

Short versus conventional term glucocorticoid therapy in acute exacerbation of chronic obstructive pulmonary disease

The "REDUCE*" trial (*Reduction in the Use of Corticosteroids in Exacerbated COPD. ISRCTN19646069). Design and baseline characteristics

Philipp Schuetz^{a, b}, Jörg D. Leuppi^{a, c}, Michael Tamm^c, Matthias Briel^{d, g}, Roland Bingisser^e, Ursula Düring^b, Beat Müller^b, Christian Schindler^f, Sebastien Viatte^h, Jonas Rutishauser^{a, h}

^a Clinic for Internal Medicine, ^b Clinic for Endocrinology, Diabetology, and Clinical Nutrition, ^c Clinic for Pneumology, ^d Basel Institute for Clinical Epidemiology and Biostatistics, ^e Emergency Department, University Hospital Basel; ^f Institute of Social and Preventive Medicine, University of Basel; Switzerland; ^g Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Canada; ^h Clinic of Internal Medicine, Hospital Centre, Biel-Bienne, Switzerland

Correspondence:

PD Dr. Jonas Rutishauser
Clinic of Internal Medicine
Hospital Center
Vogelsang 84
CH-2501 Biel-Bienne
Switzerland
j.rutishauser@unibas.ch

Summary

BACKGROUND: International guidelines advocate a 10 to 14-day course of systemic glucocorticoid therapy in the management of COPD exacerbations. The optimal duration of therapy is unknown and glucocorticoids have serious adverse effects. The aim of this trial is to demonstrate non-inferiority of a five-day compared to a 14-day course of systemic glucocorticoids with respect to COPD outcome, thereby significantly reducing steroid exposure and side effects in patients with COPD exacerbations.

METHODS: This is a randomised, placebo-controlled, non-inferiority multicentre trial. Patients with acute COPD exacerbation are randomised to receive 40 mg of prednisone-equivalent daily for 14 days (conventional arm) or glucocorticoid treatment for 5 days, followed by placebo for another 9 days (intervention arm). Follow-up is 180 days. The primary endpoint is time to next exacerbation. Secondary endpoints include cumulative glucocorticoid dose, time to open-label glucocorticoid therapy, glucocorticoid-associated side effects and complications,

duration of hospital stay, death, change in FEV₁, need for assisted ventilation, clinical outcome assessed by standardised questionnaires, and suppression of the hypothalamic-pituitary-adrenal axis.

RESULTS: Mean age (\pm SD) of patients who finished the study was 70 \pm 11 years. 12% had mild or moderate disease, whereas severe and very severe stages were found in 30 and 58%, respectively. At the time of inclusion, 20% of patients were under treatment with systemic glucocorticoids.

CONCLUSIONS: If the strategy of significantly reducing cumulative exposure to glucocorticoids while taking advantage of their beneficial short-term effects proves to be successful, it will warrant a change in common glucocorticoid prescription practice, thereby improving the management of COPD.

Key words: COPD; exacerbation; steroids; glucocorticoids; side effects

Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth commonest cause of death worldwide, posing a large socioeconomic burden [1, 2]. In Switzerland, it has been estimated that 5–7% of the population and 28% of the current smokers suffer from COPD [3]. The clinical course of the disease is characterised by progressive, irreversible airflow obstruction associated with chronic inflammation of the respiratory tract. Acute exacerbations are triggered mainly by respiratory tract infections. According to evidence-based reviews and current guidelines, systemic glucocorticoid therapy is an integral part of the management of COPD exacerbations [1, 2, 4–10]. Randomised, controlled trials suggests that systemic glucocorticoid ther-

List of abbreviations

COPD	chronic obstructive pulmonary disease
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HPA axis	hypothalamic-pituitary-adrenal axis

apy accelerates the recovery of the FEV₁ [11–16], decreases the length of hospital stay [12, 15, 16], and improves clinical outcome [14–17]. However, the optimal dose and duration of glucocorticoid therapy remain unknown. The SCCOPE trial, the largest placebo-controlled study, used cumulative prednisone doses as high as roughly 2000 and 2600 mg in the two active treatment arms, respectively, but the clinical outcomes of the active and placebo arms did not differ after 6 months of follow-up [15]. The benefit of glucocorticoids on FEV₁ improvement lasts for 3 to 5 days and levels off thereafter [15, 16]. Thus, there are no data yet to suggest a benefit of treatment beyond 5 days.

As patients with COPD frequently experience exacerbations, many will be exposed to large cumulative doses of glucocorticoids during the course of their disease. A significant number of patients remain steroid-dependent beyond the acute exacerbation. Thus, approximately 50% of eligible patients had to be excluded from the SCCOPE study because of systemic glucocorticoid use in the 30 days prior to enrolment.

The side-effects and dangers of treatment with systemic glucocorticoids are well known. Their use in patients with COPD is independently associated with increased mortality in models adjusting for multiple confounders [18]. Moreover, these patients are at enhanced risk for osteoporosis, in part due to decreased muscle mass, physical inactivity, and cigarette smoking. In a cohort of individuals with chronic pulmonary diseases, including COPD, the cumulative dose of glucocorticoids strongly correlated with vertebral fracture risk due to loss of bone mineral density [19]. Glucocorticoids contribute to muscle catabolism in COPD [20], and the cumulative dose has been found to correlate with muscle weakness [21]. In the SCCOPE study, hyperglycaemia was seen significantly more often in glucocorticoid- as compared to placebo-treated patients, and re-hospitalisation rates due to serious infections, particularly pneumonia, were high in the long-term active treatment group [15]. Moderate to high-dose (i.e., ≥ 25 mg/d prednisone equivalent) systemic glucocorticoid treatment, even if prescribed for a relatively short period (i.e., 5–30 days), may suppress the hypothalamic-pituitary-adrenal (HPA) axis as assessed by the low-dose (1 μ g) ACTH stimulation test in almost half the patients [22]. Although the clinical significance of this finding is unclear, a suppressed HPA axis may be potentially hazardous in stressful situations such as an acute exacerbation of COPD.

Thus, in order to alleviate these multiple adverse effects of glucocorticoid therapy, a strong effort should be made to minimise its cumulative dose in patients with COPD.

Patients and methods

The main objective of this trial is to test the hypothesis that in acute exacerbations of COPD, a short course (5 days) of glucocorticoid treatment will not result in an inferior clinical outcome compared to a conventional course (14 days), but will significantly decrease steroid exposure and steroid-associated side effects in patients with exacerbation of COPD. The study was approved by the institutional re-

view boards of all participating centres and is conducted in accordance with the Declaration of Helsinki.

Study design

This is a multicentre, randomised, controlled study aiming to demonstrate non-inferiority of a five-day as compared to a 14-day course of systemic glucocorticoids with respect to COPD outcome during a follow-up of 180 days. The primary endpoint will be time to next COPD exacerbation, defined as acute-onset worsening of the patient's condition beyond day-to-day variations requiring interaction with a healthcare provider [23], which may occur during the index exacerbation or during follow-up.

Secondary endpoints will be cumulative steroid dose; time to open-label standard-dose glucocorticoid therapy during the index exacerbation; need for invasive or non-invasive mechanical ventilation; change in FEV₁; clinical outcome at discharge and during follow-up as assessed according to the ATS consensus statement for dyspnoea [24] and a standardised questionnaire [25]; duration of hospital stay; all-cause mortality; steroid-associated side-effects and complications, defined as follows: development or exacerbation of hyperglycaemia (fasting plasma glucose ≥ 5.6 mmol/L or random plasma glucose ≥ 7.8 mmol/L or rise $\geq 20\%$ in daily doses of insulin or any increase in oral antidiabetic drugs or initiation of one or more antidiabetic therapeutic principle), development or worsening of hypertension (blood pressure ≥ 140 mm Hg systolic and/or ≥ 90 mm Hg diastolic or the addition of one or more anti-hypertensive drugs to previous treatment regimens), integrity of the HPA axis at study entry and during follow-up as assessed with the low dose (1 μ g) ACTH stimulation test and with a clinical questionnaire on signs and symptoms of hypocortisolism [26]; effect on bone-turnover as assessed by specific biochemical markers; secondary infections; and other potentially steroid-related adverse events (e.g., gastrointestinal bleeding or psychiatric disease).

Prior to its initiation, the study was registered (ISRCTN19646069). The protocol summary has been published on the LANCET website (<http://www.thelancet.com/protocol-reviews/05PRT-17>).

Methods

Six hospitals in the northern and central part of Switzerland participate in this trial. Patients admitted to the local emergency department because of exacerbated COPD will be consecutively assessed for eligibility. The diagnosis of exacerbated COPD is defined clinically by the presence of at least 2 of the following signs and symptoms: change in baseline dyspnoea, cough, and sputum quantity or purulence [8, 27]. Irreversible airway obstruction will be documented by a bedside post-bronchodilator spirometric evaluation performed at inclusion, and the severity of COPD will be categorised according to GOLD criteria [1]. Patients must be 40 years of age or older, with a smoking history of ≥ 20 pack-years (past or present smokers) in order to minimise contamination of the study cohort with asthmatics. Exclusion criteria are inability to give written informed consent, diagnosis of asthma, radiological diagnosis of pneumonia, severe co-existing disease making survival of >6 months unlikely, and pregnancy or lactation.

At study entry, patients will be randomly assigned to one of two treatment regimens using a centralised, computer-based randomization procedure with fixed blocks of 6. Study subjects will be randomised after stratification according to age, presence or absence of systemic glucocorticoid treatment prior to the study period, and severity of COPD according to the GOLD classification [1]. Each study subject will be randomly assigned to receive a prepared set of study medication, consisting of two drug vials. The drugs will be prepared prior to the initiation of the study and packed by the Pharmacology Department, University Hospital, Basel, according to a randomization list. All patients will receive methylprednisolone 40 mg i.v. on day 1, followed by prednisone 40 mg daily dispensed from vial 1, containing the tablets for days 2 through 5. We chose the i.v. route for the first dose in order to facilitate administration upon hospital admission, when patients are often severely distressed. On day 6, vial 2 will be started which contains either prednisone or matching placebo for nine days. Thus, the standard group will receive a 14-day course of 40 mg prednisone equivalent q.d., and the intervention group will receive 40 mg prednisone equivalent q.d. for five days. The decision to administer open-label systemic glucocorticoid therapy at any time during the trial or to increase the dose during the initial 5-days treatment phase will be entirely at the discretion of the treating physicians, without interference by the study team. The treating physicians may be hospital-based (during the in-patient phase) or the general practitioner or chest physician following the patients after discharge.

All data relevant to our primary endpoint and the secondary endpoints will be assessed daily during the hospitalisation period, on day 6, on the day of discharge, as well as on days 15, 30, 90, and 180 of follow-up. Follow-up on days 15 and 90 will be by telephone interview, and on days 30 and 180 by clinical visit. Patients who have reached the primary endpoint are followed up for the entire 180 day as specified in the protocol. Apart from the systemic glucocorticoid regimen, COPD-related treatment during hospitalisation and the 180 day follow-up will be standardised; all patients will be treated during their hospital stay with nebulised inhaled short-acting bronchodilators 4 to 6 times daily as needed, an inhaled topic steroid (fluticasone 250 µg or budesonide 400 µg b.i.d.) combined with an inhaled long-acting beta agonist, (formoterol 12 µg or salmeterol 50 µg b.i.d.), plus tiotropium 18 µg once daily. In addition, to avoid any treatment bias between groups, all patients will receive a broad spectrum antibiotic for the first 7 days of the index exacerbation. Management during the hospital phase will include physical therapy, supplemental oxygen, and ventilatory support, as indicated clinically and recommended by current ATS / ERS guidelines [8]. The inhaled topic steroid, long-acting beta agonists and tiotropium will be maintained throughout the follow-up period.

Adverse events within 180 days after inclusion into the study will be monitored by the investigators and the data safety and monitoring board. We will assess hypertension, hyperglycaemia, infections and suppression of the hypothalamic-pituitary-adrenal axis as potential adverse events of glucocorticoid therapy and document these as secondary outcomes. To assess the function of the adrenal

glands, the low-dose (1 µg) ACTH (tetracosactide; Synacthen®) test will be performed prior to the administration of study drugs at entry, on day 6, and on the day of discharge. The test will be repeated during follow-up until results have normalized. Per study protocol, glucocorticoids are not tapered. Patients discharged from the hospital with adrenal insufficiency (i.e., plasma cortisol level <500 nmol/L after stimulation with 1 µg tetracosactide) will receive instructions about stress prophylaxis therapy with hydrocortisone by means of a tutorial developed by the Clinic for Endocrinology, Diabetes and Clinical Nutrition at the University Hospital Basel.

Statistical considerations, sample size, and power calculation

This study is designed to show non-inferiority of a short-course (5 days) as compared to a standard course (14 days) glucocorticoid treatment. In order to use a reliable treatment protocol, we chose a dose of 40 mg prednisone for 14 days for the standard treatment arm, which has unequivocally shown a benefit (albeit in non-hospitalised patients) over placebo for the primary endpoint of treatment failure [17].

We chose time to next COPD exacerbation as primary endpoint because of its clinical relevance and its potential to show differences between the two groups. Other clinically relevant outcomes as well as improvement of FEV₁ achieved by glucocorticoid treatment [16], will be assessed as secondary endpoints. To estimate the frequency of our primary endpoint, we used data published in the SCOPE study [15], and own data from the “ProResp” study [28] and the ProCOLD trial on acute exacerbations of COPD [29]. Based on this information, we estimated that the primary endpoint would occur in ~50% of patients within 6 months after randomisation.

We used a modified Delphi approach to define non-inferiority with regard to the primary endpoint. Briefly, 11 board certified specialists for internal medicine, endocrinology, and pulmonology were individually asked to define the maximum increase of therapeutic failures they would be willing to accept for the benefit of shortening the glucocorticoid treatment duration. According to the results of this survey, the planning committee judged that a 15% absolute difference in the percentage of patients with an exacerbation during the 6 months of follow-up would be a clinically tolerable upper limit. Assuming the proportion of patients under standard treatment with an exacerbation during follow-up equals 50%, this non-inferiority definition implies that the proportion of patients under experimental treatment with exacerbations during follow-up must not exceed 65%. We based our power calculation on an exponential survival model with proportional hazards between groups tuned to the above non-inferiority definition. The choice of the simplest possible survival model can be justified on the grounds that the log rank test and the proportional hazard assumption are both invariant to order-preserving transformations of the time scale if censored observations only occur after maximum follow-up.

Translating the above non-inferiority scenario into a survival-analytical setting with proportional hazards and time-independent hazard provides survival functions

$$S_s(t) = 0.5^{t/180} \text{ (standard arm)}$$

and

$$S_e(t) = 0.35^{t/180} \text{ (experimental arm),}$$

where $S(t)$ = probability for event-free survival until time t and t = time from inclusion in days.

Here, 50% of subjects in the standard arm and 35% of the subjects in the experimental arm are assumed to have been without exacerbation during the entire follow-up of 180 days.

Under the constant hazard assumption characterising the exponential survival model, the critical hazard ratio corresponding to our non-inferiority scenario is given by

$$HR = \ln(0.35) / \ln(0.5) = 1.515$$

When restricted to subjects with an event during 180-day follow-up, the mean and median event times under this model are 80 and 75 days, respectively, in the standard treatment arm; and 74 and 67 days, respectively, in the experimental arm.

Providing for the possibility of loss to follow-up, the necessary group sizes under a non-inferiority scenario with $\alpha = 0.05$ and $\beta = 0.1$ are as follows (we used the algorithm based on reference [30]): 177 patients if there is no loss to follow-up; 186 patients if loss to follow-up is 10%; 195 patients if loss to follow-up is 20%; 206 patients if loss to follow-up is 30%.

To corroborate these numbers, we performed a Monte Carlo simulation study under the same scenarios (i.e., assuming exponential survival distributions with a) 195 observations per arm, b) equal exacerbation rates of 50% during follow-up under the equality hypothesis, c) 65% vs. 50% exacerbations under the inferiority hypothesis, and d) with a drop-out rate of 20% during follow-up). In each of the simulations, the decision was based on the one-sided 95%-confidence interval for the hazard ratio between the experimental and standard arm and non-inferiority was concluded if this interval did not include 1.515 (see equation above). Among 5000 simulations under the inferiority hypothesis, non-inferiority was falsely concluded in 4.5% of cases, whereas the non-inferiority hypothesis was falsely rejected in 14% of 5000 simulations conducted under the equality hypothesis.

We therefore originally planned to include a total of 390 patients in the trial. Monitoring of patient recruitment and follow-up of included patients over the first years of the trial showed that the actual recruitment was considerably slower and the drop-out rate much lower (<4%) than anticipated. Given these observations and our limited resources, we recalculated the necessary sample size using a drop-out rate of 5%, an error of 5% and a power of 85% in order to complete the trial within a realistic time-frame. Under these assumptions, 150 patients need to be recruited per arm. Reassessment using a Monte-Carlo simulation indicated that the true power might be slightly lower, but at least 80%, with our non-inferiority definition. We now plan to include a total of 300 patients in the study.

Statistical analysis

Because in non-inferiority trials intention to treat and per protocol analyses may both falsely favour the conclusion of equivalence [31, 32], we will analyse our data in both ways. To test non-inferiority of the experimental treatment, a simple Cox regression analysis will be performed. Non-inferiority will be concluded if the two-sided 90%-confidence interval for the hazard ratio between experimental and standard arm in the intention-to-treat and per protocol analysis lies below $\ln(0.35)/\ln(0.5) = 1.515$, i.e., the critical hazard ratio under the chosen non-inferiority scenario.

Since differences between the two survival curves might appear mainly at the beginning of follow-up (which would be in contradiction to the proportional hazard assumption), we will also consider the area between survival curves equalling the difference in average event-free survival time during follow-up between the two arms.

Results

Recruitment started in March 2006. So far, 211 patients have been randomised, and a total of 127 have completed the 180 days follow-up. Their mean (\pm SD) age was 70 \pm 11 years. Patients had smoked 50 \pm 23 (mean \pm SD) pack-years. 58% of the study subjects had very severe (GOLD stage IV) and 30% had severe (GOLD stage III) COPD; the remainder (12%) had mild or moderate airway obstruction (GOLD stage I and II, respectively). 20% of patients had received systemic glucocorticoids before entering the study, either for the index exacerbation or as part of their chronic COPD therapy.

The data safety and monitoring board carried out a pre-planned interim safety analysis after about 50% of the originally planned number of patients had completed the study. Based on the results of this analysis, the board recommended continuation of the trial without safety concerns.

Discussion

A 10 to 14 day course of systemic corticosteroids in patients with acute COPD exacerbations is an evidence-based treatment recommendation and has become common clinical practice. Systemic glucocorticoids improve lung function, reduce hospital stay, and decrease treatment failure. However, randomised clinical trials addressing the use of systemic glucocorticoids are relatively sparse and heterogeneous in their designs and settings [7, 10]. Notably, the optimal dose and duration of treatment remains unknown. The benefits of glucocorticoids on recovery of lung function appear to level off after 3 to 5 days [15, 16] and are compromised by complications, notably a higher rate of hyperglycaemia requiring treatment, osteoporotic bone disease, muscle catabolism, and suppression of the endogenous cortisol production. Most importantly, prolonged use of glucocorticoids raises mortality in patients with COPD [18]. This therapeutic dilemma prompted the initiation of the present multicentre trial aiming to demonstrate non-inferiority of a short course of systemic glucocorticoids as compared to a standard course, thereby significantly redu-

cing steroid exposure. Some considerations made during the planning phase of this trial warrant additional comment.

Previous studies examined the effects of systemic corticosteroids in acute exacerbations of COPD and used spirometric improvement (FEV₁) as a main outcome parameter [11, 12, 16]. However, FEV₁ is not closely associated with the perception of dyspnoea or with exercise limitation [33] and is therefore of limited patient relevance. In the SCCOPE study [15], treatment failure rates in the placebo and glucocorticoid groups were identical after 6 months of follow-up, and the primary outcome of treatment failure was defined as a composite of multiple clinical events of varying significance. We therefore decided to use “time to next exacerbation” as our primary endpoint and assess other clinical data, including FEV₁, as secondary endpoints.

In our trial, the cumulative prednisone dose in the standard arm will be 560 mg. The cumulative dose used in the largest available study for hospitalised patients (the SCCOPE study [15]) amounts to ~2000 mg prednisone-equivalent in the short (2 weeks) and ~2600 mg in the long (8 week) treatment arm. We did not see a rationale to use such high dosage in our trial other than the attempt to rigorously copy the study design used in that trial. Thus, we decided to use a more practical and ethically more justifiable dose, although this will result in a treatment difference in the standard arm as compared to the SCCOPE study.

Apart from the intervention, we decided to rigorously standardise COPD medication, particularly inhaled steroids and bronchodilators, and the use of antibiotics during the initial treatment phase. At the time our study was designed, the fixed combined use of long-acting beta agonists, inhaled steroids, and tiotropium was beyond generally accepted treatment recommendations. However, we wanted to minimise any treatment bias that might have led to falsification of the effects of systemic glucocorticoids. After our study had been initiated, the TORCH trial was published showing that, compared to placebo, inhaled long-acting beta-agonists combined with inhaled glucocorticoids reduce exacerbation rate, improve health status, and preserve lung function [34]. Similarly, in the UPLIFT study, tiotropium was shown to improve lung function and quality of life as well as reduce COPD exacerbations [35]. These results are reassuring in view of the treatment plan chosen in our study protocol. As for antimicrobial therapy, broad spectrum antibiotics have been shown to improve clinical outcome and, in hospitalised patients, reduce mortality [36].

Three previous trials conducted at the University Hospital Basel advocate procalcitonin-guided antibiotic treatment in patients with lower respiratory tract infections and exacerbated COPD [28, 29, 37]. The introduction of a procalcitonin-based treatment algorithm would have complicated our study protocol substantially. Also, published guidelines recommend antibiotic use in patients with altered sputum characteristics [2, 8], but there is a large scope for discretion as to the choice of the antibiotic and the duration of treatment [7, 36]. In the present study, an unbalanced distribution of antibiotic use in the two treatment arms has to be avoided, especially as physicians are likely to prescribe antibiotics more frequently in patients with slow improvement, which could be the case in the

short treatment arm. Thus, antibiotic treatment bias could compromise our non-inferiority design and obscure the true treatment effects from systemic corticosteroids.

We were confronted with doubts whether in the emergency room setting, the execution of an ACTH test prior to the initiation of glucocorticoid therapy is feasible. However, in a smaller trial studying the HPA axis in nine patients with exacerbated COPD, we were able to demonstrate the feasibility of this approach [38]. The low-dose (1 µg) ACTH test measures plasma cortisol at baseline and 30 min. after stimulation, omitting the value 60 min. after stimulation, which is usually measured in the conventional (250 µg) ACTH test. Thus, the low-dose ACTH test does not cause a relevant delay in treatment.

In conclusion, the REDUCE study aims to clarify whether a 5-day course of systemic glucocorticoid therapy is non-inferior to a 14-day course for COPD patients with an acute exacerbation. The trial will add significant evidence regarding the treatment of exacerbated COPD with systemic glucocorticoids. Furthermore, the study addresses other important therapeutic issues, such as the practice of glucocorticoid withdrawal and adverse effects of systemic glucocorticoids.

Funding / potential competing interests

Department of Internal Medicine, University Hospital Basel, Switzerland; Clinic of Internal Medicine, Biel-Bienne, Switzerland; Freie Akademische Gesellschaft Basel, Switzerland; Fonds für Lehre und Forschung, Basel, Switzerland; Astra-Zeneca (Switzerland); Viollier Laboratories, Allschwil, Switzerland; Gottfried und Julia Bangerter-Rhyner-Stiftung, Switzerland. None of the sponsors had a role in the development of the trial design, in the analysis of the results, or in the writing of this report.

References

- 1 Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med.* 2001;163(5):1256–76.
- 2 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (updated 2009). Available from www.goldcopd.com.
- 3 Leuppi JD, Miedinger D, Chhajed PN, Buess C, Schafroth S, Bucher HC, et al. Quality of Spirometry in Primary Care for Case Finding of Airway Obstruction in Smokers. *Respiration.* 2010;79(6):469–74.
- 4 Russi EW, Leuenberger P, Brändli 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.
- 5 McCrory DC, Brown C, Gelfand SE, Bach PB. Management of acute exacerbations of COPD: a summary and appraisal of published evidence. *Chest.* 2001;119(4):1190–209.
- 6 Snow V, Lascher S, Mottur-Pilson C. Evidence Base for Management of Acute Exacerbations of Chronic Pulmonary Disease. *Ann Intern Med.* 2001;134:595–9.

- 7 Bach PB, Brown C, Gelfand SE, McCrory DC. Management of acute exacerbations of chronic obstructive pulmonary disease: a summary and appraisal of published evidence. *Ann Intern Med.* 2001;134(7):600–20.
- 8 Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J.* 2004;23(6):932–46.
- 9 Wouters EF. Management of severe COPD. *Lancet.* 2004;364(9437):883–95.
- 10 Wood-Baker RR, Gibson PG, Hannay M, Walters EH, Walters JA. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2005;(1):CD001288.
- 11 Albert RK, Martin TR, Lewis SW. Controlled clinical trial of methylprednisolone in patients with chronic bronchitis and acute respiratory insufficiency. *Ann Intern Med.* 1980;92(6):753–8.
- 12 Emerman CL, Connors AF, Lukens TW, May ME, Effron D. A randomized controlled trial of methylprednisolone in the emergency treatment of acute exacerbations of COPD. *Chest.* 1989;95(3):563–7.
- 13 Bullard MJ, Liaw SJ, Tsai YH, Min HP. Early corticosteroid use in acute exacerbations of chronic airflow obstruction. *Am J Emerg Med.* 1996;14(2):139–43.
- 14 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.
- 15 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.
- 16 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.
- 17 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.
- 18 Groenewegen KH, Schols AM, Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. *Chest.* 2003;124(2):459–67.
- 19 Walsh LJ, Lewis SA, Wong CA, Cooper S, Osborne J, Cawte SA, et al. The impact of oral corticosteroid use on bone mineral density and vertebral fracture. *Am J Respir Crit Care Med.* 2002;166(5):691–5.
- 20 Jagoe RT, Engelen MP. Muscle wasting and changes in muscle protein metabolism in chronic obstructive pulmonary disease. *Eur Respir J Suppl.* 2003;46:52s–63s.
- 21 Decramer M, Lacquet LM, Fagard R, Rogiers P. Corticosteroids contribute to muscle weakness in chronic airflow obstruction. *Am J Respir Crit Care Med.* 1994;150(1):11–6.
- 22 Henzen C, Suter A, Lerch E, Urbinelli R, Schorno XH, Briner VA. Suppression and recovery of adrenal response after short-term, high-dose glucocorticoid treatment. *Lancet.* 2000;355(9203):542–5.
- 23 Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. *Chest.* 2000;117(5 Suppl 2):398S–401S.
- 24 Surveillance for respiratory hazards in the occupational setting [American Thoracic Society]. *Am Rev Respir Dis.* 1982;126(5):952–6.
- 25 Evans AT, Husain S, Durairaj L, Sadowski LS, Charles-Damte M, Wang Y. Azithromycin for acute bronchitis: a randomised, double-blind, controlled trial. *Lancet.* 2002;359(9318):1648–54.
- 26 Arlt W, Rosenthal C, Hahner S, Allolio B. Quality of glucocorticoid replacement in adrenal insufficiency: clinical assessment vs. timed serum cortisol measurements. *Clin Endocrinol (Oxf).* 2006;64(4):384–9.
- 27 Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med.* 1987;106(2):196–204.
- 28 Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet.* 2004;363(9409):600–7.
- 29 Stolz D, Christ-Crain M, Bingisser R, Leuppi J, Miedinger D, Müller 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.
- 30 Lachin JM, Foulkes MA. Evaluation of sample size and power for analyses of survival with allowance for nonuniform patient entry, losses to follow-up, noncompliance, and stratification. *Biometrics.* 1986;42(3):507–19.
- 31 Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: the importance of rigorous methods. *BMJ.* 1996;313(7048):36–9.
- 32 Pocock SJ. The pros and cons of noninferiority trials. *Fundam Clin Pharmacol.* 2003;17(4):483–90.
- 33 Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax.* 1999;54(7):581–6.
- 34 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.
- 35 Tashkin DP, Celli B, Senn S, Burkhardt 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.
- 36 Quon B, Gan W, Sin D. Contemporary Management of Acute Exacerbations of COPD: A Systematic Review and Metaanalysis. *Chest.* 2008;133(3):756–66.
- 37 Schuetz P, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I, et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA.* 2009;302(10):1059–66.
- 38 Schuetz P, Christ-Crain M, Schild U, Süess E, Facompre M, Baty F, et al. Effect of a 14-day course of systemic corticosteroids on the hypothalamic-pituitary-adrenal-axis in patients with acute exacerbation of chronic obstructive pulmonary disease. *BMC Pulm Med.* 2008;8(1):1–8.