.6**.

Criteria for referral for lung transplantation include COPD with progressive disease, not a candidate for endoscopic or surgical lung volume reduction, BODE index of 5 to 6, Pco_2 > 50 mmHg or 6.6 kPa and/or Pao_2 < 60 mmHg or 8.0 kPa, and FEV_1 < 25% predicted.(Weill et al. 2015) Recommended criteria for listing include one of the following: BODE index > 7, FEV_1 < 15-20% predicted, three or more severe exacerbations during the preceding year, one severe exacerbation with acute hypercapnic respiratory failure, or moderate to severe pulmonary hypertension.(Weill et al. 2015; ISHLT: The International Society for Heart & Lung Transplantation [Internet]) Key points for the use of non-pharmacological treatments are given in **Table 4.10**.

Chapter 5

Introduction:

An exacerbation of chronic obstructive pulmonary disease (COPD) is defined as an acute worsening of respiratory symptoms that results in additional therapy. (Wedzicha and Seemungal 2007; Seemungal et al. 1998) Exacerbations of COPD are important events in the management of COPD because they negatively impact health status, rates of hospitalization and readmission, and disease progression. COPD exacerbations are complex events usually associated with increased airway inflammation, increased mucus production and marked gas trapping. These changes contribute to increased dyspnea that is the key symptom of an exacerbation. Other symptoms include increased sputum purulence and volume, together with increased cough and wheeze. (Anthonisen et al. 1987) As other comorbidities that may worsen respiratory symptoms are common in COPD patients, clinical assessment to rule out

differential diagnoses should be considered before diagnosis of a COPD exacerbation (**Table 5.1**).

and

Vitamin D has an immune-modulating role and has been implicated in the pathophysiology of exacerbations. As with all chronic diseases vitamin D levels are lower in COPD than in health. Studies have shown that supplementation in subjects with severe deficiency results in a 50% reduction in episodes and hospital admission.(Jolliffe et al. 2019) Therefore it is recommended that all patients hospitalized for exacerbations should be assessed and investigated for severe deficiency (<10 ng/ml or <25 nM) followed by supplementation if required.

Added to 'Acute respiratory failure – life-threatening' section:
Mortality risk may be heightened during spells of cold weather. (Chen et al. 2019)

Added to 'Pharmacological treatment' section:

Added to 'Bronchodilators'
If a nebulizer is chosen to deliver the bronchodilator agent, air-driven bronchodilator nebulization is preferable to oxygen-driven in acute exacerbations of COPD in order to avoid the potential risk of increasing the $PaCO_2$ associated with oxygen-driven bronchodilator administration. (Bardsley et al. 2018)

Added to 'Glucocorticoids'
One observational study suggests that longer courses of oral corticosteroids for COPD exacerbations are associated with an increased risk of pneumonia and mortality. (Sivapalan, Ingebrigtsen, et al. 2019)

and

Even short bursts of corticosteroids are associated with subsequent increased risk of pneumonia, sepsis and death (Waljee et al. 2017) and use should be confined to patients with significant exacerbations. Recent studies suggest that glucocorticoids may be less efficacious to treat acute COPD exacerbations in patients with lower levels of blood eosinophils (Bafadhel et al. 2011; Bafadhel et al. 2012; Hurst et al. 2010; Sivapalan, Lapperre, et al. 2019) and more trials of steroid-sparing treatment regimens are required.

Added to 'Antibiotics'
Sputum color can safely modulate antibiotic therapy with no adverse effects if the patient's normal sputum color is white or clear in appearance. Sputum purulence has 94.4% sensitivity and 52% specificity for high bacterial load, indicative of a causative relationship. (Stockley et al. 2000)

and

Earlier studies of C-reactive protein (CRP) have reported contradictory findings.(Clark et al. 2015; Peng et al. 2013) A recent randomized trial found a marked reduction in antibiotic prescriptions without

impaired outcomes in UK primary care outpatients with AECOPD in whom antibiotics prescriptions were guided by point-of-care CRP testing.(Prins et al. 2019) Another trial in patients hospitalized for acute exacerbations of COPD in The Netherlands found similar results (reduced antibiotic use with no increase in treatment failure). These findings need confirmation in other settings before a recommendation to generalize this approach. However, recent data has indicated that antibiotic usage can be safely reduced from 77.4% to 47.7% when CRP is low. (Butler et al. 2019)

Added to 'Respiratory support' section:

High-flow nasal therapy. High-flow nasal therapy (HFNT) involves nasal delivery of heated and humidified oxygen and air gas blends via special devices (e.g., Vapotherm®, Comfort Flo®, or Optiflow®) at rates up to 8 L/min in infants and up to 60 L/min in adults.(Roca et al. 2016) In patients with acute hypoxemic respiratory failure, HFNT may be an alternative to standard oxygen therapy or noninvasive positive pressure ventilation. In observational studies, HFNT has been associated with decreased respiratory rate and effort, decreased work of breathing, improved gas exchange, improved lung volume, dynamic compliance, transpulmonary pressures and homogeneity. All these physiologic benefits may improve oxygenation and clinical outcomes in ARF patients. (Mauri et al. 2017) Some studies in COPD patients report that HFNT improves oxygenation and ventilation, and decreases hypercarbia. (Frat et al. 2017; Fraser et al. 2016) A systematic review of RCTs in patients with acute hypoxemic respiratory failure suggests that HFNT tends to reduce intubation rate, but did not meet statistical significance compared with conventional oxygen therapy or NIV, and had no effect on mortality.(Lin et al. 2017) Several randomized controlled trials have also studied the use of HFNT therapy to reduced hypercapnia and improved health-related quality of life in patients with stable hypercapnic COPD.(Nagata et al. 2018; Braunlich et al. 2019; Bruni et al. 2019) There is a need for well-designed, randomized, multicenter trials to study the effects of HFNT in both acute and chronic hypoxemic/hypercarbic respiratory failure in COPD patients.

Chapter 6

Added to 'Anxiety and depression' section:

A recent systematic review has shown that COPD patients are 1.9 times more likely to commit suicide than people without COPD. (Sampaio et al. 2019)

Added to 'COPD and lung cancer' section:

In lung cancer patients, the presence of COPD is associated with poorer outcomes and an increased rate of post-operative complications. (Lin et al. 2019)

GOLD 2020 NEW REFERENCES, FIGURES AND TABLES

The GOLD 2020 report is a revision of the GOLD 2019 report. Following systematic literature searches and double-blind review by the GOLD Science committee, the GOLD report has been updated to include key peer-reviewed research publications from January 2018 to July 2019. In total, 62 new references have been added to the GOLD 2020 report, as listed alphabetically below:

Agusti A, Fabbri LM, Singh D, et al. Inhaled corticosteroids in COPD: friend or foe? *Eur Respir J* 2018; **52**(6).

Alison JA, McKeough ZJ, Leung RWM, et al. Oxygen compared to air during exercise training in COPD with exercise-induced desaturation. *Eur Respir J* 2019; **53**(5).

Bardsley G, Pilcher J, McKinstry S, et al. Oxygen versus air-driven nebulisers for exacerbations of chronic obstructive pulmonary disease: a randomised controlled trial. *BMC Pulm Med* 2018; **18**(1): 157.

Benzo R, McEvoy C. Effect of Health Coaching Delivered by a Respiratory Therapist or Nurse on Self-Management Abilities in Severe COPD: Analysis of a Large Randomized Study. *Respir Care* 2019; **64**(9): 1065-72.

Benzo RP, Kirsch JL, Hathaway JC, McEvoy CE, Vickers KS. Health Coaching in Severe COPD After a Hospitalization: A Qualitative Analysis of a Large Randomized Study. *Respir Care* 2017; **62**(11): 1403-11.

Bhatt SP, Balte PP, Schwartz JE, et al. Discriminative Accuracy of FEV1:FVC Thresholds for COPD-Related Hospitalization and Mortality. *JAMA* 2019; **321**(24): 2438-47.

Braunlich J, Dellweg D, Bastian A, et al. Nasal high-flow versus noninvasive ventilation in patients with chronic hypercapnic COPD. *Int J Chron Obstruct Pulmon Dis* 2019; **14**: 1411-21.

Bruni A, Garofalo E, Cammarota G, et al. High Flow Through Nasal Cannula in Stable and Exacerbated Chronic Obstructive Pulmonary Disease Patients. *Rev Recent Clin Trials* 2019.

Bullen C, Howe C, Laugesen M, et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet* 2013; **382**(9905): 1629-37.

Butler CC, Gillespie D, White P, et al. C-Reactive Protein Testing to Guide Antibiotic Prescribing for COPD Exacerbations. *N Engl J Med* 2019; **381**(2): 111-20.

Celli BR, Anderson JA, Brook R, et al. Serum biomarkers and outcomes in patients with moderate COPD: a substudy of the randomised SUMMIT trial. *BMJ open respiratory research* 2019; **6**(1): e000431.

Centers for Disease Control and Prevention; U.S. Department of Health & Human Services. Outbreak of Lung Injury Associated with E-Cigarette Use, or Vaping https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html

Chan KH, Kurmi OP, Bennett DA, et al. Solid Fuel Use and Risks of Respiratory Diseases. A Cohort Study of 280,000 Chinese Never-Smokers. *Am J Respir Crit Care Med* 2019; **199**(3): 352-61.

Chen J, Yang J, Zhou M, et al. Cold spell and mortality in 31 Chinese capital cities: Definitions, vulnerability and implications. *Environ Int* 2019; **128**: 271-8.

Cho-Reyes S, Celli BR, Dembek C, Yeh K, Navaie M. Inhalation Technique Errors with Metered-Dose Inhalers Among Patients with Obstructive Lung Diseases: A Systematic Review and Meta-Analysis of U.S. Studies. *Chronic Obstr Pulm Dis* 2019; **6**(3): 267-80.

Colak Y, Nordestgaard BG, Vestbo J, Lange P, Afzal S. Prognostic significance of chronic respiratory symptoms in individuals with normal spirometry. *Eur Respir J* 2019; **54**(3).

Criner GJ, Celli BR, Brightling CE, et al. Benralizumab for the Prevention of COPD Exacerbations. *N Engl J Med* 2019; **381**(11): 1023-34.

Criner GJ, Delage A, Voelker K, et al. Improving Lung Function in Severe Heterogenous Emphysema with the Spiration(R) Valve System (EMPROVE): A Multicenter, Open-Label, Randomized, Controlled Trial. *Am J Respir Crit Care Med* 2019; **Epub Aug 01 2019**.

Criner GJ, Sue R, Wright S, et al. A Multicenter Randomized Controlled Trial of Zephyr Endobronchial

Valve Treatment in Heterogeneous Emphysema (LIBERATE). *Am J Respir Crit Care Med* 2018; **198**(9): 1151-64.

De Matteis S, Jarvis D, Darnton A, et al. The occupations at increased risk of COPD: analysis of lifetime job-histories in the population-based UK Biobank Cohort. *Eur Respir J* 2019; **54**(1).

Devereux G, Cotton S, Fielding S, et al. Effect of Theophylline as Adjunct to Inhaled Corticosteroids on Exacerbations in Patients With COPD: A Randomized Clinical Trial. *JAMA* 2018; **320**(15): 1548-59.

Doiron D, de Hoogh K, Probst-Hensch N, et al. Air pollution, lung function and COPD: results from the population-based UK Biobank study. *Eur Respir J* 2019; **54**(1).

Eklof J, Sorensen R, Ingebrigtsen TS, et al. Pseudomonas aeruginosa and risk of death and exacerbations in patients with chronic obstructive pulmonary disease: an observational cohort study of 22 053 patients. *Clin Microbiol Infect* 2019.

Ferguson GT, Rabe KF, Martinez FJ, et al. Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial. *Lancet Respir Med* 2018; **6**(10): 747-58.

Gimigliano F, Negrini S. The World Health Organization "Rehabilitation 2030: a call for action". *Eur J Phys Rehabil Med* 2017; **53**(2): 155-68.

Gordon CS, Waller JW, Cook RM, Cavalera SL, Lim WT, Osadnik CR. Effect of Pulmonary Rehabilitation on Symptoms of Anxiety and Depression in COPD: A Systematic Review and Meta-Analysis. *Chest* 2019; **156**(1): 80-91.

Gouzi F, Maury J, Heraud N, et al. Additional Effects of Nutritional Antioxidant Supplementation on Peripheral Muscle during Pulmonary Rehabilitation in COPD Patients: A Randomized Controlled Trial. *Oxid Med Cell Longev* 2019; **2019**: 5496346.

Hajek P, Phillips-Waller A, Przulj D, et al. E-cigarettes compared with nicotine replacement therapy within the UK Stop Smoking Services: the TEC RCT. *Health Technol Assess* 2019; **23**(43): 1-82.

Hartley B, Criner GJ, Dransfield MT, et al. Misinterpretation of time-to-first event curves can lead to inappropriate treatment. *Eur Respir J* 2019; **54**(3).

He T, Oks M, Esposito M, Steinberg H, Makaryus M. "Tree-in-Bloom": Severe Acute Lung Injury Induced by Vaping Cannabis Oil. *Ann Am Thorac Soc* 2017; **14**(3): 468-70.

Henry TS, Kanne JP, Kligerman SJ. Imaging of Vaping-Associated Lung Disease. *N Engl J Med* 2019; **381**(15): 1486-7.

Jolliffe DA, Greenberg L, Hooper RL, et al. Vitamin D to prevent exacerbations of COPD: systematic review and meta-analysis of individual participant data from randomised controlled trials. *Thorax* 2019; **74**(4): 337-45.

Lambe T, Adab P, Jordan RE, et al. Model-based evaluation of the long-term cost-effectiveness of systematic case-finding for COPD in primary care. *Thorax* 2019; **74**(8): 730-9.

Layden JE, Ghinai I, Pray I, et al. Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin - Preliminary Report. *N Engl J Med* 2019; **Epub Sep 06 2019**.

Liang L, Cai Y, Barratt B, et al. Associations between daily air quality and hospitalisations for acute exacerbation of chronic obstructive pulmonary disease in Beijing, 2013-17: an ecological analysis. *Lancet Planet Health* 2019; **3**(6): e270-e9.

Lin H, Lu Y, Lin L, Meng K, Fan J. Does chronic obstructive pulmonary disease relate to poor prognosis in patients with lung cancer?: A meta-analysis. *Medicine (Baltimore)* 2019; **98**(11): e14837.

Lipson DA, Barnhart F, Brealey N, et al.; IMPACT Investigators. Once-Daily Single-Inhaler Triple versus

Dual Therapy in Patients with COPD. N Engl J Med. 2018 May 3;378(18):1671-1680.

Lipson DA, Criner GJ, Day N, et al. Reduction in the Risk of All-Cause Mortality with Fluticasone Furoate/Umeclidinium/Vilanterol Compared to Umeclidinium/Vilanterol in IMPACT Including Previously Missing or Censored Vital Status Data [Rapid Abstract Poster Discussion]. *Am J Respir Crit Care Med* 2019; **199**: A7344.

Mauri T, Turrini C, Eronia N, et al. Physiologic Effects of High-Flow Nasal Cannula in Acute Hypoxemic Respiratory Failure. *Am J Respir Crit Care Med* 2017; **195**(9): 1207-15.

Ni W, Bao J, Yang D, et al. Potential of serum procalcitonin in predicting bacterial exacerbation and guiding antibiotic administration in severe COPD exacerbations: a systematic review and meta-analysis. *Infectious diseases (London, England)* 2019; **51**(9): 639-50.

Nolan CM, Kaliaraju D, Jones SE, et al. Home versus outpatient pulmonary rehabilitation in COPD: a propensity-matched cohort study. *Thorax* 2019; **74**(10): 996-8.

Pascoe S, Barnes N, Brusselle G, et al. Blood eosinophils and treatment response with triple and dual combination therapy in chronic obstructive pulmonary disease: analysis of the IMPACT trial. *The Lancet Respiratory medicine* 2019; **7**(9): 745-56.

Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. *The Lancet Respiratory medicine* 2015; **3**(6): 435-42.

Pavord ID, Chanez P, Criner GJ, et al. Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2017; **377**(17): 1613-29.

Poole P, Sathananthan K, Fortescue R. Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease. *The Cochrane database of systematic reviews* 2019; **5**: CD001287.

Prins HJ, Duijkers R, van der Valk P, et al. CRP-guided antibiotic treatment in acute exacerbations of COPD in hospital admissions. *Eur Respir J* 2019; **53**(5).

Ray R, Tombs L, Naya I, Compton C, Lipson DA, Boucot I. Efficacy and safety of the dual bronchodilator combination umeclidinium/vilanterol in COPD by age and airflow limitation severity: A pooled post hoc analysis of seven clinical trials. *Pulm Pharmacol Ther* 2019; **57**: 101802.

Robinson SA, Shimada SL, Quigley KS, Moy ML. A web-based physical activity intervention benefits persons with low self-efficacy in COPD: results from a randomized controlled trial. *J Behav Med* 2019; **Epub Apr 14 2019**.

Roca O, Hernandez G, Diaz-Lobato S, Carratala JM, Gutierrez RM, Masclans JR. Current evidence for the effectiveness of heated and humidified high flow nasal cannula supportive therapy in adult patients with respiratory failure. *Crit Care* 2016; **20**(1): 109.

Rogliani P, Matera MG, Page C, Puxeddu E, Cazzola M, Calzetta L. Efficacy and safety profile of mucolytic/antioxidant agents in chronic obstructive pulmonary disease: a comparative analysis across erdosteine, carbocysteine, and N-acetylcysteine. *Respir Res* 2019; **20**(1): 104.

Sampaio MS, Vieira WA, Bernardino IM, Herval AM, Flores-Mir C, Paranhos LR. Chronic obstructive pulmonary disease as a risk factor for suicide: A systematic review and meta-analysis. *Respir Med* 2019; **151**: 11-8.

Sanchis J, Gich I, Pedersen S, Aerosol Drug Management Improvement Team. Systematic Review of Errors in Inhaler Use: Has Patient Technique Improved Over Time? *Chest* 2016; **150**(2): 394-406.

Singh SJ, Halpin DMG, Salvi S, Kirenga BJ, Mortimer K. Exercise and pulmonary rehabilitation for people

with chronic lung disease in LMICs: challenges and opportunities. *Lancet Respir Med* 2019 Oct 16. pii: S2213-2600(19)30364-9.

Sivapalan P, Ingebrigtsen TS, Rasmussen DB, et al. COPD exacerbations: the impact of long versus short courses of oral corticosteroids on mortality and pneumonia: nationwide data on 67 000 patients with COPD followed for 12 months. *BMJ Open Resp Res* 2019; **6**(1): e000407.

Sivapalan P, Lapperre TS, Janner J, et al. Eosinophil-guided corticosteroid therapy in patients admitted to hospital with COPD exacerbation (CORTICO-COP): a multicentre, randomised, controlled, open-label, non-inferiority trial. *Lancet Respir Med* 2019; **7**(8): 699-709.

Stockley RA, Halpin DMG, Celli BR, Singh D. Chronic Obstructive Pulmonary Disease Biomarkers and Their Interpretation. *Am J Respir Crit Care Med* 2019; **199**(10): 1195-204.

Suissa S, Ariel A. Triple therapy trials in COPD: a precision medicine opportunity. *Eur Respir J* 2018; **52**(6).

Suissa S, Dell'Aniello S, Ernst P. Comparative effectiveness of LABA-ICS versus LAMA as initial treatment in COPD targeted by blood eosinophils: a population-based cohort study. *Lancet Respir Med* 2018; **6**(11): 855-62.

Suissa S, Dell'Aniello S, Ernst P. Comparative Effectiveness and Safety of LABA-LAMA vs LABA-ICS Treatment of COPD in Real-World Clinical Practice. *Chest* 2019; **155**(6): 1158-65.

van Beers M, Rutten-van Molken M, van de Bool C, et al. Clinical outcome and cost-effectiveness of a 1-year nutritional intervention programme in COPD patients with low muscle mass: The randomized controlled NUTRAIN trial. *Clin Nutr* 2019.

Vestbo J, Fabbri L, Papi A, et al. Inhaled corticosteroid containing combinations and mortality in COPD. *Eur Respir J.* 2018 Dec 13;52(6). pii: 1801230.

Waljee AK, Rogers MA, Lin P, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. *BMJ* 2017; **357**: j1415.

Wootton SL, Hill K, Alison JA, et al. Effects of Ongoing Feedback During a 12-Month Maintenance Walking Program on Daily Physical Activity in People with COPD. *Lung* 2019; **197**(3): 315-9.