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Chronic obstructive pulmonary disease – a treatable disease

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Summary

Chronic obstructive pulmonary disease (COPD) is a global health challenge and a leading cause of death worldwide. Several risk factors have been identified, with cigarette smoking being the most important. Diagnostic assessment is based on symptoms, risk of exacerbations and results of lung function testing. A fixed post-bronchodilator ratio for forced expiratory volume in one second to forced expiratory volume (FEV_1/FVC) of <0.7 is required to make the diagnosis, and the severity of airflow obstruction defines the grade according to GOLD (Global Strategy for the Diagnosis, Management, and Prevention of COPD). The GOLD strategy makes therapeutic recommendations taking into account the grade, symptomatic assessment and future risk of exacerbations.

This review focuses on the therapeutic options for COPD, in accordance with the GOLD strategy.

Smoking cessation is the most effective treatment option in all COPD stages. Bronchodilators, namely long-acting antimuscarinic drugs and long-acting beta-agonists, form the mainstay of treatment in COPD. Patients with frequent exacerbations also benefited from the addition of inhaled corticosteroids. Roflumilast is an add-on option for patients with severe COPD.

Several controversies are the subject of discussion: (1.) whether pharmacotherapy can modify the natural history of COPD; (2.) whether pharmacotherapy should be started in the early stages of COPD; (3.) the impact of therapy on comorbidities; (4.) whether patients benefit from a combination therapy with a long-acting beta-agonist, a long-acting antimuscarinic drug and an inhaled corticosteroid; (5.) step-down therapy.

This overview also reviews the evidence for recommended vaccines in COPD, as well as nonpharmacological therapies. Rehabilitation is an essential part of COPD treatment. Oxygen therapy, noninvasive nocturnal ventilation and surgical treatment options only apply to a highly selected group of patients.

Disease management programmes and guideline adherence are briefly discussed.

In conclusion, although there is debate as to the extent with which pharmacological therapies influence mortality, adherence to the GOLD strategy is recommended.

Key words: *COPD; smoking cessation; pharmacological therapy*

Introduction

Chronic obstructive pulmonary disease (COPD) is defined as a "preventable and treatable disease, which is characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases" [1]. COPD is and will be a global health challenge in the next decades. It is currently the fourth leading cause of death worldwide and is expected to rise to the third leading cause [2].

The most important risk factor for COPD is cigarette smoking, but other risk factors have been identified, and may be particularly important in women, especially in low-income countries [3–6]. Air pollution and occupational exposure have also been linked to the development of COPD [5]. The diagnosis of COPD is based on exposure to risk factors, symptoms (possibly underreported because patients have adapted to these) and a fixed post-bronchodilator ratio of forced expiratory volume in one second (FEV_1) to forced expiratory volume (FVC) of <0.7 [1].

Therapeutic options include smoking cessation, which has the greatest impact on the natural history of COPD, pharmacological therapy, mainly inhaled bronchodilators, and nonpharmacological treatment options such as rehabilitation [1].

This review will focus on the therapeutic scope in COPD and give an overview of the different possibilities and their impact on disease progress and symptom control.

Diagnosis and assessment

Common symptoms of COPD include dyspnoea, chronic cough and sputum production. Spirometry is needed to confirm a suspected diagnosis of COPD. The presence of

airflow limitation with a fixed post-bronchodilator ratio of FEV_1/FVC <0.7 is required to make the diagnosis. With the fixed ratio criterion there is some risk of misdiagnosis in the elderly population and in persons below 45 years of age [7]. There seems to be an overestimation of COPD diagnosis in the elderly [8–11], whereas in younger subjects with existing airflow limitation some cases might be missed when the fixed cut-off criterion are used [11, 12]. However, a definition based on a cut-off using the lower limit of normal values for FEV_1/FVC has not been validated by longitudinal studies and depends on reference equations that have not been validated either [13]. Further, age and risk of COPD due to previous exposures may interact to increase significantly the probability of having an obstructive ratio that points to the presence of airflow limitation [14].

Generally, many people with COPD remain undiagnosed, especially those with mild and moderate disease [15, 16]. This can also be assumed to be the case in Switzerland [17]. Although screening asymptomatic patients with spirometry is not warranted [18], case finding may be a cost-effective strategy that identifies patients who will respond to interventions for COPD [19–21].

The GOLD strategy

The "Global Strategy for the Diagnosis, Management, and Prevention of COPD" (GOLD strategy), revised in 2011, summarises current evidence on management and prevention strategies.

Depending on the severity of airflow obstruction, four grades are classified by GOLD: mild disease (FEV_1 ≥80% predicted), moderate disease (50% ≤ FEV_1 <80% predicted), severe disease (30% ≤ FEV_1 <50%), and very severe disease (FEV_1 <30% predicted), and the results of this classification lead to treatment choice [1]. However, FEV_1 has only limited value in predicting disease impact [22] and this is taken into account by including symptoms and the risk of exacerbations in the assessment for treatment choice [1]. GOLD strategy recommends use of the modified British Medical Research Council (mMRC) questionnaire or the COPD Assessment Test (CAT) to assess symptoms. Together with the frequency of exacerbations within the last year (defined as an acute event with worsening of symptoms that leads to a change in medication) patients are placed in categories A–D and treatment recommendations are based on the spirometric evaluation as well as the symptomatic assessment (table 1) [1].

Therapeutic options

The first and most important step in COPD therapy, at all stages, is smoking cessation, which reduces the yearly decline in FEV_1 and lowers mortality [23–25]. Advice from doctors or nurses, counselling and pharmacotherapy supports and increases successful quit rates compared with brief smoking cessation advice alone [26]. There is little evidence as to whether biomedical risk assessment such as interpretation of spirometric results, measurement of exhaled carbon monoxide or visualising plaque formation in the carotid artery will help patients to quit smoking [27]. However, ongoing studies in the primary care setting aim to clarify if structured information about spirometric results will lead to higher smoking cessation rates [28, 29]. Higher quit rates can be achieved by offering nicotine replacement therapy in any available form [30]. Bupropion [31] and varenicline [32] have also been shown to promote abstinence. Combined pharmacotherapy and behavioural support increase successful smoking cessation compared with pharmacotherapy or behavioural support alone, and offering more intense behavioural interventions, as well as face-to-face contact, might have a greater effect than telephone contact offered by quitlines [33]. Implementing tobacco control policies would also reduce smoking prevalence [34].

Pharmacological therapies

Pharmacological therapy aims to reduce symptoms and exacerbations, and to improve quality of life and exercise tolerance. The GOLD strategy recommends a stepwise treatment plan taking into account the COPD grade based on spirometry, symptoms and the future risk of exacerbations [1].

Bronchodilators form the mainstay of therapy for COPD. Short-acting beta-agonists are used on an as-needed basis or regularly for symptomatic relief in the early stages or

Table 1: First-choice treatment recommendations according to the GOLD strategy.

Patient category	Severity of airflow limitation	Risk of exacerbations per year	Severity of symptoms	Initial pharmacotherapy
A	GOLD 1: FEV_1 ≥80% predicted or GOLD 2: 50% ≤ FEV_1 <80% predicted	0–1	mMRC 0–1 or CAT <10	Short-acting anticholinergic OR short-acting $beta_2$-agonist
B	GOLD 1: FEV_1 ≥80% predicted or GOLD 2: 50% ≤ FEV_1 <80% predicted	0–1	mMRC ≥2 or CAT ≥10	Long-acting anticholinergic OR Long-acting $beta_2$-agonist
C	GOLD 3: 30% ≤ FEV_1 <50% predicted or GOLD 4: FEV_1 <30% predicted	≥2	mMRC 0–1 or CAT <10	Inhaled corticosteroid AND long-acting $beta_2$ agonist OR Long-acting anticholinergic
D	GOLD 3: 30% ≤ FEV_1 <50% predicted or GOLD 4: FEV_1 <30% predicted	≥2	mMRC ≥2 or CAT ≥10	Inhaled corticosteroid AND long-acting $beta_2$ agonist AND/OR Long-acting anticholinergic

GOLD = Global Initiative for Chronic Obstructive Lung Disease; FEV_1 = forced expiratory volume in one second; mMRC = modified British Medical Research Council questionnaire; CAT= COPD Assessment Test

in COPD patients with a low symptom burden, and have been shown to reduce dyspnoea intensity [35]. Long-acting beta-agonists and the long-acting antimuscarinic drug tiotropium improve health status and reduce the number and severity of exacerbations [36–38]. The ultra–long-acting beta-agonist indacaterol has also been shown to have a good profile of tolerability regardless of COPD severity or concurrent inhaled corticosteroid use [39].

For patients whose symptoms are not controlled by the use of a long-acting beta-agonist or long-acting antimuscarinic drug, combination of these is recommended [1]. Compared with single-agent therapy the aforementioned combination therapy resulted in symptomatic improvements as well as less airflow obstruction [39–43]. However, long-term data are missing [44].

To date, the major anti-inflammatory treatment for COPD has been inhaled corticosteroids, which improve quality of life and reduce exacerbation rate especially in patients with severe diseases. No benefit with regard to disease progression or mortality has been shown in several studies when inhaled corticosteroids used as monotherapy are compared with placebo [37, 45–48]. Lower respiratory tract infections and pneumonia are reported with greater frequency in COPD patients treated with inhaled corticosteroids [45].

However, patients benefited from the fixed combination of inhaled long-acting beta-agonists and corticosteroids in large interventional trials, and the combination was superior to the individual components [37, 49, 50]. Withdrawal of inhaled corticosteroids causes an increased exacerbation rate and this has fed the controversy on inhaled corticosteroid intervention studies [51, 52].

In severe and very severe COPD, roflumilast, a new oral phosphodiesterase-4 inhibitor, decreased the frequency of exacerbations [53] and improved lung function when given in combination with inhaled salmeterol or tiotropium [54]. The most common side effect of roflumilast is diarrhoea; other common side effects include insomnia and weight loss [55]. Data on the effect of roflumilast when added to an existing treatment of inhaled bronchodilator and inhaled corticosteroids are expected for 2014 [55].

Owing to the side effects of prolonged treatment with oral corticosteroids, there is limited data on their effect in stable COPD [56, 57]. Their value, however, has been shown in the treatment of acute exacerbations [58] although the optimal duration of therapy has yet to be defined [59].

Long-term antibiotic treatment in stable COPD is a subject of debate. There are data suggesting a reduction in the risk of exacerbations with continuous treatment with azithromycin [60, 61]. There might also be a benefit with pulsed therapy with moxifloxacin with regard to reducing the exacerbation rate [62]. There is increasing evidence that prompt antibiotic therapy reduces the frequency and duration of COPD exacerbations [63, 64].

Since oxidative stress and mucus formation play an important role in the pathogenesis of COPD, antioxidative and mucolytic agents such as N-acetyl-L-cysteine have been used in the treatment of patients with COPD, with mixed results [65]. A review of smaller studies showed an effect in reducing exacerbations [66]; however, one large randomised controlled trial did not show any benefit in terms of reducing the rate of exacerbations with 600 mg of N-acetyl-L-cysteine daily [67]. Whether higher doses of N-acetyl-L-cysteine are effective and safe to use in patients with COPD is currently being investigated [68].

Oral bacterial lysates (e.g. Broncho-vaxom) have been used in patients with COPD to reduce exacerbations. Although, some studies have shown a clinical benefit in terms of reducing exacerbations [69, 70], there is no clear and consistent evidence to recommend this treatment for a well-defined patient group with COPD [71, 72].

Despite effective treatment for COPD, several controversial issues remain

The first question is whether pharmacotherapy can modify the natural history of COPD. To date, there is no direct evidence showing conclusively that recommended therapy slows the rate of decline in FEV_1 [23, 46–48, 73]. Smoking cessation is the only effective step for slowing the decline of FEV_1 [23, 24] and lowering mortality [25]; the latter also applies for oxygen therapy for a selected group of patients. A fixed combination of an inhaled long-acting beta-agonist and a corticosteroid showed a trend toward lower mortality in one of the landmark studies [37], but this needs to be confirmed in other large prospective trials. Also, a *post-hoc* analysis of the TORCH trial showed a small effect on decline of FEV_1 with a fixed combination treatment of salmeterol and fluticasone propionate [74].

The second question is whether pharmacotherapy should be started in the early stages of COPD (GOLD stages 1 and 2). Evidence is scarce as the large interventional studies did not specifically target this group of patients [75]. However, subgroup analysis of the two landmark studies showed a beneficial effect regarding FEV_1 decline in patients with GOLD stage 2 COPD for salmeterol [76] and tiotropium [77]. Airway hyper-responsiveness testing with inhaled mannitol might identify patients who will benefit from add-on therapy with inhaled corticosteroids in the early stages of COPD [78].

More frequent exacerbations are associated with faster FEV_1 decline [79] and more than 20% of patients with GOLD stage 2 have frequent exacerbations [80]. So, early and effective treatment and possibly prevention of exacerbations should result in a reduced rate of decline.

Tiotropium was more effective than salmeterol in reducing exacerbations in patients with COPD GOLD stages 2–4 [36]. Patients with a predicted FEV_1 of >70% were excluded in the aforementioned big studies and therefore the question as to whether therapy with long-acting bronchodilators or combinations with inhaled corticosteroids is warranted in these patients remains unanswered.

Antibiotics and oral corticosteroids are usually used to treat acute exacerbations. Lung function improves with systemic corticosteroids in exacerbations, and recovery time is shorter [81–85]. The use of antibiotics in exacerbations has been a subject of debate because exacerbations might be precipitated by a viral or bacterial infection. Patients with rather severe COPD and more purulent sputum probably benefit from antibiotic therapy [64]. Also, antibiotics may prolong the time to a subsequent exacerbation when added to oral corticosteroids in an acute exacerbation [63]. The measurement of procalcitonin, as a marker for bacterial infection, can be used as guidance for the use of antibiotics in

acute exacerbations of COPD [86]. However, it is not always readily available.

Thirdly, comorbidities must be taken into account. Will the treatment with bronchodilators or inhaled corticosteroids have an effect on comorbidities [87]? There are no data to give an answer to this question. Statins, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have been shown to reduce morbidity and mortality in patients with COPD [88]. Treatment with cardioselective beta-blockers may also be beneficial for patients in COPD as they seem to lower the exacerbation rate [89] and reduce mortality [89, 90].

In addition, there is debate as to which patients benefit from combination therapy with a long-acting beta-agonist, a long-acting antimuscarinic and inhaled corticosteroid therapy (triple therapy), and as to which patients benefit from a combination of just two components. Studies have shown improvements in quality of life, symptom burden and use of relief medication [39, 91–93], and one study showed a reduction in severe exacerbations [91]. However, no long-term studies exist and therefore it is too early to draw reliable conclusions on the efficacy and safety of triple therapy [42, 94].

Lastly, the GOLD strategy gives guidelines for the initial therapy of patients with COPD, but there are no specific recommendations for a step-down of therapy and what such a decision should be based on. Further studies are needed to address this important question.

Vaccines

The Swiss Respiratory Society recommends yearly vaccination against influenza and pneumococcal vaccination in persons with COPD, particularly those over 65 years of age [95]. There might be a risk reduction for acute exacerbations with influenza vaccines, but data are very limited regarding the effectiveness of influenza vaccination in persons with COPD [96, 97]. Pneumococcal vaccination might reduce morbidity in subjects with COPD, but evidence that allows reliable conclusions is lacking [98, 99]. It is possible that the newer conjugated pneumococcal vaccines will have greater efficacy in reducing pneumonia incidence and mortality in COPD, but this is yet to be tested [100, 101].

Nonpharmacological therapies

Rehabilitation

Rehabilitation with exercise training as a core component is an essential part of the treatment of COPD. It is safe, and improves symptoms and quality of life [102]. There might even be a mortality benefit, but studies have been underpowered to show conclusively a lower mortality with rehabilitation [103]. Patients of all disease stages and ages profit from rehabilitation programmes [104], and even starting rehabilitation during an exacerbation seems to be safe and feasible [105]. Rehabilitation should include education about COPD and treatment options, exercise training, nutritional intervention and psychosocial support. Effectiveness has been well documented for in-patient, outpatient and home-based programmes [103].

Oxygen therapy and noninvasive ventilation

The administration of oxygen >15 hours per day improves survival in COPD patients with chronic respiratory failure and severe resting hypoxaemia [106]. In patients without resting hypoxaemia a clear benefit has not been shown for oxygen supplementation and it is currently not recommended [107].

A survival benefit was noted for nocturnal noninvasive ventilation in patients with very severe, oxygen-dependent COPD and daytime hypercapnia. However, this intervention reduced their quality of life [108].

Surgical treatments

Surgical treatments such as lung volume reduction surgery, bronchoscopic lung volume reduction, bullectomy and lung transplantation are treatment options for very selected groups of patients. Patients with severe, predominately upper lobe emphysema and low exercise capacity after rehabilitation show improved survival with lung volume reduction surgery, and patients with high exercise capacity after rehabilitation show improved quality of life and exercise capacity after lung volume reduction surgery [109]. Bronchoscopic lung volume reduction entails the positioning of endobronchial valves. Patients with advanced heterogeneous emphysema profited from endobronchial valves, with increased lung function and exercise capacity. However, this might be at the cost of a higher rate of subsequent exacerbations [110], pneumonia and haemoptysis [110]. As mentioned before, this treatment option only applies to a highly selected group of patients with COPD. Bullectomy in patients with a single giant bulla results in improved quality of life, and improves symptoms and lung function [111].

Lung transplantation in COPD is limited by the availability of donor organs. Carefully selected patients with very severe COPD benefit in terms of better functional capacity and quality of life [112].

Disease management strategies

Self-management education in patients with COPD might be associated with a reduction in hospital admissions, but there is still insufficient evidence to make clear recommendations on the form and content of these programmes [113]. A recent study of a comprehensive care management programme including individual educational sessions, an action plan and proactive telephone calls was stopped early because of excess mortality in the intervention group [114]. Another recent study of self-management interventions in the primary care setting showed no benefit in terms of quality of life, self efficacy or frequency of exacerbations with ongoing telephone support and tailored sessions or routine monitoring compared with usual care [115].

Guideline adherence

Although the GOLD strategy summarises the evidence for the different treatment options and makes therapeutic recommendations, many patients with COPD are not treated in accordance with these guidelines [116–119]. One study found no benefit for Swiss patients treated in accordance with guidelines, as compared with those that were not, in terms of rate of exacerbation and lung function decline

within one year of follow-up [117]. Lower costs have, however, been associated with adherence to the GOLD strategy [120]. The most recent GOLD strategy recommends assessment of symptoms and exacerbation history in addition to the GOLD stage, in order to estimate risk and decide on appropriate therapy [1]. This new paradigm has yet to be tested formally in relation to its impact on COPD outcomes.

Conclusion

Effective treatment for COPD exists. Smoking cessation is paramount. Although there is still debate as to the extent with which pharmacological therapies influence mortality, adherence to the GOLD strategy is recommended.

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References

1 Goldcopd.org. Global Strategy for the Diagnosis, Management, and Prevention of COPD; [updated 2011 December; cited 2012 April 21]. Available from: www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html

2 WHO.int. World Health Statistics; [updated 2008; cited 2012 April 25]. Available from: http://www.who.int/whosis/whostat/EN_WHS08_Full.pdf

3 Behrendt CE. Mild and moderate-to-severe COPD in nonsmokers: distinct demographic profiles. Chest. 2005;128(3):1239–44.

4 Celli BR, Halbert RJ, Nordyke RJ, Schau B. Airway obstruction in never smokers: results from the Third National Health and Nutrition Examination Survey. Am J Med. 2005;118(12):1364–72.

5 Eisner MD, Anthonisen N, Coultas D, Kuenzli N, Perez-Padilla R, Postma D, et al. An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2010;182(5):693–718.

6 Lamprecht B, McBurnie MA, Vollmer WM, Gudmundsson G, Welte T, Nizankowska-Mogilnicka E, et al. COPD in never smokers: results from the population-based burden of obstructive lung disease study. Chest. 2011;139(4):752–63.

7 Vollmer WM, Gislason T, Burney P, Enright PL, Gulsvik A, Kocabas A, et al. Comparison of spirometry criteria for the diagnosis of COPD: results from the BOLD study. Eur Respir J. 2009;34(3):588–97.

8 Hardie JA, Buist AS, Vollmer WM, Ellingsen I, Bakke PS, Morkve O. Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers. Eur Respir J. 2002;20(5):1117–22.

9 Celli BR, Halbert RJ, Isonaka S, Schau B. Population impact of different definitions of airway obstruction. Eur Respir J. 2003;22(2):268–73.

10 Shirtcliffe P, Weatherall M, Marsh S, Travers J, Hansell A, McNaughton A, et al. COPD prevalence in a random population survey: a matter of definition. Eur Respir J. 2007;30(2):232–9.

11 Hnizdo E, Glindmeyer HW, Petsonk EL, Enright P, Buist AS. Case definitions for chronic obstructive pulmonary disease. COPD. 2006;3(2):95–100.

12 Cerveri I, Corsico AG, Accordini S, Niniano R, Ansaldo E, Anto JM, et al. Underestimation of airflow obstruction among young adults using FEV_1/FVC <70% as a fixed cut-off: a longitudinal evaluation of clinical and functional outcomes. Thorax. 2008;63(12):1040–5.

13 Mohamed Hoesein FA, Zanen P, Lammers JW. Lower limit of normal or FEV_1/FVC <0.70 in diagnosing COPD: an evidence-based review. Respir Med. 2011;105(6):907–15.

14 Marks GB. Are reference equations for spirometry an appropriate criterion for diagnosing disease and predicting prognosis? Thorax. 2012;67(1):85–87.

15 Miravitlles M, Soriano JB, Garcia-Rio F, Munoz L, Duran-Tauleria E, Sanchez G, et al. Prevalence of COPD in Spain: impact of undiagnosed COPD on quality of life and daily life activities. Thorax. 2009;64(10):863–8.

16 Hvidsten SC, Storesund L, Wentzel-Larsen T, Gulsvik A, Lehmann S. Prevalence and predictors of undiagnosed chronic obstructive pulmonary disease in a Norwegian adult general population. Clin Respir J. 2010;4(1):13–21.

17 Jochmann A, Neubauer F, Miedinger D, Schafroth S, Tamm M, Leuppi JD. General practitioner's adherence to the COPD GOLD guidelines: baseline data of the Swiss COPD Cohort Study. Swiss Med Wkly. Epub 2010 Apr 21.

18 Lin K, Watkins B, Johnson T, Rodriguez JA, Barton MB. Screening for chronic obstructive pulmonary disease using spirometry: summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2008;148(7):535–43.

19 Price D, Crockett A, Arne M, Garbe B, Jones RC, Kaplan A, et al. Spirometry in primary care case-identification, diagnosis and management of COPD. Prim Care Respir J. 2009;18(3):216–23.

20 Jordan RE, Lam KB, Cheng KK, Miller MR, Marsh JL, Ayres JG, et al. Case finding for chronic obstructive pulmonary disease: a model for optimising a targeted approach. Thorax. 2010;65(6):492–8.

21 Frith P, Crockett A, Beilby J, Marshall D, Attewell R, Ratnanesan A, et al. Simplified COPD screening: validation of the PiKo-6(R) in primary care. Prim Care Respir J. 2011;20(2):190–8.

22 Agusti A, Calverley PM, Celli B, Coxson HO, Edwards LD, Lomas DA, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res. 2010;11:122.

23 Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV_1. The Lung Health Study. JAMA. 1994;272(19):1497–505.

24 Anthonisen NR, Connett JE, Murray RP. Smoking and lung function of Lung Health Study participants after 11 years. Am J Respir Crit Care Med. 2002;166(5):675–9.

25 Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Ann Intern Med. 2005;142(4):233–9.

26 Lancaster T, Stead L, Silagy C, Sowden A. Effectiveness of interventions to help people stop smoking: findings from the Cochrane Library. BMJ. 2000;321(7257):355–8.

27 Bize R, Burnand B, Mueller Y, Rege-Walther M, Camain JY, Cornuz J. Biomedical risk assessment as an aid for smoking cessation. Cochrane Database Syst Rev. 2012;12:CD004705.

28 Martin-Lujan F, Pinol-Moreso JL, Martin-Vergara N, Basora-Gallisa J, Pascual-Palacios I, Sagarra-Alamo R, et al. Effectiveness of a structured motivational intervention including smoking cessation advice and spirometry information in the primary care setting: the ESPITAP study. BMC Public Health. 2011;11:859.

29 Rodriguez-Alvarez M, Toran-Monserrat P, Munoz-Ortiz L, Negrete-Palma A, Montero-Alia JJ, Jimenez-Gonzalez M, et al. Effectiveness of regular reporting of spirometric results combined with a smoking cessation advice by a primary care physician on smoking quit rate in adult smokers: a randomized controlled trial. ESPIROTAB study. BMC Fam Pract. 2011;12:61.

30 Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev. 2004;(3):CD000146.

31 Tashkin D, Kanner R, Bailey W, Buist S, Anderson P, Nides M, et al. Smoking cessation in patients with chronic obstructive pulmonary

disease: a double-blind, placebo-controlled, randomised trial. Lancet. 2001;357(9268):1571–5.

32 Tashkin DP, Rennard S, Hays JT, Ma W, Lawrence D, Lee TC. Effects of varenicline on smoking cessation in patients with mild to moderate COPD: a randomized controlled trial. Chest. 2011;139(3):591–9.

33 Stead LF, Lancaster T. Behavioural interventions as adjuncts to pharmacotherapy for smoking cessation. Cochrane Database Syst Rev. 2012;12:CD009670.

34 Mendez D, Alshanqeety O, Warner KE. The potential impact of smoking control policies on future global smoking trends. Tob Control. 2013;22(1):46–51.

35 O'Donnell DE, Laveneziana P, Ora J, Webb KA, Lam YM, Ofir D. Evaluation of acute bronchodilator reversibility in patients with symptoms of GOLD stage I COPD. Thorax. 2009;64(3):216–23.

36 Vogelmeier C, Hederer B, Glaab T, Schmidt H, Rutten-van Molken MP, Beeh KM, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. N Engl J Med. 2011;364(12):1093–103.

37 Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356(8):775–89.

38 Barr RG, Bourbeau J, Camargo CA, Ram FS. Inhaled tiotropium for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2005;(2):CD002876.

39 Decramer M, Dahl R, Kornmann O, Korn S, Lawrence D, McBryan D. Effects of long-acting bronchodilators in COPD patients according to COPD severity and ICS use. Respir Med. 2013;107(2):223–32.

40 van Noord JA, Aumann JL, Janssens E, Smeets JJ, Zaagsma J, Mueller A, et al. Combining tiotropium and salmeterol in COPD: Effects on airflow obstruction and symptoms. Respir Med. 2010;104(7):995–1004.

41 Tashkin DP, Pearle J, Iezzoni D, Varghese ST. Formoterol and tiotropium compared with tiotropium alone for treatment of COPD. COPD. 2009;6(1):17–25.

42 Rodrigo GJ, Plaza V, Castro-Rodriguez JA. Comparison of three combined pharmacological approaches with tiotropium monotherapy in stable moderate to severe COPD: a systematic review. Pulm Pharmacol Ther. 2012;25(1):40–7.

43 Tashkin DP, Varghese ST. Combined treatment with formoterol and tiotropium is more efficacious than treatment with tiotropium alone in patients with chronic obstructive pulmonary disease, regardless of smoking status, inhaled corticosteroid use, baseline severity, or gender. Pulm Pharmacol Ther. 2011;24(1):147–52.

44 Sethi S, Cote C. Bronchodilator combination therapy for the treatment of chronic obstructive pulmonary disease. Curr Clin Pharmacol. 2011;6(1):48–61.

45 Drummond MB, Dasenbrook EC, Pitz MW, Murphy DJ, Fan E. Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA. 2008;300(20):2407–16.

46 Pauwels RA, Lofdahl CG, Laitinen LA, Schouten JP, Postma DS, Pride NB, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. N Engl J Med. 1999;340(25):1948–53.

47 Vestbo J, Sorensen T, Lange P, Brix A, Torre P, Viskum K. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. Lancet. 1999;353(9167):1819–23.

48 Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ. 2000;320(7245):1297–303.

49 Szafranski W, Cukier A, Ramirez A, Menga G, Sansores R, Nahabedian S, et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. Eur Respir J. 2003;21(1):74–81.

50 Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. Eur Respir J. 2003;22(6):912–9.

51 Choudhury AB, Dawson CM, Kilvington HE, Eldridge S, James WY, Wedzicha JA, et al. Withdrawal of inhaled corticosteroids in people with COPD in primary care: a randomised controlled trial. Respir Res. 2007;8:93.

52 Schermer TR, Hendriks AJ, Chavannes NH, Dekhuijzen PN, Wouters EF, van den Hoogen H, et al. Probability and determinants of relapse after discontinuation of inhaled corticosteroids in patients with COPD treated in general practice. Prim Care Respir J. 2004;13(1):48–55.

53 Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. Lancet. 2009;374(9691):685–94.

54 Fabbri LM, Calverley PM, Izquierdo-Alonso JL, Bundschuh DS, Brose M, Martinez FJ, et al. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. Lancet. 2009;374(9691):695–703.

55 Taegtmeyer AB, Leuppi JD, Kullak-Ublick GA. Roflumilast – a phosphodiesterase-4 inhibitor licensed for add-on therapy in severe COPD. Swiss Med Wkly. 2012;142:w13628.

56 Renkema TE, Schouten JP, Koeter GH, Postma DS. Effects of long-term treatment with corticosteroids in COPD. Chest. 1996;109(5):1156–62.

57 Rice KL, Rubins JB, Lebahn F, Parenti CM, Duane PG, Kuskowski M, et al. Withdrawal of chronic systemic corticosteroids in patients with COPD: a randomized trial. Am J Respir Crit Care Med. 2000;162(1):174–8.

58 Walters JA, Gibson PG, Wood-Baker R, Hannay M, Walters EH. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2009;(1):CD001288.

59 Schuetz P, Leuppi JD, Tamm M, Briel M, Bingisser R, Durring U, et al. Short versus conventional term glucocorticoid therapy in acute exacerbation of chronic obstructive pulmonary disease – the "REDUCE" trial. Swiss Med Wkly. 2010;140:w13109.

60 Seemungal TA, Wilkinson TM, Hurst JR, Perera WR, Sapsford RJ, Wedzicha JA. Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. Am J Respir Crit Care Med. 2008;178(11):1139–47.

61 Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA, Jr., Criner GJ, et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med. 2011;365(8):689–98.

62 Sethi S, Jones PW, Theron MS, Miravitlles M, Rubinstein E, Wedzicha JA, et al. Pulsed moxifloxacin for the prevention of exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. Respir Res. 2010;11:10.

63 Roede BM, Bresser P, Prins JM, Schellevis F, Verheij TJ, Bindels PJ. Reduced risk of next exacerbation and mortality associated with antibiotic use in COPD. Eur Respir J. 2009;33(2):282–8.

64 Daniels JM, Snijders D, de Graaff CS, Vlaspolder F, Jansen HM, Boersma WG. Antibiotics in addition to systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2010;181(2):150–7.

65 Rahman I, MacNee W. Antioxidant pharmacological therapies for COPD. Curr Opin Pharmacol. 2012;12(3):256–65.

66 Stey C, Steurer J, Bachmann S, Medici TC, Tramer MR. The effect of oral N-acetylcysteine in chronic bronchitis: a quantitative systematic review. Eur Respir J. 2000;16(2):253–62.

67 Decramer M, Dekhuijzen PN, Troosters T, van Herwaarden C, Rutten-van Molken M, van Schayck CP, et al. The Bronchitis Randomized On NAC Cost-Utility Study (BRONCUS): hypothesis and design. BRONCUS-trial Committee. Eur Respir J. 2001;17(3):329–36.

68 Zheng JP, Wen FQ, Bai CX, Wan HY, Kang J, Chen P, et al. High-Dose N-Acetylcysteine in the Prevention of COPD Exacerbations: Rationale and Design of the PANTHEON Study. COPD. Epub 2012 Oct 12.

69 Soler M, Mutterlein R, Cozma G. Double-blind study of OM-85 in patients with chronic bronchitis or mild chronic obstructive pulmonary disease. Respiration. 2007;74(1):26–32.

70 Cazzola M, Noschese P, Di Perna F. Value of adding a polyvalent mechanical bacterial lysate to therapy of COPD patients under regular

treatment with salmeterol/fluticasone. Ther Adv Respir Dis. 2009;3(2):59–63.

71 Braido F, Tarantini F, Ghiglione V, Melioli G, Canonica GW. Bacterial lysate in the prevention of acute exacerbation of COPD and in respiratory recurrent infections. Int J Chron Obstruct Pulmon Dis. 2007;2(3):335–45.

72 Sprenkle MD, Niewoehner DE, MacDonald R, Rutks I, Wilt TJ. Clinical efficacy of OM-85 BV in COPD and chronic bronchitis: a systematic review. COPD. 2005;2(1):167–75.

73 Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med. 2008;359(15):1543–54.

74 Celli BR, Thomas NE, Anderson JA, Ferguson GT, Jenkins CR, Jones PW, et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. Am J Respir Crit Care Med. 2008;178(4):332–8.

75 Rabe KF, Wedzicha JA. Controversies in treatment of chronic obstructive pulmonary disease. Lancet. 2011;378(9795):1038–47.

76 Jenkins CR, Jones PW, Calverley PM, Celli B, Anderson JA, Ferguson GT, et al. Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study. Respir Res. 2009;10:59.

77 Decramer M, Celli B, Kesten S, Lystig T, Mehra S, Tashkin DP. Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. Lancet. 2009;374(9696):1171–8.

78 Scherr A, Schafroth Torok S, Jochmann A, Miedinger D, Maier S, Taegtmeyer AB, et al. Response to add-on inhaled corticosteroids in COPD based on airway hyperresponsiveness to mannitol. Chest. Epub 2012 Mar 29.

79 Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax. 2002;57(10):847–52.

80 Hurst JR, Vestbo J, Anzueto A, Locantore N, Mullerova H, Tal-Singer R, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010;363(12):1128–38.

81 Davies L, Angus RM, Calverley PM. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. Lancet. 1999;354(9177):456–60.

82 Maltais F, Ostinelli J, Bourbeau J, Tonnel AB, Jacquemet N, Haddon J, et al. Comparison of nebulized budesonide and oral prednisolone with placebo in the treatment of acute exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. Am J Respir Crit Care Med. 2002;165(5):698–703.

83 Niewoehner DE, Erbland ML, Deupree RH, Collins D, Gross NJ, Light RW, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. N Engl J Med. 1999;340(25):1941–7.

84 Thompson WH, Nielson CP, Carvalho P, Charan NB, Crowley JJ. Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. Am J Respir Crit Care Med. 1996;154(2 Pt 1):407–12.

85 Aaron SD, Vandemheen KL, Hebert P, Dales R, Stiell IG, Ahuja J, et al. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. N Engl J Med. 2003;348(26):2618–25.

86 Stolz D, Christ-Crain M, Bingisser R, Leuppi J, Miedinger D, Muller C, et al. Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. Chest. 2007;131(1):9–19.

87 Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. Lancet. 2012;379(9823):1341–51.

88 Mancini GB, Etminan M, Zhang B, Levesque LE, FitzGerald JM, Brophy JM. Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. J Am Coll Cardiol. 2006;47(12):2554–60.

89 Rutten FH, Zuithoff NP, Hak E, Grobbee DE, Hoes AW. Beta-blockers may reduce mortality and risk of exacerbations in patients with chronic obstructive pulmonary disease. Arch Intern Med. 2010;170(10):880–7.

90 van Gestel YR, Hoeks SE, Sin DD, Welten GM, Schouten O, Witteveen HJ, et al. Impact of cardioselective beta-blockers on mortality in patients with chronic obstructive pulmonary disease and atherosclerosis. Am J Respir Crit Care Med. 2008;178(7):695–700.

91 Welte T, Miravitlles M, Hernandez P, Eriksson G, Peterson S, Polanowski T, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2009;180(8):741–50.

92 Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med. 2007;146(8):545–55.

93 Cazzola M, Ando F, Santus P, Ruggeri P, Di Marco F, Sanduzzi A, et al. A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium on the airflow obstruction of patients with severe-to-very severe COPD. Pulm Pharmacol Ther. 2007;20(5):556–61.

94 Karner C, Cates CJ. Combination inhaled steroid and long-acting beta(2)-agonist in addition to tiotropium versus tiotropium or combination alone for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2011;(3):CD008532.

95 Russi EW, Leuenberger P, Brandli O, Frey JG, Grebski E, Gugger M, et al. Management of chronic obstructive pulmonary disease: the Swiss guidelines. Official Guidelines of the Swiss Respiratory Society. Swiss Med Wkly. 2002;132(5-6):67–78.

96 Poole PJ, Chacko E, Wood-Baker RW, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2006;(1):CD002733.

97 Michiels B, Govaerts F, Remmen R, Vermeire E, Coenen S. A systematic review of the evidence on the effectiveness and risks of inactivated influenza vaccines in different target groups. Vaccine. 2011;29(49):9159–70.

98 Walters JA, Smith S, Poole P, Granger RH, Wood-Baker R. Injectable vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2010;(11):CD001390.

99 Vila-Corcoles A, Ochoa-Gondar O. Pneumococcal vaccination among adults with chronic respiratory diseases: a historical overview. Expert Rev Vaccines. 2012;11(2):221–36.

100 Schembri S, Morant S, Winter JH, MacDonald TM. Influenza but not pneumococcal vaccination protects against all-cause mortality in patients with COPD. Thorax. 2009;64(7):567–72.

101 Pitsiou GG, Kioumis IP. Pneumococcal vaccination in adults: does it really work? Respir Med. 2011;105(12):1776–83.

102 Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2006;(4):CD003793.

103 de Blasio F, Polverino M. Current best practice in pulmonary rehabilitation for chronic obstructive pulmonary disease. Ther Adv Respir Dis. 2012;6(4):221–37.

104 Corhay JL, Nguyen D, Duysinx B, Graas C, Pirnay F, Bury T, et al. Should we exclude elderly patients with chronic obstructive pulmonary disease from a long-time ambulatory pulmonary rehabilitation programme? J Rehabil Med. 2012;44(5):466–72.

105 Tang CY, Blackstock FC, Clarence M, Taylor NF. Early Rehabilitation Exercise Program for Inpatients During an Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Randomized Controlled Trial. J Cardiopulm Rehabil Prev. 2012;32(3):163–9.

106 Stoller JK, Panos RJ, Krachman S, Doherty DE, Make B. Oxygen therapy for patients with COPD: current evidence and the long-term oxygen treatment trial. Chest. 2010;138(1):179–87.

107 Moore RP, Berlowitz DJ, Denehy L, Pretto JJ, Brazzale DJ, Sharpe K, et al. A randomised trial of domiciliary, ambulatory oxygen in patients with COPD and dyspnoea but without resting hypoxaemia. Thorax. 2011;66(1):32–7.

108 McEvoy RD, Pierce RJ, Hillman D, Esterman A, Ellis EE, Catcheside PG, et al. Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. Thorax. 2009;64(7):561–6.

109 Naunheim KS, Wood DE, Mohsenifar Z, Sternberg AL, Criner GJ, DeCamp MM, et al. Long-term follow-up of patients receiving lung-volume-reduction surgery versus medical therapy for severe emphysema by the National Emphysema Treatment Trial Research Group. Ann Thorac Surg. 2006;82(2):431–43.

110 Sciurba FC, Ernst A, Herth FJ, Strange C, Criner GJ, Marquette CH, et al. A randomized study of endobronchial valves for advanced emphysema. N Engl J Med. 2010;363(13):1233–44.

111 Lederer DJ, Arcasoy SM. Update in surgical therapy for chronic obstructive pulmonary disease. Clin Chest Med. 2007;28(3):639–53.

112 Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dobbels F, Kirk R, et al. The Registry of the International Society for Heart and Lung Transplantation: Twenty-eighth Adult Lung and Heart-Lung Transplant Report – 2011. J Heart Lung Transplant. 2011;30(10):1104–22.

113 Effing T, Monninkhof EM, van der Valk PD, van der Palen J, van Herwaarden CL, Partidge MR, et al. Self-management education for patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2007;(4):CD002990.

114 Fan VS, Gaziano JM, Lew R, Bourbeau J, Adams SG, Leatherman S, et al. A comprehensive care management program to prevent chronic obstructive pulmonary disease hospitalizations: a randomized, controlled trial. Ann Intern Med. 2012;156(10):673–83.

115 Bischoff EW, Akkermans R, Bourbeau J, van Weel C, Vercoulen JH, Schermer TR. Comprehensive self management and routine monitoring in chronic obstructive pulmonary disease patients in general practice: randomised controlled trial. BMJ. 2012;345:e7642.

116 Miravitlles M. Guidelines versus clinical practice in the treatment of chronic obstructive pulmonary disease. Eur Respir J. 2002;20(1):243–4.

117 Jochmann A, Scherr A, Jochmann DC, Miedinger D, Torok SS, Chhajed PN, et al. Impact of adherence to the GOLD guidelines on symptom prevalence, lung function decline and exacerbation rate in the Swiss COPD cohort. Swiss Med Wkly. 2012;142:w13567.

118 Miravitlles M, Mayordomo C, Artes M, Sanchez-Agudo L, Nicolau F, Segu JL. Treatment of chronic obstructive pulmonary disease and its exacerbations in general practice. EOLO Group. Estudio Observacional de la Limitacion Obstructiva al Flujo aEreo. Respir Med. 1999;93(3):173–9.

119 Roche N, Lepage T, Bourcereau J, Terrioux P. Guidelines versus clinical practice in the treatment of chronic obstructive pulmonary disease. Eur Respir J. 2001;18(6):903–8.

120 Asche CV, Leader S, Plauschinat C, Raparla S, Yan M, Ye X, et al. Adherence to current guidelines for chronic obstructive pulmonary disease (COPD) among patients treated with combination of long-acting bronchodilators or inhaled corticosteroids. Int J Chron Obstruct Pulmon Dis. 2012;7:201–9.