

The Best Use of Systemic Corticosteroids in the Intensive Care Units, Review

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Rec date: Jan 13, 2015, Acc date: Jan 29, 2015, Pub date: Feb 25, 2015

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Abstract

Corticosteroids are one of the most common medications that are used in the intensive care units (ICUs); corticosteroids are used for a variety of indications, including septic shock, acute respiratory distress syndrome (ARDS), bacterial meningitis, tuberculous meningitis, lupus nephritis, severe chronic obstructive pulmonary disease (COPD) exacerbations and many others.

Corticosteroids are associated with many severe side effects that affect morbidity and mortality of the patients like increased risk of infections, glucose intolerance, hypokalemia, sodium retention, edema, hypertension, myopathy etc. In order to make the best use of these medications and to minimize the unwanted side effects we should follow some particular protocol. Please keep in our mind that there is controversy about dosing and tapering of steroids, so effort has been made to include the best available evidence.

This review discusses mainly the most common indications of corticosteroids in ICU, dosing of corticosteroids in those indications and how to taper corticosteroids according to the best evidence that recommends their use.

Literature search was done using Medline, BMJ, Uptodate, Chochrane database, Google scholar and the best evidence based guidelines in which steroids are recommended to treat ICU related disorders. Sex hormones are not discussed in this review since its use is rare in the intensive care units.

Keywords: Corticosteroids; Tapering; Steroids; Withdrawal symptoms; Intensive care

Abbreviations

ACTH: Adrenocorticotrophic Hormone; ARDS: Acute Respiratory Distress Syndrome; COPD: Chronic Obstructive Pulmonary Disease; CSF: *Cerebrospinal Fluid*; ETT: *Endotracheal Tube*; ICU: Intensive Care Unit; IPF: Idiopathic Pulmonary Fibrosis; IV: Intravenous; NIH: National Institutes of Health; PEF: Peak Expiratory Flow Rate; PO: per os; SLE: *Systemic Lupus Erythematosus*; TB: Tuberculous.

Introduction

Corticosteroids are molecules produced by the adrenal cortex (the outer part of the adrenal gland), Corticosteroids are classified to either glucocorticoids that are produced in response to stress and have important effects on intermediary metabolism and immune function or mineralocorticoids that maintain the balance of salt and water

within the body. The major glucocorticoid in humans is cortisol which its release is mainly controlled by adrenocorticotrophic hormone (ACTH) and the most important mineralocorticoid is aldosterone which its release is mainly controlled by angiotensin [1]. These medications (glucocorticoids and mineralocorticoids) are associated with severe side effects that sometimes cause their discontinuation in many patients.

We observed many times that we are not using these medications properly in patients by using wrong doses of steroids, using inappropriate tapering regimens and sometimes by using steroids for indications that literature does not support their use in such indications. To avoid the recurrence of medication errors and side effects that are associated with corticosteroids we wrote this review that can be used by health care providers who are working in different Intensive Care Units. This review discusses mainly the most common indications of corticosteroids in ICU, dosing of corticosteroids in those indications and how to taper corticosteroids according to the best evidence that recommends their use (Tables 1 and 2).

Compound	Anti-inflammatory potency	of	Na retaining potency	Duration of action	Equivalent dose
Cortisol	1		1	S	20
Cortisone	0.8		0.8	S	25

Dexamethasone	25	0	L	0.75
Prednisone	4	0.8	I	5
Prednisolone	4	0.8	I	5
Methylprednisolone	5	0.5	I	4
Triamcinolone	5	0	L	4
Betamethasone	25	0	L	0.75

Equivalent doses apply only to oral or intravenous preparations-S Short (8-12 Hrs), L- Long (36-72 Hrs), and I Intermediate (12-36 Hrs). Prednisone and prednisolone are potent glucocorticoids and weak mineralocorticoids. Methylprednisolone and dexamethasone have no mineralocorticoid effect. NOTE: Glucocorticoid doses which provide a mineralocorticoid effect that is approximately equivalent to 0.1 mg fludrocortisone are: prednisone or prednisolone 50 mg, or hydrocortisone 20 mg. Equivalent dose shown is for oral or IV administration. Relative potency for intra-articular or intramuscular administration may vary considerably. Data for cortisol, endogenous corticosteroid hormone, are included for comparison with synthetic preparations listed. Fludri cortisone is not used for an anti-inflammatory effect its minaralo corticoid activity is 125 and its antiinflammatory activity is 10. Prednisone itself is biologically inactive, but it is rapidly converted to the active form prednisolone. However, patients with severe liver disease may have difficulty converting prednisone to prednisolone; in such patients, it is possible that one might not get the same effect from prednisone as from prednisolone. In addition, certain drug interactions can affect the metabolism and bioavailability of prednisone. As an example, phenytoin, barbiturates or rifampin, attenuate the biological effects of glucocorticoids.

Table 1: Comparison of various corticosteroids.

Indication of corticosteroids*	Dosing regimen and tapering §
1) Septic shock	Hydrocortisone at a dose of 200 mg per day as continuous infusion. Should be tapered when vasopressors are no longer required
2) Airway edema	Dexamethasone is 0.5-2 mg/kg divided over 4-6 hrs started 24 hours before extubation and continued for 24 hours after extubation
3) Spinal cord injury	Methylprednisolone should be initiated within eight hours of injury using an initial bolus of 30 mg/kg by IV for 15 minutes followed 45 minutes later by a continuous infusion of 5.4 mg/kg/hour for 23 hours
4) ARDS	loading dose of 1 mg/kg of methyl prnsisolone followed by an infusion of 1 mg/kg/d from day 1 to day 14, then 0.5 mg/kg/d from day 15 to day 21, then 0.25 mg/kg/d from day 22 to day 25, and finally 0.125 mg/kg/d from day 26 to day 28. In the study if the patient was extubated between days 1 and 14, the patient was advanced to day 15 of drug therapy and tapered according to schedule
5) Bacterial meningitis	Dexamethasone 0.15 mg/kg q6 h for 2-4 days with the first dose administered 10-20 min before, or at least concomitant with, the first dose of antimicrobial therapy
6) Tuberculous (TB) meningitis	Patients with grade II or III disease should receive intravenous treatment of dexamethasone for four weeks (0.4 mg per kilogram per day for the first week, 0.3 mg per kilogram per day for the second week, 0.2 mg per kilogram per day for the third week, and 0.1 mg per kilogram per day for the fourth week) and then oral treatment for four weeks, starting at a total of 4 mg per day and decreasing by 1 mg each week Patients with grade I disease should receive lower dose of intravenous dexamethasone therapy with shorter duration of two weeks (0.3 mg per kilogram per day for the first week and 0.2 mg per kilogram per day for the second week) and then four weeks of oral therapy (0.1 mg per kilogram per day for the third week, then a total of 3 mg per day, decreasing by 1 mg each week)
7) Pneumocystis jirovecii pneumonia	Prednisone 40 mg q 12 hrs <i>per os</i> (PO) for 5 days followed by 40 mg q24 hrs PO for 5 days and then 20 mg q24 hrs PO for 11 days
8) Lupus Nephritis	IV pulse methylprednisolone of 1 gram per day for 3 days monthly for 6 months, with 0.5-1.5 mg of oral prednisone per kilogram between pulses
9) COPD exacerbations	Methyl prednisolone succinate IV 125 mg every 6 hours for 3 days then 60 mg daily for 4 days then 40 mg daily for 4 days then 20 mg daily for 4 days.
10) Asthma exacerbations	120 to 180 mg/day of prednisone, prednisolone, or methylprednisolone in 3 or 4 divided doses for 48 hours and then 60 to 80 mg/day until peak expiratory flow rate (PEFR) reaches 70% of predicted
11) Brain edema.	Dexamethasone with initial dose of 10 mg intravenously or orally, followed by 4 mg every 6 hours Corticosteroids should be tapered within 2 to 3 weeks. This can be done by decreasing the dose by 50% every 4 days
12) Anaphylaxis	Prednisone 1 mg/kg up to 50 mg orally or hydrocortisone 1.5-3 mg/kg IV

13) Pulmonary fibrosis	Methyl prednisolone pulse therapy (1000 mg/day for 3 days, 500 mg/day for 2 days, 250 mg/day for 2 days, 125 mg/day for 2 days, and 80 mg/day for 2 days), followed by oral prednisolone (1 mg per kilogram per day, reduced by about 20% each week)
14) Thyroid storm	Hydrocortisone 300 mg intravenous loading followed by 100 mg every 8 hours
15) Myxedema	Intravenous hydrocortisone should be given at a dosage of 100 mg every eight hours
16) Brain dead patients that are candidates for organ donation	Methylprednisolone 15 mg/kg IV every 24 hours
* Many other indications of corticosteroids are not covered like autoimmune hemolytic anemia, prevention and treatment of rejection of transplanted organs, hypercalcemia and many others because their incidence in the ICUs is rare.	
§ There is controversy about dosing and tapering of steroids, so effort has been made to include the best available evidence.	

The Most Common Indications of Corticosteroids in ICU

Septic shock

A plenty of data is available in the literature about using and dosing of corticosteroids in septic shock. In this review we included the recommendation of the latest Surviving Sepsis Campaign guideline that was published in Feb.2013. The guideline recommended not using intravenous hydrocortisone to treat adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this case is not achievable, the intravenous hydrocortisone alone at a dose of 200 mg per day as continuous infusion is suggested, repetitive bolus application of hydrocortisone leads to a significant increase in blood glucose; this peak effect was not detectable during continuous infusion [2]. Other recommendations about corticosteroids that were included in the aforementioned guideline were not using the Adrenocorticotrophic hormone (ACTH) stimulation test to identify adults with septic shock who should receive hydrocortisone, not using corticosteroids for the treatment of sepsis in the absence of shock and corticosteroids should be tapered when vasopressors are no longer required [2].

Airway edema

Laryngeal edema is one of the most common complications in ICU that can cause stridor, dyspnoea and reintubation. These complications, especially reintubation, can result in many adverse outcomes, including longer hospital stay, higher costs and increased mortality. Risk factors of laryngeal edema and the development of postextubation stridor include older age, female gender, low Glasgow Coma Scale score, excessive *endotracheal tube* (ETT) size, elevated Acute Physiologic and Chronic Health Evaluation II score and a prolonged intubation period (more than 36 hrs) [3].

Corticosteroids (mainly dexamethasone and methylprednisolone) were shown to be effective in decreasing the incidence of postextubation stridor in adult patients at high risk to develop airway obstruction [3].

The dose of dexamethasone is 0.5-2 mg/kg divided over 4-6 hrs started 24 hours before extubation and continued for 24 hours after extubation [4]. Current evidence also suggests that prophylactic intravenous (IV) methylprednisolone therapy (20-40 mg every 4-6 h) should be considered 12-24 hours prior to a planned extubation in patients at high-risk for postextubation laryngeal edema [5].

Usually laryngeal edema occurs within eight hours after extubation, that's why the administration of steroids immediately after extubation might be too late. The benefit of steroids before selected extubation is assumed to be due to protection against or treating mucosal edema in the glottic region caused by pressure or irritation from the endotracheal tube [6].

Spinal cord injury

A phase three randomized trial proved the efficacy of methylprednisolone sodium succinate in enhancing sustained neurologic recovery after spinal cord injury [7]. Methylprednisolone should be initiated within eight hours of injury using an initial bolus of 30 mg/kg by IV for 15 minutes followed 45 minutes later by a continuous infusion of 5.4 mg/kg/hour for 23 hours. If the maintenance therapy is extended for 48 hours, further improvement in motor function recovery has been shown to occur. This is evident when the initial bolus dose could only be administered three to eight hours after the trauma.

ARDS

Corticosteroids were studied to prevent and to treat early and late ARDS. While using corticosteroids in preventing ARDS showed higher mortality and rate of ARDS development, there is a mixed data about its role in treating early ARDS. These drugs have no benefits in late stage of ARDS and are associated with bad outcomes [8].

Since the direction of the systemic inflammatory response is established in the early stage of ARDS, we suggest to use low-dose methylprednisolone (1 mg/kg/d) tested in early ARDS (within 72 h of diagnosis) since it was tested and was shown to down regulate systemic inflammation and lead to earlier resolution of pulmonary organ dysfunction and a reduction in duration of mechanical ventilation and ICU stay according to a randomized controlled trial that was done by Meduri [9].

The regimen that was used in the aforementioned study is the beginning of administration of a loading dose of 1 mg/kg of methyl prnsinolone followed by an infusion of 1 mg/kg/d from day 1 to day 14, then 0.5 mg/kg/d from day 15 to day 21, then 0.25 mg/kg/d from day 22 to day 25, and finally 0.125 mg/kg/d from day 26 to day 28. In the study if the patient was extubated between days 1 and 14, the patient was advanced to day 15 of drug therapy and tapered according to schedule [9].

Bacterial meningitis

Corticosteroids reduce brain edema, intracranial hypertension and meningeal inflammation in experimental models of bacterial meningitis. It is also proven to be associated with reduced mortality and lower frequency of hearing loss and neuropsychological sequelae in adult patients [10].

However, there is a concern about impaired antibiotics penetration as a consequence of dexamethasone therapy [11].

Dexamethasone (0.15 mg/kg q6 h for 2–4 days with the first dose administered 10–20 min before, or at least concomitant with, the first dose of antimicrobial therapy) in adults with suspected or proven pneumococcal meningitis [10]. Dexamethasone should only be continued if the *cerebrospinal fluid* (CSF) Gram stain reveals gram-positive diplococci, or if blood or CSF cultures are positive for *S. pneumoniae* [10].

Adjunctive dexamethasone should not be given to adult patients who have already received antimicrobial therapy [10].

Delayed treatment is not beneficial as dexamethasone does not reverse existing brain edema or intracranial hypertension in later stages of meningitis [11].

Tuberculous meningitis

As in bacterial meningitis corticosteroids are also effective in reducing the risk of death or disabling residual neurological deficit. However, corticosteroids in TB meningitis are used for prolonged period (6 to 8 weeks) rather than 2 to 4 days (as in bacterial meningitis), so all patients with TB meningitis receive adjunctive corticosteroids regardless of disease severity at presentation [12]. Dexamethasone and prednisolone were mainly given for TB meningitis with variable dosing regimens and there is no data from controlled trials comparing different corticosteroid regimens [13].

There is insufficient evidence to recommend routine adjunctive corticosteroids for all patients with tuberculomas without meningitis, or with spinal cord tuberculosis. However, they may be helpful in those patients whose symptoms are not controlled, or are worsening, on anti-tuberculosis therapy, or who have acute spinal cord compression secondary to vertebral tuberculosis [12].

Patients with grade II or III disease should receive intravenous treatment of dexamethasone for four weeks (0.4 mg per kilogram per day for the first week, 0.3 mg per kilogram per day for the second week, 0.2 mg per kilogram per day for the third week, and 0.1 mg per kilogram per day for the fourth week) and then oral treatment for four weeks, starting at a total of 4 mg per day and decreasing by 1 mg each week [12].

Patients with grade I disease should receive lower dose of intravenous dexamethasone therapy with shorter duration of two weeks (0.3 mg per kilogram per day for the first week and 0.2 mg per kilogram per day for the second week) and then four weeks of oral therapy (0.1 mg per kilogram per day for the third week, then a total of 3 mg per day, decreasing by 1 mg each week) [12].

Corticosteroids are not recommended in other forms of Tuberculosis except in tuberculous pericarditis where some evidence suggests its use in this indication [14].

Pneumocystis jirovecii pneumonia

Corticosteroids are used as adjunctive initial therapy only in patients with HIV infection who have severe *P. jirovecii* pneumonia as defined by an arterial-alveolar O₂ gradient that exceeds 35 mm Hg or a room air arterial oxygen pressure of less than 70 mm Hg or. In patients without HIV infection adjunctive steroids are not recommended [15].

During antimicrobial therapy microbial degradation and clearance may result in further inflammation that can exacerbate a severe inflammatory response that includes the production of cytokines and other inflammatory markers and cells to dying organisms in the lungs that often worsens after therapy is begun. Adjunctive steroids can blunt this inflammatory response that result in lung tissue damage [15]. Consequently, this will lead to good outcomes by improving survival, decreasing episodes of respiratory decompensation and decreasing the need for mechanical ventilation.

Prednisone 40 mg q 12 hrs *per os* (PO) for 5 days followed by 40 mg q24 hrs PO for 5 days and then 20 mg q24 hrs PO for 11 days [15].

Methylprednisolone at 75% of the respective prednisolone dose should be administered if intravenous therapy is necessary [15].

Lupus Nephritis

Corticosteroid therapy is a major component in therapeutic regimens for *systemic lupus erythematosus* (SLE). It is known to suppress the clinical expression of disease and is considered by many to be a major factor in the improved survival and prognosis. Although most clinical trials of corticosteroid therapy in SLE patients have been conducted in patients with severe lupus nephritis, the evidence suggests that they are also effective in the treatment of severe and life threatening cases of, pneumonitis, polyserositis, vasculitis, thrombocytopenia, CNS disease and other clinical manifestations [16].

The IV pulse methylprednisolone is used for life- or organ-threatening disease which is defined by courses of 1 gram per day for 3 days monthly for 6 months, with 0.5-1.5 mg of oral prednisone per kilogram between pulses, to control both renal and extra-renal manifestations. It is usually used as initial management of active nephritis, sole therapy to avoid cumulative adverse effects of long-term daily corticosteroid therapy, or regimen for exacerbations of severe cases not responsive to daily oral steroids [17,18].

Severe COPD exacerbations

Intravenous corticosteroids are helpful in the treatment of severe exacerbations of COPD. Corticosteroid therapy can improve lung function (FEV₁) and hypoxemia (PaO₂), reduces recovery time, ICU stay, cost of admission and may reduce the risk of early relapse [19]. The optimal dose and duration of steroids in COPD exacerbations are unknown. According to a recent meta-analysis the low-dose regimen (initial dose 30-80 mg/day of prednisolone) is proper for treating COPD exacerbations. However, the high-dose group did not show obviously higher risk of side effects [20].

We included the recommendation of the Systemic Corticosteroids in Chronic Obstructive Pulmonary Disease Exacerbations (SCCOPE) trial [21].

Methylprednisolone succinate IV 125 mg every 6 hours for 3 days than 60 mg daily for 4 days than 40 mg daily for 4 days than 20 mg daily for 4 days.

Severe asthma exacerbation

In severe asthma there is airway obstruction and airway inflammation. In order to reduce the inflammation systemic corticosteroids must be included as part of the regimen in all patients with acute severe asthma.

Receptor-binding affinities of lung corticosteroid receptors are reduced in the face of airway inflammation, that's why multiple daily dosing of systemic corticosteroids for the initial therapy of acute asthma exacerbations appears necessary. As in severe COPD exacerbations, the optimal dose and duration of steroids in severe asthma exacerbations are unknown. The oral and IV routes are equally effective, so that the oral route may be used if patients can swallow. However, in ICU settings patients are intubated and mechanically ventilated so we prefer to use the intravenous form [16].

Regarding the duration a 7 day-day course in adults has been found to be as effective as 14-day course [22].

The National Institutes of Health (NIH) guidelines recommend 120 to 180 mg/day of prednisone, prednisolone, or methylprednisolone in 3 or 4 divided doses for 48 hours and then 60 to 80 mg/day until peak expiratory flow rate (PEFR) reaches 70% of predicted. The anti-inflammatory effect of corticosteroids as measured by improvement in pulmonary function is not immediate and can take up to 24 hours to occur [23].

Brain edema

Four types of cerebral edema are present: the vasogenic cerebral edema that results from an increased permeability of the endothelium of cerebral capillaries to albumin and other plasma proteins due to the breakdown of the tight endothelial junctions; the cytotoxic cerebral edema in which the blood brain barrier is not affected but there is imbalance in cellular metabolism that weakens the functioning of the sodium and potassium pump in the glial cell membrane; the osmotic cerebral edema that results when the blood becomes diluted; and the interstitial cerebral edema that results in obstructive hydrocephalus

Glucocorticoids are very effective in reducing the vasogenic edema that occurs in many clinical conditions like inflammatory conditions, tumors, and other disorders. However, steroids are not helpful to treat cytotoxic edema and are harmful in patients with brain ischemia [24]. In patients with severe head injury the use of glucocorticoids are not recommended for improving outcome or reducing *Intracranial pressure (ICP)* [25].

Dexamethasone is the preferred agent due to its very low mineralocorticoid activity. The usual initial dose is 10 mg intravenously or orally, followed by 4 mg every 6 hours [25].

Corticosteroids should be tapered within 2 to 3 weeks. This can be done by decreasing the dose by 50% every 4 days [25].

Anaphylaxis

There are many theoretical benefits of using steroids in patients with anaphylaxis. However, there are no placebo-controlled trials to confirm these assumed benefits of steroids in anaphylaxis. The use of prednisone 1 mg/kg up to 50 mg orally or hydrocortisone 1.5-3 mg/kg IV is suggested [26].

Pulmonary fibrosis

The latest international evidence-based guideline on the diagnosis and management of idiopathic pulmonary fibrosis (IPF) that was published in 2011 recommended against the use of corticosteroid monotherapy in patients with IPF. Also the recommendation for corticosteroids in patients with acute exacerbation of IPF is weak; that is, corticosteroids should be used in the majority of patients with acute exacerbation of IPF, but not using corticosteroids may be a reasonable choice in a minority [27]. Corticosteroids (e.g. prednisone, methylprednisolone) are used in the majority of patients who suffer an acute exacerbation of IPF, usually in pulse doses. We recommend using methyl prednisolone pulse therapy (1000 mg/day for 3 days, 500 mg/day for 2 days, 250 mg/day for 2 days, 125 mg/day for 2 days, and 80 mg/day for 2 days), followed by oral prednisolone (1 mg per kilogram per day, reduced by about 20% each week) [28].

Thyroid storm

The benefits of steroids in thyroid storm are mainly blocking T4-to-T3 conversion and prophylaxis against relative adrenal insufficiency.

Hydrocortisone 300 mg intravenous loading followed by 100 mg every 8 hours [29].

Myxedema

In myxedema there is a possibility of secondary hypothyroidism and associated hypopituitarism, so hydrocortisone should be administered until adrenal insufficiency is excluded. Intravenous hydrocortisone should be given at a dosage of 100 mg every eight hours. Not treating adrenal insufficiency with hydrocortisone may precipitate adrenal crisis. Before therapy a random cortisol level should be drawn, and if not depressed, the hydrocortisone can be stopped without tapering [30].

Brain dead patients who are candidates for organ donation

Methylprednisolone 15 mg/kg IV every 24 hours as part of the triple hormonal therapy that includes the use of levothyroxine and vasopressin infusion [31].

Conclusions

Corticosteroids are one of the most common medications that are used for a variety of indications in the intensive care units. Due to the diverse adverse effects of corticosteroids that affect the morbidity and mortality of critically ill patients and because of the high number of medication errors that are associated with these medications, we wrote this review that can be used as a guide for health care professionals who are taking care of critically ill patients that are receiving corticosteroids. This review covers mainly the most common indications of corticosteroids in ICU and also how to taper corticosteroids according to the best evidence that recommends their use. Many other indications of corticosteroids are not covered like autoimmune hemolytic anemia, prevention and treatment of rejection of transplanted organs, hypercalcemia and many others because their incidence in the ICUs is rare.

Competing Interests

The authors declare no financial, professional, political, personal, religious, ideological, academic, intellectual, commercial or other

relationship that would be a conflict of interest in the interpretation of any information related to this review.

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