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Short Communication

A Survey of Corticosteroid Dosing for Exacerbations of Chronic Obstructive Pulmonary Disease Requiring Assisted Ventilation

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Abstract

Background: For over 40 years, systemic corticosteroids have been a mainstay of treatment for patients with exacerbations of chronic obstructive pulmonary disease (COPD). Surprisingly, the optimal dosage of corticosteroids is unknown in critically ill patients requiring assisted ventilation, a group with high morbidity and mortality.

Methods: We surveyed 39 academic physicians within the United States Critical Illness and Injury Trials Group (USCIITG) and the Prevention and Early Treatment of Acute Lung Injury Trials Network (PETAL) to determine the range of corticosteroid dosages used to treat patients with COPD exacerbations requiring assisted ventilation. We also asked if these physicians believe that a clinical trial is needed to determine the optimal dosage of corticosteroids in this population.

Results: Thirty-two physicians (82%) responded to the survey. Usual practice was to start intravenous methylprednisolone at a median dose of 120mg/day (range 40-500mg/day). In the context of a clinical trial, 78% of physicians were comfortable initiating methylprednisolone at a dose as low as 40mg/day. In contrast, physicians were split on the highest acceptable methylprednisolone dose, with 44% comfortable initiating doses as high as 500mg/day, 44% at 240mg/day, and 12% at doses less than 240mg/day. Ninety-four percent of respondents believed that a randomized controlled trial is needed to determine the optimal corticosteroid dose to treat patients with COPD exacerbations requiring assisted ventilation.

Conclusions: These results demonstrate sufficient clinical equipoise to support the conduct of a clinical trial to identify the optimal dose of systemic corticosteroids for patients with COPD exacerbations requiring assisted ventilation.

Abbreviations: chronic obstructive pulmonary disease, **COPD**; United States Critical Illness and Injury Trials Group, **USCIITG**; Prevention and Early Treatment of Acute Lung Injury Trials Network, **PETAL**; research electronic data capture, **REDCap**; acute exacerbation of COPD, **AECOPD**; intensive care unit, **ICU**; randomized controlled trial, **RCT**; methylpredniosolone, **MP**; length of stay, **LOS**

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Introduction

Exacerbations of chronic obstructive pulmonary disease (COPD) account for 60% of our national expenditure for COPD, herald a steep decline in quality of life, and markedly increase the risk of death.[1] In patients with respiratory failure who need assisted ventilation, mortality and hospital costs soar by ~15 times compared to those without respiratory failure, with mortality rates of ~25%-30% in the hospital[2,3] and 59% at 1-year.[3] Patients who survive to hospital discharge are commonly transferred to long-term care facilities.[4] After returning home, most patients suffer severe reductions in activities of daily living, as well as increased depression, anxiety, and social difficulties requiring assistance with at least one activity of daily living 6-months after returning home.[4,5]

Systemic corticosteroids are a critical therapy for COPD exacerbations, because they decrease treatment failure and prevent readmissions in patients without respiratory failure.[6] In contrast, very little is known about the effect of corticosteroids in patients with respiratory failure, prompting a 2014 Cochrane Review to conclude that "there is a need for more studies in severe exacerbations of COPD in people who require assisted ventilation."[6] This knowledge gap has occurred because the majority of large studies evaluating steroid dosing during COPD exacerbations have specifically avoided studying patients requiring assisted ventilation (e.g., those needing invasive or noninvasive mechanical ventilation).[7,8] Some of these studies excluded patients with respiratory failure because the primary outcome of *treatment failure* was, in part, defined by the need for assisted ventilation. Simply put, investigators could not include patients who presented with the study outcome (e.g., assisted ventilation).

Given the high potential for poor outcomes and lack of definitive data, physicians likely choose higher steroid dosages in patients requiring assisted ventilation because of their severity of illness and the perception that higher intravenous doses may lead to better treatment efficacy. A potential consequence is that physicians administer steroid dosages that are up to 12 times higher than are routinely used for patients without respiratory failure,[9] exposing them to a greater risk for adverse effects without clear clinical benefit.

The objective of this study was to describe corticosteroid dosing regimens used in patients hospitalized at academic institutions with a COPD exacerbation requiring assisted ventilation and to determine if there is physician support for a clinical trial to establish the optimal systemic corticosteroid dose. Additionally, we sought to determine the range of corticosteroid dosages that would be appropriate to evaluate if a clinical trial were to be conducted.

Methods

The Colorado Multiple Institution Review Board approved this study. Response to the survey was voluntary and anonymous. Completion of the survey indicated the respondent's consent to participate in this research study. The survey was conducted via email invitations using research electronic data capture (REDCap) at the University of Colorado Anschutz Medical Campus.

We surveyed intensive care unit physicians within 2 networks about clinical practice in patients hospitalized with a COPD exacerbation requiring assisted ventilation: Twenty-nine physicians from the United States Critical Illness and Injury Trials Group (USCIITG), and 12 pulmonary and critical care physician principal investigators from the Prevention and Early Treatment of Acute Lung Injury Trials Network (PETAL). Two physicians who were members of both groups were only invited to participate in the survey once, yielding a total eligible survey population of 39. Physicians were asked for their opinion regarding: (1) the usual daily dose of corticosteroids (in methylprednisolone equivalents) that they utilize to initially treat this patient population, (2) the need for a clinical trial to compare corticosteroid dosing strategies for COPD exacerbation patients

requiring assisted ventilation, and (3) the highest and (4) the lowest daily dose of methylprednisolone that they would be comfortable using as part of a clinical trial testing different dosing regimens (Figure 1). Survey respondents were provided with a summary of recent literature[7,9-12] surrounding corticosteroid dosing in hospitalized patients that they could utilize when answering survey questions (Table 1).

Data are presented as proportions or median (range). Corticosteroid dosages are presented in methylprednisolone equivalents (e.g., prednisone 5mg = 4mg methylprednisolone).

Figure 1. Survey of Corticosteroid Dosing for Acute Exacerbations of COPD with Respiratory Failure

Systemic corticosteroids are administered to the majority of patients admitted with respiratory failure secondary to an acute exacerbation of COPD (AECOPD). Observational data indicate that intensive care unit (ICU) physicians initially treat these patients with a wide range of corticosteroid doses. The purpose of this survey is to gain insight into the potential importance and design of a clinical trial to optimize steroid dosing in patients admitted with respiratory failure secondary to an AECOPD. A table is provided below that summarizes the relevant observational and clinical trials. Please note that steroid dosing is presented in methylprednisolone equivalents, which is 20% more potent than prednisone.

Conversion of methylprednisolone equivalents to prednisone:
Methyprednisolone 40 mg/day= Prednisone 50 mg/day
Methylprednisolone 500 mg/day (e.g., 125 mg q6h per day) = Prednisone 625 mg/day

1) Do you believe that it is important to perform a large clinical trial to determine the optimal corticosteroid dosing regimen for patients admitted to the ICU with an AECOPD and respiratory failure requiring invasive or non-invasive ventilation?
   a. Yes
   b. No

2) What is the **usual total daily dose** of corticosteroids (in methylprednisolone equivalents) that you use to initially treat patients admitted with an AECOPD and respiratory failure requiring invasive or non-invasive ventilation?
   a. 500 mg/day
   b. 240 mg/day
   c. 120 mg/day
   d. 80 mg/day
   e. 40 mg/day
   f. Other - please provide your preferred dose in blank

3) What is the **highest total daily dose** of corticosteroids (in methylprednisolone equivalents) that you would be comfortable using to initially treat a patient admitted with an AECOPD and respiratory failure requiring invasive or non-invasive ventilation?
   a. 500 mg/day
   b. 240 mg/day
   c. 120 mg/day
   d. Other - please provide your preferred dose in blank

4) What is the **lowest total daily dose** of corticosteroid (in methylprednisolone equivalents) that you would be comfortable using to initially treat a patient admitted with an AECOPD and respiratory failure requiring invasive or non-invasive ventilation?
   a. 40 mg/day
   b. 80 mg/day
   c. 120 mg/day
   d. Other - please provide your preferred dose in blank

Table 1. Selected Literature Evaluating Corticosteroids for Acute Exacerbation of COPD

Reference	Design	Treatment Groups	Outcomes	Results
Niewoehner et al, *New Eng J Med.* 1999; 340:1941-1947.	• RCT • 3 Groups • N=271 Inclusion • AECOPD Exclusion • Ventilation	**Group 1:** • MP 125mg IV q6h on days 1-3 • Prednisone taper on days 4-14 **Group 2:** • MP 125mg IV q6h on days 1-3 • Prednisone taper on days 4-56 **Group 3:** • Placebo	**1° Outcome** • Treatment failure: o Death o Intubation o COPD readmission o Intensified therapy **2° Outcomes** • Hospital LOS • Hyperglycemia	**1° Outcome** • Both steroid regimens decreased treatment failure **2° Outcomes** • Steroids decreased hospital LOS • Steroids increased hyperglycemia
Alia et al, *Arch Intern Med.* 2011; 71:1939-1046.	• RCT • 2 Groups • N=83 Inclusion • AECOPD • Ventilation	**Group 1:** • MP 0.5mg/kg IV q6h on days 1-3 • MP taper on days 4-10 **Group 2:** • Placebo	**1° Outcome** • Ventilation time • ICU LOS • Noninvasive ventilation failure **2° Outcomes** • Hospital LOS • Hospital Mortality • Hyperglycemia	**1° Outcome** • Steroids decreased ventilation time • Steroids decreased noninvasive ventilation failure **2° Outcomes** • Steroids did not alter: o Hospital LOS o Hospital Mortality • Steroids increased hyperglycemia
Leuppi et al, *JAMA.*2013; 309:2223-2231.	• RCT • 2 Groups • Noninferiority • N=256 Inclusion • AECOPD • Ventilation	**Group 1:** • Prednisone 40mg daily x 5 days **Group 2:** • Prednisone 40mg daily x 14 days	**1° Outcome** • Time to next AECOPD within 6 months **2° Outcomes** • Mortality • Hospital LOS • Need for ventilation • Open-label steroids • Hyperglycemia	**1° Outcome** • No effect on time to next AECOPD **2° Outcomes** • No effect on o Mortality o Ventilation o Open-label steroids o Hyperglycemia • Short-course steroids decreased hospital LOS
Abroug et al, *Eur Respir J.* 2014; 43:717-724.	• RCT • 2 Groups • N=217 Inclusion • AECOPD • Ventilation	**Group 1:** • Prednisone 1mg/kg/day until discharge or 10 days **Group 2:** • Usual Care/No Steroids	**1° Outcome** • ICU Mortality **2° Outcomes** • Ventilation time • ICU LOS • Noninvasive ventilation failure • Hyperglycemia	**1° Outcome** • Steroids did not alter ICU mortality **2° Outcomes** • Steroids did not alter o Ventilation time o ICU LOS o Noninvasive failure • Steroids increased hyperglycemia
Kiser et al, *Am J Resp Crit Care Med.*2014; 189:1052-1064.	• Observation • 2 Groups • N=17239 Inclusion • AECOPD • ICU • Ventilation	**Group 1:** • High dose: >240mg/day in MP equivalent within first 48 hours **Group 2:** • Lower dose: ≤240mg/day in MP equivalent within first 48 hours	**1° Outcome** • Hospital Mortality **2° Outcomes** • Hospital LOS • ICU LOS • Total Cost • Hyperglycemia	**1° Outcome** • Lower-dose steroids did not decrease mortality (p=0.06) **2° Outcomes** • Lower dose steroids associated with: o Lower Hospital LOS o Lower ICU LOS o Lower Total Cost o Decreased Hyperglycemia

AECOPD=acute exacerbation of COPD; ICU=intensive care unit, RCT=randomized controlled trial; MP= methylprednisolone; LOS=length of stay

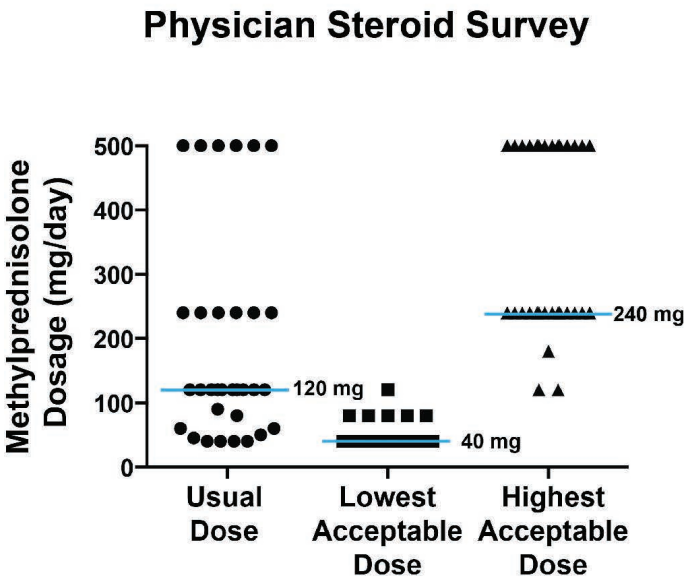
Results

Thirty-two physicians (82%) responded to the survey (Table 2). Usual practice is to start methylprednisolone over a range of 40 to 500mg/day, with a median of 120mg/day (Figure 2). A total of 19% of physician respondents start corticosteroids at >240mg/day and 81% begin corticosteroids at ≤240mg/day. Within the context of a clinical trial, 88% of physician respondents would be comfortable administering methylprednisolone at dosages as low as 40mg/day to patients admitted with a COPD exacerbation requiring assisted ventilation (Figure 2). In contrast, 44% of physician respondents would be comfortable initiating dosages as high as 500mg/day, 44% as high as 240mg/day and 12% at dosages less than 240mg/day (Figure 2). A total of 94% of respondents believed that a large randomized, controlled clinical trial is needed to determine the best corticosteroid dose for COPD exacerbations requiring assisted ventilation.

Table 2. Survey Responses

	Survey Responses (N=32)
Is a clinical trial warranted? (% yes)	94%
Usual total daily dose prescribed in methylprednisolone equivalents? [median (range)]	120mg (40-500mg)
Highest total daily dose would utilize for treatment [median (range)]	240mg (120-500mg)
Lowest total daily dose would utilize for treatment [median (range)]	40mg (40-120mg)

Figure 2. Steroid Survey



Physicians within the United States Critical Illness and Injury Trials Group (USCIITG) and the Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network (PETAL) were surveyed to determine current practice as it pertains to steroid treatment of AECOPDs with respiratory failure. Physicians were asked for the usual, lowest, and highest total daily dose in methylprednisolone equivalents that they would use to begin therapy for AECOPDs with respiratory failure. Blue line = group median.

Discussion

The results of our survey indicate that corticosteroid dosing for COPD exacerbations requiring assisted ventilation varies widely from a low of 40mg to a high of 500mg/day of methylprednisolone equivalents, with a median of 120mg/day. This large variability in prescribing patterns is supported by large epidemiologic studies that have evaluated corticosteroid dosing in patients hospitalized with COPD exacerbations, both with and without respiratory failure.[8,9] The lack of consensus among respondents reflects the variability of dosing strategies used in clinical trials to date[7,10-12] and highlights the paucity of guidance provided by clinical trials in COPD patients with respiratory failure.

Only 2 randomized, controlled clinical trials have specifically examined corticosteroid dosing during COPD exacerbations requiring assisted ventilation, and both of these studies compared treatment with corticosteroids to no treatment/placebo.[10,12] Alia et al found that methylprednisolone initiated at 2mg/kg/day (e.g., 160mg/day for an 80kg person) decreased noninvasive ventilator failures and the duration of ventilation compared to placebo.[10] In contrast, Abroug et al found that prednisone initiated at 1mg/kg/day (e.g., ~64mg/day of methylprednisolone for an 80kg person) did not improve outcomes compared to usual care without steroids.[12] The reasons for these divergent

findings are not known. But it is possible that the threshold for a positive corticosteroid effect is higher during COPD exacerbations with respiratory failure compared to no respiratory failure, perhaps because of increased steroid resistance. This would suggest that some commonly used corticosteroid dosages may be too low to optimally treat COPD exacerbations requiring assisted ventilation. Conducting mechanistic studies to determine if a different steroid response phenotype exists in COPD exacerbation patients with respiratory failure may be an important step to both designing steroid dosing regimens and justifying the need for a randomized controlled study in this patient population.

To determine corticosteroid prescribing patterns and to examine the effectiveness of high versus lower dose corticosteroids, we performed a pharmacoepidemiologic cohort study in 17239 patients admitted to the intensive care unit with a COPD exacerbation between 2003 and 2008.[9] During this period physicians started methylprednisolone at a median dosage of ~240mg/day. Methylprednisolone was initiated at >240mg/day in 66% of patients, indicating that high dosages were preferred at that time. Despite this preference, methylprednisolone dosages ≤240mg/day (median of ~100mg/day) were associated with many positive outcomes including a nearly significant reduction in mortality (p=0.06). Our survey shows that a decade later only 19% of physicians start corticosteroids at >240mg/day and that methylprednisolone is started at a median of 120mg/day, suggesting that physician dosing for COPD exacerbations with assisted ventilation may be evolving toward lower doses compared with 2003-2008.[9]

To our knowledge, a survey has never been performed to assess physician corticosteroid prescribing patterns and the perceived need for a clinical trial of steroid dosing for COPD exacerbations requiring assisted ventilation. Our study indicates strong support by academic critical care and pulmonary physicians for such a trial. Given the variable prescribing patterns, it also suggests the presence of clinical equipoise. An efficacy trial design could be performed to determine if either of 2 corticosteroid dosages is superior or equivalent under optimal clinical trial conditions. Alternatively, an effectiveness or comparative effectiveness approach would have the advantage of answering the same question under real world conditions. Our survey supports a clinical trial comparing an initial methylprednisolone equivalent dose as low as 40mg/day with either 240mg/day or 500mg/day. An alternative approach could compare an initial low methylprednisolone equivalent dosage of 40mg/day with a high dosage of 2mg/kg/day. The advantage of this dosing approach is that methylprednisolone initiated at 2mg/kg/day and tapered over 10 days is the only corticosteroid dosing strategy that has yielded positive outcomes for patients with a COPD exacerbation requiring assisted ventilation.[10]

Our study is the first to establish current physician corticosteroid prescribing patterns and degree of equipoise by academic physicians who perform research within critical illness research networks. It is also the first to determine the highest and lowest acceptable corticosteroid dosages that these physicians would deem acceptable within the auspices of a clinical trial. Both of these elements are critical to design and implement a successful clinical study. The study is also limited because it only surveyed academic physicians from 2 clinical trial groups (USCIITG and PETAL), which may not represent physicians from all clinical settings. The number of respondents was also small and the responses do not elucidate the rationale for prescriber preferences.

Conclusion

To date there are no randomized controlled clinical trials comparing different dosages of corticosteroids in the treatment of patients with a COPD exacerbation either with or without respiratory failure.[13] The absence of guidance, other than a single epidemiologic study,[9] is particularly important for COPD exacerbation patients with respiratory failure because they are exposed to the highest risk and stand to lose the most.[2] Our study demonstrates the variability in physician practice regarding the initial steroid dosing in these critically ill patients, and underscores the fact that in medicine disagreement is common in the absence of data. Accordingly, a prospective, randomized controlled trial is warranted and supported by physicians to determine the optimal dose of systemic steroids for patients with a COPD exacerbation and respiratory failure requiring assisted ventilation.

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Declaration of Interests

The authors have no relevant conflicts of interest to declare.

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