Review Article: Determining the Optimal Steroid Treatment Regimen for COPD Exacerbations: A Review of the Literature

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Jena Torpin, PharmD[1]; Erica Ottis, PharmD, BCPS[2]

[1] Department of Pharmacy, Internal Medicine, University of Missouri Health Care, Columbia, MO

[2] Department of Pharmacy, University of Missouri-Kansas City School of Pharmacy at MU, Columbia, MO

Address Correspondence to Jena Torpin

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Background

The literature has established that the use of systemic corticosteroids in COPD exacerbations decreased time to recovery, decreased hypoxemia, and improved FEV1.1,2,3,4 However, the dose and duration of corticosteroids used to treat COPD exacerbations is highly variable and has been widely debated. Previous Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend 30-40mg of oral prednisolone daily for 10-14 days.5 The most recent iteration of the guidelines recommended considering even shorter durations of 5 days based on the findings from the recently published REDUCE trial.6,7 Due to side effects of steroids such as blood glucose elevations, emotional lability, and predisposition to fractures, especially at cumulative doses >1g prednisone or the equivalent,8,9 it is important to limit exposure if possible. This review offers some considerations when treating COPD exacerbations in a variety of patient populations.

Treatment considerations

IV vs. PO

One of the founding studies demonstrating the clear role of glucocorticoids in the management of COPD exacerbations was published in 1999 by Niewoehner and colleagues.3 This study comparing placebo versus 2 and 8 weeks of steroid therapy found that prolonged steroid use did not have an advantage over 2 weeks of therapy. Because of this, many clinicians adopted this 2 week treatment regimen of IV methylprednisolone on days 1-3 at 125mg every 6 hours followed by 60mg of prednisone tapered by 20mg every 4 days3 as their standard of care. While this regimen did demonstrate a clear benefit, further studies have shown that high-dose IV steroids are likely not required in the management of acute exacerbations in most patients.10,11

Clinician adoption of high-dose IV steroid administration was demonstrated in a pharmacoepidemiological cohort study that looked at 79,985 patients admitted for COPD exacerbations. Investigators found that despite recommendations to utilize low-dose oral therapy for the initial management of exacerbations, 92% of patients were started on high-dose IV steroids. The authors also found that initiating patients on low-dose oral steroids did not increase risk of treatment failure and that patients had lower median hospitalization costs.10 Another study evaluating 60mg of IV methylprednisolone compared to 60mg of oral prednisolone for 5 days, followed by 30mg of prednisolone tapered over 6 days in both treatment arms, also supported the claim that oral steroids are non-inferior to IV steroids with regard to treatment failure.11

In addition to clinical equivalence, oral prednisone has a favorable pharmacokinetic profile with a bioavailability between 50-90% and peak serum levels occurring within 2 hours of ingestion.12 Because oral therapy has been shown to be equivalent to IV therapy, is less expensive, and decreases the risk of line-infections/complications,10 low-dose oral corticosteroids should be utilized for treating most patients' COPD exacerbations. However, certain patients may benefit from IV corticosteroid therapy and these special considerations are discussed below.

Duration

In the recently published prospective, randomized, non-inferiority REDUCE trial, 5 days of steroid treatment was found to be equivalent to 14 days of therapy with regards to 6 month re-exacerbation rates for patients presenting to the hospital with a COPD exacerbation. In this study, patients received an initial IV dose of methylprednisolone at 40mg, followed by prednisone 40mg daily. The majority of patients were classified as GOLD grades 3-4, demonstrating that shorter courses of systemic corticosteroids can be beneficial, even in patients with more severe COPD. New infections and new or worsening hyperglycemia and hypertension were similar in both treatment arms, but the cumulative steroid dose was only 379mg in the short-term treatment arm compared with 793mg in the conventional arm.6 Unfortunately, the level of care required on admission and the patients' history of exacerbations in the previous year were not noted in the patients' baseline characteristics.6 Since past exacerbations are the best predictor of future exacerbations,13 the GOLD guidelines denotes patients who have had two or more exacerbations in the past year to be at "high risk" for further exacerbations.5 This information would have been helpful in determining if 5 days of therapy is still optimal for these "high-risk" patients.

The use of short steroid tapers (e.g. less than 14 days) versus burst therapy has not been specifically addressed in the literature.14 Because of this, it is difficult to determine which (if any) patients would benefit from these therapies. Potential candidates for steroid tapers may include patients who fail burst therapy, have frequent exacerbations of 2 or more per year, and patients on chronic steroids.

Special considerations

COPD exacerbation, steroids, corticosteroids The aforementioned treatment considerations do not generally apply to COPD exacerbations requiring admission to the ICU. In many of the previously mentioned studies, this subset of patients were either excluded from analysis or the level of care was not addressed in the baseline characteristics.6,10,11,15 Two major studies specifically evaluating the efficacy of steroids in COPD exacerbations requiring ICU admission have been recently conducted. In a placebo-controlled, double-blind trial comparing placebo to IV methylprednisolone (0.5mg/kg every 6 hours days 1-3; 0.5mg/kg every 12 hours days 4-6; 0.5mg/kg daily days 7-10) in 83 ICU patients requiring mechanical ventilator support, Alia and colleagues found that patients receiving steroids required a shorter time on mechanical ventilation (median of 3 versus 4 days; p=0.04). The duration of mechanical ventilation was a composite outcome combining both conventional mechanical ventilation and non-invasive mechanical ventilation (NIMV) with the difference being driven largely by the NIMV subgroup. Additionally, investigators found that there was a decreased incidence of NIMV failure in the steroid treatment arm (0% versus 37%; p=0.004).16 Conversely, in their open-label, prospective, randomized controlled trial involving 217 mechanically ventilated patients admitted to the ICU for COPD exacerbation, Abroug and colleagues found no difference in duration of ventilation (median of 6 versus 6 days; p=0.87) or NIMV failure (15.7% versus 12.7%; p=0.59) for patients who received oral prednisone at 1mg/kg daily until discharge or up to a 10 day maximum when compared to usual care. Usual care was defined as receiving ventilator assistance, nebulized ipratropium and beta-2 agonists, and antibiotics if clinically indicated.15 While this study was underpowered to detect a difference in these outcomes, it may offer some insight into more optimal treatment regimens for patients requiring ICU admission. Patients in the Alia study received twice the amount of steroids for the first few days of admission compared to the Abroug study and this high-dose of IV steroids may have contributed to the difference seen in duration of mechanical ventilation.15

Because there is limited information regarding optimal treatment in this subgroup of patients, the dosing recommendations found in the Alia and colleagues study may be the best evidence-based treatment regimen for this patient population, especially during the first few days of treatment. Given the fact that IV steroid treatment is equivalent to oral therapy in non-ICU patients, it would be reasonable to transition to an appropriate dose of oral steroids once patients begin to clinically improve.

Summary

In reviewing the literature, there is not a uniform approach to corticosteroid treatment when managing patients with COPD exacerbations. In general it is important to remember:

- Oral corticosteroids are as effective as IV corticosteroids in the management of most COPD exacerbations not requiring ICU admission.
- Short courses of prednisone (40mg daily for 5 days) are appropriate for most COPD exacerbations.
- Patients with frequent exacerbations of 2 or more per year or patients on chronic steroids may require a prolonged course of treatment.
- ICU patients have largely been excluded or not specifically studied in most analyses. Available literature shows that this subset of patients may benefit most from high-dose IV therapy for the first few days of treatment. Once patients are clinically improving, it would be reasonable to deescalate to oral therapy to limit unnecessary exposure.

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Case Report: Transient Gestation-associated Diabetes Insipidus (GDI)

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Syed H Naqvi, MD, FACP 1 Jonathan B Menezes, MD 2, Syed Ali Awon, MBBS 3,

[1]Division of Hospital Medicine, Department of Medicine, University of Missouri, School of Medicine, Columbia, MO

[2]Division of Geriatric Medicine, George Washington University School of Medicine, Washington, DC

[3]Missouri University Clinical Research Center, University of Missouri School of Medicine, Columbia, MO<?

Address Correspondence to: Syed H Naqvi

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