Corticosteroid Therapy for Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease

A Systematic Review

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Objective: To determine whether systemic corticosteroids are of benefit to patients with acute exacerbations of chronic obstructive pulmonary disease (COPD).

Methods: An English-language search of MEDLINE (1966 to February 2002) and the Cochrane Library and a bibliographic review was performed to identify published clinical trials of systemic corticosteroid administration in acute exacerbations of COPD. All relevant English-language, randomized, placebo-controlled clinical trials were considered. Trials investigating the adverse effects of systemic steroids were also retrieved. Studies were assigned a quality rating according to explicit criteria. Clinically relevant end points, such as treatment failure and duration of hospital stay, were considered preferentially. To compare outcomes across all qualifying studies, we considered the difference in spirometric measures between treatment and placebo groups. Potential confounding factors and bias relating to patient selection, treatment protocols, and outcome measurement were considered independently for each study.

Results: Among the 8 studies that met all criteria, 5 found that significant improvement in forced expiratory volume in 1 second (FEV₁) (>20%) was associated with steroid administration. Two studies found improvement in clinically relevant outcomes. One published study and 2 study abstracts did not find significant improvement in spirometric measures with corticosteroid administration.

Conclusion: Short courses of systemic corticosteroids in acute exacerbations of COPD have been shown to improve spirometric outcomes (good-quality evidence) and clinical outcomes (good-quality evidence).

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CHRONIC OBSTRUCTIVE pulmonary disease (COPD) is a heterogeneous group of diseases characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. Pathologic changes in COPD are heterogeneous and affect the airways, lung parenchyma, and pulmonary vasculature. Internal airway diameter in COPD is reduced as a consequence of structural airway remodeling, chronic inflammation, and hyperplasia of mucous-secreting cells. Destruction of lung parenchyma is most often observed in the form of centrilobular emphysema, in which the walls of the air spaces distal to the terminal bronchioles are destroyed without obvious fibrosis. The clinical picture and symptoms experienced by patients is variable and not perfectly related to the measured airflow obstruction. The management of COPD is largely symptom driven, thus a staging scheme based on clinical symptoms as well as physiologic pulmonary function measurements has been suggested.

It has been estimated that 16 million Americans have chronic bronchitis, emphysema, or both. The prevalence of smoking, the major risk factor for COPD, has decreased little in the last decade. The relative prevalence of smoking among younger individuals, particularly women, suggests that COPD will remain a common disorder in the future among both sexes. Whereas other major causes of death have seen declines in their respective mortality rates, COPD mortality has increased 67% since 1980, causing 124,181 deaths in the United States in 1997.

The clinical course of COPD is that of chronic, stable airway obstruction punctuated by acute episodes of worsening respiratory function or “exacerbations,” manifesting clinically by an increase in cough, a change in quantity or color of sputum, and/or worsening dyspnea. One community-based study found that patients with COPD experienced an average of 1.3...
(range, 0.9-6) exacerbations per year, most often associated with upper respiratory tract infections.7 Exacerbations are significant events in the long-term management of COPD. Most exacerbations are managed in the ambulatory setting, but patients who require inpatient care have hospitalizations averaging 8 to 9 days and have a mean in-hospital mortality of approximately 6%.8 One study found the median cost of hospitalization for an acute exacerbation of COPD to be US $7100.9 Relapse of exacerbations is common, and 17% of patients discharged following emergency department treatment of their COPD exacerbation have recurrent symptoms requiring hospitalization within 14 days.10 Historically, treatment approaches to COPD have mirrored the treatment of asthma. Patients with stable COPD have minimal corticosteroid responsiveness compared with patients with asthma, and physiological evidence for systemic steroid administration for COPD is weaker. Despite this, up to 80% of patients with COPD who require treatment for acute respiratory failure receive parenteral corticosteroids,11 and their administration has been endorsed in major guideline statements.1

Systemic steroid administration is associated with important adverse effects.12,13 Until recently, the use of short-course systemic steroids for COPD exacerbations has been poorly studied. The recent publication of several guideline statements has helped to unify the diagnostic criteria and management strategy for patients with COPD.1,14 The publication of clinical studies evaluating the role of systemic corticosteroids in the management of acute exacerbations of COPD has made this topic suitable for review. Our objective was to review the literature systematically to determine whether corticosteroids are of demonstrable benefit to patients with acute exacerbations of COPD.

### METHODS

#### DATA SOURCES

A literature search using the MEDLINE database was carried out to identify relevant English-language publications between 1966 and February 2002. This search included the Medical Subject Headings (MeSH) terms steroids, obstructive lung disease, respiratory insufficiency and the text word exacerbation. Retrieved publications were limited to English-language, human studies, and clinical trials. Publications pertaining to obstructive lung diseases that included the subject heading asthma were excluded. Bibliographies of retrieved publications were reviewed to identify sources not obtained in our search. Publications in abstract form were included to minimize publication bias.

#### QUALITY ASSESSMENT

The Cochrane Library was searched with the headings obstructive lung disease, respiratory insufficiency, and exacerbation.

The adverse effects of systemic steroid therapy were then reviewed separately through a limited search to identify clinical trials and review articles that were indexed with the MEDLINE keywords steroids—adverse effects and obstructive lung disease. These trials were limited to English-language and human studies.

#### STUDY SELECTION

Studies were included for review if they were published, placebo-controlled, randomized control trials investigating the administration of systemic corticosteroids to patients with COPD exacerbations. Owing to the historical lack of unifying diagnostic criteria for both COPD and acute exacerbation, the diagnostic criteria for these conditions were not considered in study selection, but were instead reviewed and considered in the quality assessment. Publications describing adverse effects of steroid administration, regardless of design, were included in the adverse effect section of the review. As most adverse effects of corticosteroids are not disease specific, with the exception of those in the setting of immunosuppression, populations other than those with COPD who were not immunosuppressed were also included.

#### DATA EXTRACTION AND QUALITY ASSESSMENT

Chronic obstructive pulmonary disease study characteristics and results were extracted and independently verified by two of us (J.M.S. and V.A.P.). The study criteria retrieved were those affecting trial quality as well as factors specific to COPD that might have an important effect on results. Generic criteria were (1) an adequate randomization resulting in assembly of comparable groups; (2) maintenance of comparable groups by attention to attrition, crossover, compliance, and contamination; (3) clinically important loss to follow-up; (4) clear definition of interventions; (5) important outcomes were assessed (in a blinded fashion); (6) measurement methods used were equal, reliable, and valid; and (7) analysis used was intention to treat. Instead of a score, a broader quality rating of “good,” “fair,” or “poor,” based on the methodology of the US Preventive Services Task Force, was assigned as outlined in Table 1.15 All studies were randomized controlled trials and as such were graded level I or IIa evidence.

### Table 1. Criteria for Assigning Levels of Quality to Randomized Trials

<table>
<thead>
<tr>
<th>Studies Are Graded “Good” Only If All of the Following Are Met</th>
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<tbody>
<tr>
<td>Comparable groups assembled initially and maintained throughout the study</td>
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<tr>
<td>Follow-up at least 80%</td>
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<td>Interventions are defined clearly</td>
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<tr>
<td>All important outcomes are considered, and outcome assessment is blinded</td>
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<tr>
<td>Reliable and valid measurement instruments are used and applied equally to the groups</td>
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<tr>
<td>Appropriate attention to confounders in analysis</td>
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<tr>
<td>Intention to treat is used</td>
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<tr>
<th>Studies Are Graded Fair If Any of the Following Problems Occur, Without the Fatal Flaws Listed in the “Poor” Category</th>
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<tbody>
<tr>
<td>Generally comparable groups or some minor problems with follow-up</td>
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<tr>
<td>Some but not all important outcomes are considered</td>
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<tr>
<td>Measurement instruments acceptable, although not ideal, and generally applied equally</td>
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<tr>
<td>Some but not all important confounders are accounted for</td>
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<tr>
<th>Studies Are Graded Poor If Any of the Following Fatal Flaws Exist</th>
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<tr>
<td>Groups assembled are not comparable either initially or throughout study</td>
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<tr>
<td>Unreliable or invalid measurements are used or are not applied equally</td>
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<tr>
<td>Lack of blinding to outcome assessment</td>
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<tr>
<td>Key confounders are not addressed</td>
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<tr>
<td>Intention-to-treat analysis is lacking</td>
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<td>Inadequate power of study to detect equivalence</td>
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Some COPD-specific factors were also evaluated. Under the category of comparability of groups, all studies were evaluated for possible sources of contamination including the reported administration of open-label steroids and the use of high-dose inhaled corticosteroids. Under the category of outcome assessment methods, trials were required to have an adequate observation period to allow for steroid effect to occur. Physiological studies have demonstrated that the intracellular effects of steroids may not be apparent for up to 72 hours and subsequently, patients should be observed for at least 72 hours to ensure the detection of any potential effect of steroid administration. In addition, clinical outcomes were given greater weight than spirometric outcomes. For example, a study assessing clinical outcomes and forced expiratory volume in 1 second (FEV1) would meet the good rating for this category, but a study assessing only FEV1 would meet the fair rating. A study only assessing clinical outcomes would still meet the good rating for this category. Clinically relevant outcome measures were defined as any outcome variables that were directly relevant to the clinical status of the patient. Such variables included mortality, hospitalization rates, length of hospital stay, relapse rates and failure of medical treatment as defined by admission to the intensive care unit, intubation, or intensification of treatment with open-label steroids. Finally, statistical power was not included in the category list but has historically been a major problem in negative studies evaluating systemic steroid administration in COPD. Consequently, the lack of adequate power to detect equivalency of treatment between groups was considered a “fatal flaw” and resulted in a poor rating.

In the consideration of adverse effects, any numerical information related to steroid use was extracted. No specific quality assessment was conducted of studies evaluating adverse effects.

DATA SYNTHESIS AND VALUES

Weighted numerical combination of the results of individual trials was not considered owing to the wide variations in trial quality. Conclusions for the effectiveness of steroid use in COPD exacerbations were thus based on the strength of evidence, in which good was considered stronger evidence than fair, which in turn was considered stronger evidence than poor-quality studies. Given the potential deleterious effects of steroid administration and that patient safety is a priority, we regarded evidence of a lower quality to be relevant when considering adverse effect of steroid administration.

RESULTS

Twenty-six publications fulfilling the search criteria were retrieved from a search of the available databases. Review of the bibliographies of collected publications yielded 2 abstracts of clinical trials that were not subsequently published.10,17 The search of the Cochrane Collaboration Database of Systematic Reviews yielded 1 meta-analysis, which analyzed 7 published studies of systemic steroid administration in COPD exacerbations.18 This meta-analysis was not included in the data extraction of this systematic review, but was reviewed because it also contained some unpublished data obtained from the authors of 3 published trials. Twenty of these publications were not directly relevant to the study and were discarded for the following reasons: 8 trials addressed inhaled steroid preparations in COPD19-26; 4 considered patients with stable COPD27-30; 4 were not placebo-controlled trials31-34; 1 described a study design and presented no clinical data35; 1 presented data from a sub-study of an included published trial36; and 2 were not relevant trials of respiratory disease.37,38 The 8 remaining double-blind, randomized, placebo-controlled trials studied either intravenous or oral corticosteroid administration in patients with acute COPD exacerbations. The details of these studies are outlined in Table 2. All but 2 studies excluded patients with evidence of airway hyperreactivity.17,39 Three studies measured a clinical primary end point (treatment failure and/or duration of hospital stay), while all studies evaluated changes in spirometry. A summary of the quality assessment criteria used in grading study quality is given in Table 3 and Table 4.

EFFECTIVENESS OF STEROIDS AT REDUCING COPD EXACERBATION SYMPTOMS AND SEVERITY

Spirometric Measures

The most commonly studied outcomes were spirometric indexes, particularly FEV1. Despite its widespread use as a surrogate marker of clinical outcomes, there is little evidence correlating acute improvement in FEV1 to clinical improvement.

The best evidence for changes in spirometric measures with steroid administration comes from the study by Niewoehner et al.40 In this large study, steroid-treated patients had a more rapid rate of improvement in FEV1 compared with patients receiving placebo. The maximal difference in FEV1, equivalent to 0.120 L, was evident on the first day of observation, and a significant difference persisted through 3 days of observation. After 2 weeks, there was no difference in FEV1 between those patients who had received steroids and those who had received placebo. Although FEV1 was studied as a secondary end point, several factors make this the most robust data for the effect of steroids on spirometric outcomes. This study,40 which met the criteria for a good quality study, was the largest of the selected trials (n = 271) and was designed as an equivalence study to compare the administration of steroids with placebo in hospitalized patients with severe airway obstruction. As such, patients received aggressive, standardized treatment with bronchodilators, antibiotics, and inhaled steroids and were randomized to 1 of 3 arms (placebo or a 2-week or 8-week course of relatively high-dose intravenous and oral steroids). The results were analyzed according to intention to treat. The aggressive administration of the interventions, including inhaled corticosteroids, would serve to obscure the effects of systemic steroid administration, thus the observed effect likely represents a true benefit.

Davies and colleagues41 published a good-quality study that reported benefit from a nontapered course of low-dose oral steroids for COPD exacerbations. The rate of change in postbronchodilator FEV1 in patients receiving corticosteroids was 3 times that of patients receiving placebo (90 vs 30 mL/d). Maximum improvement in FEV1 was also seen by day 5 in the steroid-treated patients, significantly earlier than in the placebo arm, but these benefits did not last beyond the immediate hospitalization. Throughout this study, more patients dropped out of placebo arm,
and as a group, the withdrawn patients had more severe airway obstruction on admission. The analysis of spirometric data according to protocol may have underestimated the treatment effect of corticosteroids; while the sickest patients dropped out more often from the placebo arm, the observed rate of recovery in the remaining patients would increase, thus improving the spirometric outcomes in the placebo group.

Thompson et al42 addressed the role of oral steroids in the outpa-
tient management of COPD exacerbations. The study population included preenrolled patients with known stable COPD who reported an exacerbation to the investigators for randomization into 1 of 2 treatment arms. Patients receiving steroids had a faster recovery of FEV₁ during treatment and had a greater FEV₁ at the end of the 10-day observation period. This was the only study to address moderate as opposed to severe airflow obstruction, with the pretreatment FEV₁ being 1.3 L.

In a fair-quality study, Albert et al.⁴³ compared intravenous steroids and placebo in patients with chronic bronchitis hospitalized for acute respiratory insufficiency and severe airway obstruction (FEV₁ < 700 mL). Patients were monitored with spirometry for just 3 days during which the steroid-treated patients had significantly greater improvement in FEV₁. Increases in FEV₁ greater than 40% were more often observed when patients received steroids, suggesting that patients with airway hyperreactivity may have been included.

The remaining 3 trials measuring spirometric outcomes received poor quality ratings. Bullard et al.³⁹ found a beneficial effect of steroids. Patients presenting to the emergency department with exacerbations of suspected chronic airflow obstruction were randomized to receive intravenous and oral

Table 4. Quality Criteria for Randomized Controlled Trials of Systemic Steroid Administration in COPD Exacerbations*

<table>
<thead>
<tr>
<th>Source</th>
<th>Confounding Factors</th>
<th>Contamination</th>
<th>Power</th>
<th>Analysis Carried Out by Intention to Treat</th>
<th>Adequate Follow-up (&gt;80%)</th>
</tr>
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<tbody>
<tr>
<td>Niewoehner et al.⁴⁰ 1999</td>
<td>Standardized β₂-agonist, anticholinergic agent inhaled steroids. Theophylline, high-dose inhaled steroids, or open-label systemic steroid not allowed. Compliance confirmed by pill check (&gt;85%).</td>
<td>Open-label steroids administered as “intensification of therapy” in 72% of cases</td>
<td>85% to detect difference of 7.5% in treatment failure rates</td>
<td>All analyses were intention-to-treat; 2- and 8-wk groups combined because equivalent outcomes</td>
<td>Yes</td>
</tr>
<tr>
<td>Davies et al.⁴¹ 1999</td>
<td>Open-label inhaled steroids. Antibiotics at discretion of admitting physician. Standardized bronchodilatation with β₂-agonist and anticholinergic agent.</td>
<td>Withdrawn patients were offered open-label steroids</td>
<td>80% to detect 0.05 L/d in improvement in mean FEV₁ slope between groups</td>
<td>Length of stay analyzed by intention-to-treat; spirometric data analyzed according to protocol</td>
<td>Yes; 6 of 56 patients were withdrawn; withdrawn patients had worse baseline spirometry</td>
</tr>
<tr>
<td>Thompson et al.⁴² 1996</td>
<td>Standardized β₂-agonist administration. Nonstandardized use of ipratropium, inhaled corticosteroid, and theophylline. Antibiotics indicated if sputum microscopy positive. More patients in placebo group took triamcinolone.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Yes; 1 patient failed to complete study</td>
</tr>
<tr>
<td>Albert et al.⁴³ 1980</td>
<td>Standardized treatment with aminophylline, isoproterenol, antibiotics, and oxygen.</td>
<td>NA</td>
<td>80% to detect difference of 25% in spirometry (FEV₁)</td>
<td>NA</td>
<td>Yes; 4 patients failed to complete study</td>
</tr>
<tr>
<td>Bullard et al.³⁹ 1996</td>
<td>Standardized treatment with fenoterol, ipratropium bromide, and aminophylline.</td>
<td>Open-label hydrocortisone (100 mg every 4 h, at discretion of physician)</td>
<td>NA</td>
<td>NA</td>
<td>Yes (only for emergency department data); 7 patients failed to complete study</td>
</tr>
<tr>
<td>Rostom et al.⁴⁶ 1994</td>
<td>Oxygen, β₂-agonists, theophylline, and antibiotics</td>
<td>NA</td>
<td>Not noted; likely underpowered to detect a difference in primary outcome measure (N = 24)</td>
<td>NA</td>
<td>No; 6 patients failed to complete study</td>
</tr>
<tr>
<td>Wood-Baker et al.³⁷ 1998</td>
<td>Oxygen, bronchodilators, and antibiotics</td>
<td>NA</td>
<td>Not noted; likely underpowered to detect a difference in primary outcome measure (N = 27)</td>
<td>NA</td>
<td>No; 20 of 47 patients were withdrawn</td>
</tr>
<tr>
<td>Emerman et al.⁴⁴ 1989</td>
<td>Isoetharine, oxygen, aminophylline. No antibiotics.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Yes; 4 patients failed to complete the study</td>
</tr>
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</table>

*COPD indicates chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; and NA, not applicable.
corticosteroid or matching placebo. This study did not exclude patients with asthma. At 6 hours, patients treated with systemic corticosteroids benefited from significant improvements in spirometric indexes compared with patients receiving placebo. Unfortunately, follow-up of patients admitted to the hospital was confounded by breaks in protocol, thus clinically relevant end points such as length of stay and readmission were not considered in the published analysis. As was found in the study by Albert et al, more of the patients receiving steroids exhibited increases in FEV₁ greater than 40%.

Three studies did not find a beneficial effect of steroids. Emerman et al evaluated the role of parenteral steroid administration in the emergency department and found no significant difference in spirometry between the steroid and placebo groups. This study was sufficiently powered to detect as little as a 7% difference between the 2 groups, but the mean observation time was short (4.5 hours), which may not have been sufficiently long to detect a beneficial effect of corticosteroids. The randomized, double-blind, placebo-controlled trial by Rostom et al, evaluating methylprednisolone administration to inpatients with acute COPD exacerbations, failed to show any difference in spirometric outcomes compared with placebo. The study was small and lacked sufficient power to detect small differences in FEV₁ between groups. Wood-Baker et al compared 2 regimens of steroid administration with placebo and found no significant difference in spirometric indexes. Unfortunately, the study had an excessive number of withdrawals due to protocol violations and treatment failure, limiting the number of patients completing the 2-week follow-up period. Consequently, this study was likely underpowered to detect a significant difference in spirometric outcomes.

**Health Care Measures**

Several studies measured clinically relevant outcomes and measures of health care consumption. Measures such as augmentation of therapy, length of hospitalization, and relapse rate are discussed in the following sections.

**Treatment Failure/Relapse.** The primary outcome measure in the trial by Niewoehner et al was treatment failure, defined explicitly as death, intubation, augmentation of the therapeutic regimen, or return for medical care after discharge. Compared with the placebo group, steroid-treated patients had a significant decrease in the rate of treatment failure (37% vs 48%). The most common manifestation of treatment failure was intensification of therapy, which included open-label systemic steroids in over three quarters of cases. The duration of treatment (2 vs 8 weeks) had no significant effect on treatment failure, and the benefit of steroids in reducing the rate of treatment failure was not evident at 6 months. Thompson et al found that over half of the placebo-treated patients required admission and received open-label steroids, while no outpatient treatment failures occurred in the steroid group.

**Length of Hospitalization.** In the study by Niewoehner and colleagues, the steroid arm had a small decrease in the length of hospital stay (8.5 days vs 9.7 days). Davies et al found that patients receiving steroids also benefited from significantly shorter hospital stays (7 vs 9 days), but there were no differences between the 2 treatment arms at 6 weeks with respect to subsequent exacerbations, readmission, or treatment augmentation. The length of stay data was analyzed according to intention to treat. Wood-Baker et al found that there was no difference in hospital stay between patients receiving placebo and 2 regimens of steroid, but this study likely had insufficient power to detect a difference in this outcome. In a post hoc analysis, Niewoehner et al found that the steroid-treated patients spent more days in hospital over a 6-month period, but this difference was not significant (14.8 vs 12.9; P = .80). It was suggested that this difference might have been in part due to an excessive number of severe infections, particularly pneumonia, in the 8-week steroid group.

**REGIMEN OF SYSTEMIC CORTICOSTEROID ADMINISTRATION**

The optimal dose of steroid and duration of treatment for COPD exacerbations remains unknown. The wide range of studied doses and regimens has included 100 mg of hydrocortisone as well as 125 mg of intravenous methylprednisolone. One regimen of 30 mg of prednisolone daily showed similar benefit to a more aggressive, higher-dose steroid regimen. Niewoehner et al found no advantage to 8 weeks of oral prednisone therapy compared with 2 weeks, and the rates of serious infection may have been higher in those patients receiving 8 weeks of steroid treatment. Two other studies showed that most of the treatment effects were seen within 5 days, with little subsequent additional benefit. A recent study of 34 patients admitted with COPD exacerbations demonstrated that patients treated with a 10-day course of systemic steroids had greater improvements in FEV₁, forced vital capacity, and oxygenation compared with patients receiving only a 3-day course of steroid, although there was no difference in relapse rate at 6 months. The steroid burden placed on patients with obstructive lung disease is substantial, and determination of the shortest course that provides adequate benefit would favorably reduce a patient’s total steroid exposure.

No published studies comparing parenteral corticosteroids with oral steroids in the treatment of COPD exacerbations were found. Oral steroids are generally well absorbed and are less expensive. When parenteral and oral steroids have been compared in the management of acute asthma in pediatric patients, it has not been possible to show an advantage to parenteral administration.

**RISKS OF THERAPY**

The adverse effects of systemic corticosteroids can be categorized as reversible and nonreversible. Reversible effects include diabetes mellitus, hypertension, truncal obesity, skin changes, psychological...
disturbance, osteoporosis, hypokalemia, and metabolic alkalosis. Severe reactions such as steroid-induced myopathy and avascular necrosis are thought to be related to high-dose, long-term steroid courses.

**Effects on the Musculoskeletal System**

Systemic steroid administration is a well-established risk for osteoporosis. Patients with COPD may also be at increased risk of osteoporosis owing to their smoking history and the decreased physical activity associated with severe COPD. Because of this baseline risk, the long-term effects of systemic steroid administration to patients with COPD warrant analysis with disease-matched controls, but to our knowledge, there are no such prospective studies. Patients with COPD are more likely to have decreased lumbar spine bone mineral density, decreased markers of new bone formation, and evidence of vertebral spine fractures, and those patients receiving treatment with corticosteroids have lower bone mineral density, and higher fracture rates compared with age- and sex-matched controls.

Compared with trials evaluating adverse effects of steroids in other disease states, the cumulative steroid exposure of patients treated for COPD exacerbations is relatively low, and the mean age of the patient population is usually significantly higher. It appears that the risk of musculoskeletal adverse events is dose dependent; a cross-sectional study found that the increased evidence of vertebral fractures in older men with COPD was related to long-term use of relatively high doses of prednisone (18 mg/d). Intermittent use of systemic steroids (average cumulative dose of 2.8 g) was not associated with a statistically significant increase in risk compared with those who had never received steroids. This finding has also been observed in another case-control study.

Although it is not appropriate to directly extrapolate data from other disease states, there is good-quality evidence suggesting that bone mineral density is adversely affected by long courses of systemic steroids. Prospective evaluation of patients with active rheumatoid arthritis demonstrated decreased trabecular bone mineral density in patients who were treated with low-dose prednisone (≤ 10 mg/d) for 20 weeks. However, the clinical implication of decreases in trabecular bone was not measured. A meta-analysis of trials studying systemic corticosteroid administration in the treatment of various medical disorders found that osteoporosis was diagnosed more frequently in those patients who received corticosteroids.

Pietrogrande and Mastromarino first made the association between nontraumatic osteonecrosis and corticosteroid therapy in 1957. Avascular necrosis of the femoral head is accepted as an adverse effect of long-term steroid therapy and has also been reported after shorter courses of steroids.

There are study design factors that may lead to either an underestimation or overestimation of steroid effect. These stem from both the definition and identification of the disease as well as the quality and validity of outcome measurements in clinical trials.

**Glucose Intolerance**

Glucose intolerance is a common adverse effect of systemic steroid administration. Several retrospective studies that included populations of patients with COPD have documented an increased rate of glucose intolerance and diabetes in patients receiving long-term treatment with systemic corticosteroids. Three of the trials reviewed herein prospectively looked for adverse effects of steroids. All found that the development of hyperglycemia or glycosuria was more common in patients who received systemic corticosteroids and was the only adverse effect that could be clearly attributed to steroid administration.

**Infection**

There is evidence to suggest that patients who receive systemic steroids are at increased risk of infection. One meta-analysis found that patients receiving corticosteroid treatment were at increased risk of lethal and nonlethal infections. This association was dose dependent, although there was no increase in risk observed with either cumulative doses of prednisone less than 700 mg or daily doses of prednisone less than 10 mg. In a post hoc analysis, Niewoehner et al observed a higher incidence of serious infections such as pneumonia in the patients receiving an 8-week course of systemic steroids compared with those receiving only a 2-week course of steroids or placebo. This increased rate did not reach statistical significance.

**Comment**

There are study design factors that may lead to either an underestimation or overestimation of steroid effect. These stem from both the definition and identification of the disease as well as the quality and validity of outcome measurements in clinical trials.

**Problems in Diagnosis**

Despite the publication of recent guideline statements, difficulties in the precise diagnosis of COPD have confounded the evaluation of steroid administration in COPD exacerbations. The diagnosis of COPD and its differentiation from asthma is based on the finding of minimally reversible airflow obstruction. The gold standard for diagnosis is thus an objective measure of lung function, such as spirometry. In the absence of spirometry, the diagnosis is usually based on historical and physical findings—a practice that is fraught with bias. Inclusion criteria among the reviewed studies varied considerably in both historical and spirometric criteria: one study included patients 50 years and older with a minimum 30-pack-year history of smoking and a baseline FEV1 of 1.5 L or less. Another study permitted the recruitment of individuals as young as 40 years with smoking histories as low as 20 pack-years and an FEV1 as high as 70% of the predicted normal value.

Presumptive diagnosis of COPD by physicians may underestimate the prevalence of asthma in the study.
population. Benefit from steroid administration in asthma is well documented, and the inclusion of patients with asthma in COPD studies will overestimate steroid benefit. Most studies excluded patients with a history of asthma, one excluded patients with significant reversibility of airflow obstruction on spirometry, and one excluded patients with positive skin prick tests. Despite this, it is possible that some of the patients studied had either asthma or a combination of asthma and COPD. Despite concerns with respect to diagnostic accuracy, the overall implication of the reported trials remains valid: patients who present to their physicians with symptoms of a COPD exacerbation are likely to benefit immediately from systemic corticosteroid therapy regardless of whether their true diagnosis is COPD or asthma. However, the management algorithms for these 2 disorders differ substantially, particularly with respect to long-term inhaled corticosteroid use, thus the correct diagnosis should be pursued when the patient becomes stable.

DEFINITION OF EXACERBATION

The lack of an objective definition for “exacerbations” of COPD presents an obstacle in the selection of patients for study. Most COPD exacerbations are due to worsening airflow obstruction caused by respiratory tract infections. However, patients with severe airflow obstruction may experience dyspnea from any increase in ventilatory demand that exceeds their limited capacity. Thus, patients with fever or pain may report dyspnea in the absence of any change in lung structure or function. In addition, noninfective phenomena ranging from congestive heart failure to pulmonary embolus can present with symptoms mimicking a COPD exacerbation. The inclusion of patients with causes of dyspnea other than airflow infections would minimize apparent treatment benefit.

SURROGATE OUTCOMES

Most comparative clinical trials of interventions directed at relieving airflow obstruction in COPD measure continuous spirometric indexes to assess patient response. Although a measure of physiologic airway obstruction, spirometry is a surrogate marker of clinical disease severity and has been demonstrated to correlate poorly with functional capacity and dyspnea scores. Cross-sectional studies have produced conflicting information regarding the clinical significance of changes of FEV1 in response to bronchodilator.

Consequently, differences in spirometric observations in clinical studies should not only reach statistical significance but should be of a clinically significant magnitude. It remains unclear with respect to what change in FEV1 is clinically significant. There are recent data documenting the prognostic utility of measuring FEV1 early in the course of a COPD exacerbation, as well as changes in FEV1 in response to steroid therapy. A change in FEV1 of 100 mL within the first 2 days of hospitalization was associated with a decreased risk of treatment failure. One study determined that the minimal increase in FEV1 that could be perceived by patients was 112 mL, or 4% of the predicted FEV1. Unfortunately, few studies have reported absolute changes in FEV1, making it impossible to apply this evaluative criterion to all studies.

Outcome measures of trials studying treatment of COPD exacerbations should represent the clinical status of the patient. Because inhospital mortality for COPD exacerbation is approximately 6%, it is often impractical to use mortality as a primary end point in clinical trials. Other outcomes related to the treatment of COPD exacerbations are often confounded by factors other than the patient’s clinical status. Inpatient care of COPD exacerbations is common, but prospectively validated criteria for hospital admission are lacking, thus standardization of admission is difficult. Duration of hospital stay is often related to other factors such as comorbid states, complications unrelated to COPD, and patient convenience.

CONCLUSIONS

There is good-quality randomized, placebo-controlled trial evidence that systemic corticosteroid administration modestly reduces treatment failure rates and duration of hospitalization and improves FEV1 when given to patients experiencing acute exacerbations of COPD. The benefit from corticosteroid administration is evident within the first day of therapy and lasts for at least the first 5 days of therapy (good- and fair-quality evidence, respectively). There is no evidence suggesting a benefit of steroids lasting beyond the first 5 days of therapy or the immediate hospital admission. The observed benefit is of an absolute magnitude that patients are likely to be able to detect, making it clinically significant, although patients in whom this has been well demonstrated have generally had an FEV1 of 1 L or greater. There appears to be no advantage to courses of oral steroid longer than 2 weeks (good-quality evidence); the shortest useful duration of therapy is unknown. Studies using oral steroids alone appear to demonstrate similar clinical benefit to studies using parenteral steroids (good-quality evidence).

There is evidence from good-quality randomized trials that steroid use results in an increased incidence of hyperglycemia and potentially life-threatening infections (among patients receiving very high doses for 8 weeks). There is evidence to suggest that the administration of systemic corticosteroids to patients with COPD exacerbations has deleterious effects on bone mineral density, and this effect is likely dose dependent. The clinical implications of this remain unknown. The total steroid dose given to the “average” patient with COPD (1.3 exacerbations per year) probably does not carry a significantly increased risk of bone loss. Among patients with frequent exacerbations, however, the clinician should weigh the adverse effects carefully against the benefit observed in that patient.

Given the modest but significant effect of steroids seen among patients with COPD exacerbations, and the significant burden of illness of this disease, further research is needed to characterize the optimal dose, route and duration of treatment, and long-term risks of therapy.
Recent consensus guidelines that have set definitions for COPD may improve patient selection in future clinical research, thus allowing easier interpretation and clinical application of trial results.

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