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Systemic Corticotherapy for Acute Exacerbation of Chronic Obstructive Pulmonary Disease: What is New? / What is Important?

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ABSTRACT

Acute exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD), the most relevant event affecting COPD mortality, is catastrophic event during clinical course of the disease. Whereas its pharmacological management relies mostly on three families of drugs: inhaled bronchodilators, antibiotics and systemic corticosteroids, this review is limited to systemic corticotherapy only. The review aims to update current indications to systemic corticotherapy in the management of AECOPD, including choice of drug, dosage and duration of therapy. Systemic corticotherapy, undoubtedly, has a significant role in the management of AECOPD as it alleviates clinical symptoms, improves pulmonary function, shortens hospitalization(s) and decreases relapse rate. There is compelling evidence that such patients should be treated with the lowest possible dose of corticosteroids for the minimum duration possible. It has been shown that short -course therapy of 40 mg prednisone equivalent, with or after food, per day for 5 days is sufficient for successful management of AECOPD and is non-inferior to, previously employed, duration of 10-21 days. Moreover, it is no longer necessary to taper the dose, which further simplifies the treatment and improves compliance.

Keywords: AECOPD, Systemic corticotherapy, Eosinophilic AECOPD.

KEY MESSAGES

*Systemic corticosteroids have significant role in the overall management of patients with AECOPD as they alleviate clinical symptoms by reducing airway inflammation and pulmonary edema. They have been shown to improve pulmonary function, shorten hospitalization(s) and decrease relapse rate.

*There is compelling evidence that the patients with AECOPD should be treated with the lowest possible dose of corticosteroids for the minimum duration possible.

*The short-course therapy of 40 mg prednisone equivalent, with or after food, per day for 5 days is sufficient for successful management of AECOPD and is non-inferior to previously employed 10-21 days duration.

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INTRODUCTION

Exacerbations of COPD are characterized by acute worsening of respiratory symptoms such as breathlessness, cough, sputum volume, and purulence [1]. In addition, they have well-documented acute and long-term adverse effects on health status of the patients, beyond pulmones. The NICE Guidelines define an exacerbation: "*a sustained worsening of the patient's symptoms from their usual stable state which is beyond normal day-to-day variations and is acute in onset*" [2]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has updated its definition in 2024 as: "*an event characterized by dyspnea and/or cough and sputum that worsen in < 14 days which may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by infection, pollution, or other insults to the airways*" [3].

This review aims to update current indications to systemic corticotherapy in the management of AECOPD, including choice of drug, dosage and duration of therapy.

Corticosteroids: Role in the Management of AECOPD

The term corticosteroid is used clinically to describe agents with glucocorticoid activity, available in topical and systemic forms. Systemic corticosteroids are used for pharmacologic purposes to suppress inflammation and immune system reactions. Their potency is expressed compared to hydrocortisone and is useful in determining comparable doses [4]. Conversion from one systemic steroid to another requires knowledge of equipotent dosages. Frequency of dosage is decided by the half-life and duration of action for individual corticosteroids. Hydrocortisone is considered a short-acting corticosteroid (8-12 hours). Prednisone/ Prednisolone/ Methyl prednisolone are recognized as intermediate-acting (12-36 hours) while Dexamethasone (36-72 hours) has long biological life [5].

Prednisone is a synthetic, anti-inflammatory corticosteroid that derives from cortisone. It is biologically inert and converted to prednisolone in the liver [6]. The hepatic conversion is nearly 100%, even in the presence of significant hepatic dysfunction, so the effects of these two agents are identical [7]. However, methyl prednisolone should be preferred in those with severe hepatic damage. Cortisone also undergoes hepatic conversion to hydrocortisone, and this activation is impaired in patients with significant hepatic dysfunction, which limits the use of this therapy.

The pharmacological management of AECOPD relies mostly on three families of drugs: inhaled bronchodilators (to relieve dyspnea), antibiotics (when sputum is purulent) and systemic corticosteroids [8]. Both long and short courses are available, the impact being different. Corticosteroids "key stone in pulmonary medicine" have a significant role in the overall management of patients with AECOPD. They provide a therapeutic effect by inhibiting bronchoconstriction, promoting bronchodilation, suppressing the immune response, and having an overall anti-inflammatory effect [9].

Systemic Corticotherapy: Dosage and Duration Options

Whereas their dosage and duration in the management of AECOPD still remain unclear [10], the extent of both therapeutic and adverse effects of systemic corticosteroids is linked to the dosage and duration of their administration. The balance of the desirable (alleviating the clinical symptomatology by reducing airway inflammation and pulmonary edema) and undesirable effects (fluid retention, hyperglycemia, steroid-induced psychiatric symptoms, and increased risk for opportunistic infections) varies according to the steroid dose. Prolonged use of prednisone (>2 weeks) especially at >40 mg/day, can cause serious adverse effects. The suppression of the hypothalamic-pituitary-adrenal axis may persist for as long as 6 to 12 months following steroid withdrawal in such cases [11]. In fact, corticotherapy is a "*double-edged sword*." It is, therefore, crucial to minimize their unnecessary exposure [12].

A single-center retrospective cohort study, in a US community hospital, was conducted to determine whether low dose corticotherapy for AECOPD, provides the lowest risk of adverse effects, without increasing length of stay or readmission rate. The 3 inpatient cumulative dose range groups were low: ≤250-mg prednisone equivalents, medium: 251 to 500 mg, and high: ≥501 mg. The lowest dose range of corticosteroids was associated with the lowest rate of impaired blood glucose without a statistically significant increase in length of stay or readmission rate [13]. In another meta-analysis investigating efficacy and safety of different doses of prednisone equivalent (PE/d) in patients with AECOPD, the indirect treatment comparison was performed between low-dose (ie, initial dose ≤ 40 mg prednisone equivalent/d [PE/d]), medium-dose (initial dose = 40-100 mg PE/d, and high-dose (initial dose > 100 mg PE/d) groups. It was shown that the low dose was not only safer but, in addition, non-inferior to the higher doses [14].

What is the impact of long versus short courses of systemic corticosteroids? A Danish study, using nationwide data on 67,000 patients with COPD followed for 12 months, was conducted to assess the impact of long course (37.5

mg prednisolone daily for 10 days) versus short courses (37.5 mg prednisolone daily for 5 days) on mortality and pneumonia. This definition of long and short courses was based on Danish Guidelines and prednisolone prescription practice. The long course was associated with an increased 1-year risk of pneumonia hospitalization or all-cause mortality as compared with the short course. These results were confirmed in several sensitivity analyses [15]. The change of recommendations, in Danish health system, from long courses to short courses for AECOPD, in 2014, was well rewarding, as documented by a decrease in pneumonia admissions and all-cause mortality, in favor of short courses [15]. In the Swiss REDUCE randomized clinical trial a 5-day treatment with prednisolone 40 mg daily was non-inferior to 14-day treatment and significantly reduced corticosteroids exposure [16]. Moreover, in randomized controlled trials comparing different durations of corticosteroids therapy, the 5-day course was found to be sufficient for treatment of AECOPD [17].

What should be the optimal dose of systemic corticosteroids in the management of AECOPD? Whereas the NICE Guidelines recommend 30 mg oral prednisolone daily for 5 days [2], the American Family Physician [18], American Thoracic Society [19] and the GOLD 2024 Report [3] recommend a dose of 40 mg prednisone-equivalent per day (PE/d) for 5 days.

What should be the preferable route of delivery? Tablets for oral route and parenteral preparations (intravenous and intramuscular) are available for systemic use. Oral formulations are available for various corticosteroids with the most popular ones being prednisone, methylprednisolone, hydrocortisone, and dexamethasone. The ATS Clinical Practice Guidelines recommend that oral therapy should be preferable, being more cost effective [19]. Of note, there is no need to opt for enteric coated tablets. In a study of comparing pharmacokinetics of plain (un-coated) and enteric coated prednisolone tablets, it was found that, for more predictable corticosteroid absorption, plain prednisolone tablets are preferable [20].

The intravenous route should be reserved for patients who are unable to take medication orally. There is no evidence that admitting a patient solely to receive intravenous corticosteroids is superior to treatment with oral corticosteroids [19]. In a Netherlander randomized controlled double- blind study, the therapy with oral prednisolone was found equally effective to intravenous administration [21]. Similarly, in randomized controlled trials, there was no evidence of benefit for parenteral treatment compared with oral treatment with corticosteroid on treatment failure, relapse or mortality [22]. Rather, the increase in adverse drug effects with corticotherapy was greater with parenteral administration compared with oral route [22].

Eosinophilia and Systemic Corticotherapy

There is significant clinical heterogeneity in patients with AECOPD [23]. The blood eosinophil count, a marker for eosinophilic airway inflammation, is the only blood-based biomarker that has proved reliable for clinical practice. The levels could be used as a biomarker to predict which patients will respond best to systemic corticotherapy. In the Bafadhel study, a cut-off at 2% of blood eosinophil counts distinguished between eosinophilic and non-eosinophilic AECOPD with a 90% sensitivity [24].

In a case control Italian study, it was revealed that a higher blood eosinophil cell count ((≥200 cells/μL and/or ≥2%), at admission for AECOPD, was associated with a favorable response to systemic corticotherapy with resultant shorter hospital stay as compared to those with blood eosinophilia <2% at admission [25]. Of note, the eosinophil count is known to fall by >50% within the first four hours following systemic corticosteroids administration [26]. In a retrospective observational Chinese study, it was found that the eosinophils guide clinical treatment. Additionally, they are used as an index to predict the clinical outcome and prognosis of those with AECOPD [27].

The main conclusion drawn from the observational, prospective, longitudinal mono-centric study, evaluating newly diagnosed cases of COPD referred to the pulmonology department at the Masih Daneshvari Hospital in Tehran, Iran, was the strong predictive value of the initial blood eosinophilic count on the increasing risk of annual AECOPD events. Eosinophil counts >600 cells/microliter and 900 cells/microliter had a sensitivity of 64.3% and of 71.1% respectively, in predicting the occurrence of more than one AECOPD, annually [28].

The studying acute exacerbations and response (STARR2) study was a non-inferiority, multicentre, double-blind, placebo-controlled, randomized controlled trial, conducted in 14 primary care practices in the UK. It was concluded that blood eosinophil-directed prednisolone therapy of AECOPD is non-inferior to standard care and can be used to safely reduce systemic prednisolone use in clinical practice [29].

“Should All Patients with COPD Exacerbations Receive Oral Steroids?” is the searching question raised by David

Amrol [30]. There is increasing evidence that systemic corticosteroids do have an important role in AECOPD but only in eosinophil-high exacerbations. A nationwide, multicenter, double-blind randomized controlled trial in China confirms that patients with severe AECOPD and low blood eosinophil counts are safely manageable without systemic corticosteroids, reducing the risk of potential side-effects associated with this therapy [31].

DISCUSSION

Approximately, 30% to 50% of those with COPD have at least one exacerbation a year [1]. Even a single AECOPD results in accelerated lung function decline and disease progression [32]. The risk factors for frequent Flare-ups include but not limited to smoking, frequent respiratory infections, cardiovascular disease and advancing age. In the London COPD Cohort, it was concluded that they are not random events but cluster together in such a way that there is a high-risk period for recurrent exacerbation in the 8-week period after a first exacerbation [33]. People experiencing two or more exacerbations per year are regarded as having frequent exacerbations [1]. In the UK Routine Health Care Data Study, increasing number and severity of exacerbations were not only associated with increasing risk of subsequent exacerbations but also linked to all-cause mortality and COPD-related mortality [34]. Such events are episodes of worsening of symptoms, abruptly interrupting the stable course of the disease and are indicative of an unstoppable decline of pulmonary function, with resultant substantial morbidity and mortality.

AECOPD afflict millions of patients with COPD annually and account for substantial health care costs [35]. In addition, they are a major cause of economic and social burden. They have a significant detrimental impact on quality of life. This impact can be evaluated from both individual (patient outcome) and collective (resource burden) perspectives [36]. It has been estimated that recurrent AECOPD have significant impact on direct costs (increased use of drugs, emergency department visits and hospitalization) and indirect costs (absenteeism (loss of productivity due to sick leave) and presenteeism (loss of productivity due to reduced work capacity), early retirement or permanent reduction in work capacity) [37]. There is dire need of preventing and managing AECOPD which is a "*catastrophic event during the clinical course of the disease*" and is acute in onset [38]. The significant role of systemic corticosteroids in the overall management of patients with AECOPD is well proven. They alleviate clinical symptoms by reducing airway inflammation and pulmonary edema, improve pulmonary function, shorten hospitalization(s) and decrease relapse rate. However, to maintain the balance of the desirable and undesirable effects of corticotherapy, the AECOPD should be treated with the lowest possible dose for the minimum duration possible.

CONCLUSION

"The art of practicing medicine lies in remaining in the safe zone within the margins of therapeutic effects and side effects"

Prof. Mahjuba Salam [39]

Corticosteroids have a significant role in the overall management of patients with AECOPD. However, there is compelling evidence that, to avoid serious untoward effects, such patients should be treated with the lowest possible dose for the minimum duration possible. It has been shown that short-course therapy of 40 mg prednisone equivalent, with or after food, per day for 5 days is sufficient for successful management of AECOPD and is non-inferior to previously employed 10-21 days courses. Moreover, it is no longer necessary to taper the dose, which simplifies the treatment and improves compliance.

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CONFLICTS OF INTERESTS

The author declares that there are no conflicts of interest to disclose.

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