

CORTICOSTEROIDS USAGE IN THE INTENSIVE CARE UNIT: SPECIFIC RECOMMENDATIONS BASED ON RECENT EVIDENCE

AWAD AHA*, ABDELBAKY AM, SHOAI B MI, ELMASRY WG

Medical Intensive Care Unit, Rashid Hospital, Dubai Health, Dubai UAE

*Corresponding author's email address: ahmedhossam79@gmail.com

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ABSTRACT

Corticosteroids are a class of drugs that mimic the effects of cortisol, a hormone naturally produced by the adrenal glands. They exert a wide range of effects on the body's immune, metabolic, and inflammatory responses. In the context of critically ill patients in the intensive care unit (ICU), corticosteroids are frequently utilised due to their potent anti-inflammatory and immunosuppressive properties. In the ICU setting, corticosteroids are commonly employed to manage various conditions such as severe sepsis, acute respiratory distress syndrome (ARDS), exacerbations of chronic obstructive pulmonary disease (COPD), and adrenal insufficiency. Their mechanism of action involves suppression of pro-inflammatory cytokines, inhibition of leukocyte migration, and stabilisation of cell membranes, among other effects. The choice of corticosteroid, dosing regimen, and duration of therapy in the ICU depends on the specific clinical condition being treated and individual patient factors. For instance, corticosteroids such as hydrocortisone are often administered to attenuate the systemic inflammatory response and improve hemodynamic stability in the management of septic shock. Dosing may vary but commonly involves an initial bolus followed by continuous infusion or intermittent dosing. In ARDS, corticosteroids may reduce lung inflammation and prevent further tissue damage. Methylprednisolone is a commonly utilised corticosteroid in this context, with dosing typically initiated at a high dose and then tapered gradually based on clinical response. For patients with exacerbations of COPD, corticosteroids help to reduce airway inflammation and improve lung function. Oral or intravenous corticosteroids such as prednisone or methylprednisolone are often prescribed for a short duration during exacerbations. In cases of adrenal insufficiency, corticosteroid replacement therapy is essential to restore physiological cortisol levels and prevent adrenal crisis. Hydrocortisone is the corticosteroid of choice in this scenario, with dosing adjusted based on the degree of adrenal dysfunction and stress level. Despite their efficacy, corticosteroids are associated with a range of potential adverse effects, including immunosuppression, hyperglycemia, fluid retention, electrolyte abnormalities, and increased risk of infection. Therefore, carefully monitoring patients receiving corticosteroid therapy in the ICU is paramount, with adjustments to minimise risks while optimising therapeutic benefits. In summary, corticosteroids play a crucial role in managing critically ill patients in the ICU, offering potent anti-inflammatory and immunomodulatory effects. However, their use requires careful consideration of the underlying condition, patient characteristics, and potential adverse effects, with dosing and duration tailored to individual needs.

Keywords: Adrenal Insufficiency, Acute Respiratory Distress Syndrome (ARDS), Chronic Obstructive Pulmonary Disease (COPD) Exacerbations, Corticosteroids, Immunomodulatory, Septic Shock

Pharmacology and Basic Aspects of Corticosteroids:

Hormones called corticosteroids are produced from cholesterol in the adrenal cortex. They fall into two categories: glucocorticoids and mineralocorticoids. Corticosteroids play a role in multiple metabolic processes, such as water and electrolyte equilibrium, anti-inflammatory qualities, blood pressure regulation, immunosuppression, and control of glycemic levels, among many others. Exogenous and synthetic corticosteroids display both mineralocorticoid and glucocorticoid qualities to different extents. Most circulating hormones attach to plasma proteins, including corticosteroid binding globulin (CBG), albumin, and alpha-1 acid protein. Critically sick individuals (e.g., septicemia, severe burns, or acute myocardial infarction) have a fast reduction in CBG plasma concentration, leading

to an increase in free glucocorticoids capable of controlling inflammation, gluconeogenesis, and stress. Cortisol's effectiveness may be impacted by adrenal insufficiency and corticosteroid resistance, leading to an aggravated and extended inflammatory response. Exogenous corticosteroids penetrate cells through the glucocorticoid receptor and act in the nucleus via binding to DNA, thus reducing the production of inflammatory chemicals. Moderate or high dosages may cause increased infection rates, leading to more extended ICU stays, prolonged ventilator time, and elevated mortality. Large doses can also cause myopathies, gastrointestinal bleeding, retention of fluids, and acute psychosis. This article reviews corticosteroid pharmacology and provides evidence-based guidelines for ICU use.

Table 1: Drugs and Equivalent Dosage of Corticosteroids

	Equivalent dose of glucocorticoid (mg)	Potency relative to hydrocortisone		Half-life (hours)
		Anti-inflammatory	Mineralocorticoid	
Glucocorticoids				
Short-acting				
Hydrocortisone	20	1	1	7-12
Intermediate-acting				
Prednisone	5	4	0.8	10-36
Prednisolone	5	4	0.8	10-36

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Methylprednisolone	4	5	0.5	10-36
Long-acting				
Dexamethasone	0.75	25	0.5	30-50
Mineralocorticoid				
Fludrocortisone	N/A	15	130	25-35

Septic shock

For more than 50 years, corticosteroids have been studied as a supportive treatment for septic shock. In the most recent meta-analysis, the relative risk (RR) for mortality at ninety days among individuals with shock evaluating hydrocortisone to placebo was 0.93. This value was 0.86 for using hydrocortisone and fludrocortisone and 0.96 when lacking fludrocortisone. Corticosteroids should be administered once a norepinephrine dosage of 0.25 mcg/kg/min is attained.

Community-acquired pneumonia

A randomised controlled investigation found that individuals suffering from severe community-acquired pneumonia (CAP) who received invasive or non-invasive mechanical ventilation using a minimum of 5 cm H₂O of PEEP, high-flow nasal cannulas, PaO₂/FiO₂ fewer than 300, and Pneumonia Severity Index (PSI) of a minimum of 130 points had a lower mortality rate. The study indicated that patients using hydrocortisone had a lower mortality rate (absolute difference, -5.6%, 95% CI, -9.6 to -1.7; p=0.006), fewer intubations (HR, 0.59; 95% CI, 0.40 to 0.86), and Reduced usage of vasopressors (HR, 0.59; 95% CI, 0.43 to 0.82) (1). A meta-analysis found that corticosteroids decreased overall mortality among CAP (RR: 0.69, 95% CI: 0.53-0.89), particularly in young patients (2, 3).

A review of the literature and meta-analyses found that administering 40 mg of prednisone twice per day for five days, followed by 40 mg every day for the following five days and 20 mg every day for the remaining eleven days, resulted in a lower mortality rate among individuals with pneumocystis jirovecii pneumonia (21 days) (RR 0.59, 95% CI, 0.41 to 0.85) (4).

COVID 19 Pneumonia

The RECOVERY trial on COVID-19 found that administering 6 mg of dexamethasone each day to patients getting oxygen supplementation or respiratory support reduced 28-day mortality rates in those having IMV (RR 0.64; 95% CI, 0.51 to 0.81) as well as those getting oxygen support (RR 0.82; 95% CI, 0.72 to 0.94) (5).

A meta-analysis evaluating the usage of corticosteroids in COVID-19 pneumonia patients found a reduction in mortality (OR 0.72, 95% CI 0.57-0.87). This group had higher rates of viral clearance, superinfections, and antibiotic usage. (6).

Acute Respiratory Distress Syndrome (ARDS).

Corticosteroids should only be used in individuals with acute respiratory distress syndrome (ARDS) if the aetiology is CAP, COVID-19, pneumocystis jirovecii, or diffuse alveolar haemorrhage. Corticosteroids should not be started after 14 days of Invasive Mechanical Ventilation (IMV), and potential side effects such as immunosuppression and bacterial, fungal, parasitic, or mycobacterial infections should be monitored. (7)

Post-extubation laryngeal edema

If a patient fails the cuff leak evaluation but is otherwise ready for extubation, corticosteroid medication should be administered at least four hours before extubation. Giving four doses of 20 mg methylprednisolone over twelve hours reduces Postextubation laryngeal oedema (3% vs 22%, p < 0.0001), overall reintubations (4% vs 8%, p = 0.02), and reintubations due to laryngeal oedema (8% vs 54%, p = 0.005) (8).

COPD Exacerbation

The GOLD 2024 recommendations propose systemic corticosteroids for COPD exacerbations for a maximum period of five days and a daily dosage of 40 mg of prednisone. This therapy is equally successful when administered enterally or parenterally. (9).

Corticosteroids can lower the incidence of recurrence and hospitalisations in COPD patients. Compared to placebo, there was a substantial improvement in lung function outcomes and a lower probability of unsuccessful treatment in both outpatient care and hospitalized patients (OR 0.48; 95% CI 0.35, 0.67), but no significant change in mortality. (10).

Acute Severe Asthma

Inhaled corticosteroids have long been proposed for treating aggravated asthma symptoms. This treatment offers benefits such as immediate symptom alleviation, lesser chance of severe asthma episodes, reduced hospitalisation, and prevention of oral corticosteroid use. (11). If inhaled corticosteroids do not help symptoms throughout an asthma attack, patients should consider taking oral corticosteroids. The suggested dose for prednisone is 40-50 mg/day for 5-7 days. (12). Corticosteroids may be administered intravenously, orally, intramuscularly, or inhaled during the first hour of emergency room admission for patients with asthma exacerbation. This approach has been demonstrated to cut hospitalisation risk by 50% (13).

Adrenal Crisis

Adrenal crisis or insufficiency is an immediate decline in health caused by absolute hypotension (systolic blood pressure less than 100 mmHg) that resolves with parenteral glucocorticoids. The signs and symptoms improve within two hours (14). There are no supervised clinical studies for this therapy. The administration of injectable hydrocortisone is recommended. The medication is given as a bolus shot of 100 mg IV or IM (while seeking IV access). After the first bolus, 200 mg of hydrocortisone should be given daily via continuous IV infusion or every six hours by IV or IM injection with a 50 mg dosage (15).

Bacterial Meningitis

A comprehensive review of randomised controlled trials on bacterial meningitis indicates that individuals treated with dexamethasone had considerably reduced incidence of severe hearing loss compared to placebo. (16). Corticosteroids effectively treated Streptococcus pneumoniae meningitis with a decreased fatality rate (RR 0.84; 95% CI: 0.72 to 0.98). Most trials used a four-day dexamethasone treatment (0.3 or 0.6 mg/kg/day) with four doses per day (16).

Tuberculous Meningitis

A systematic review and meta-analysis of randomised controlled trials on tuberculous meningitis found that corticosteroids lower mortality risk by twenty-five per cent between 2 months to 2 years of t (RR 0.75; 95% CI 0.65 to 0.87). Most studies used a one-month dexamethasone dosage decrease protocol, with the following distribution: In weeks 1 to 4, provide 0.4 mg/kg/day for seven days, 0.3 mg/kg/day for Seven days, and 0.1 mg/kg/day for seven days. (17).

Cysticercosis

To address widespread cerebral oedema caused by viable intraparenchymal neurocysticercosis, anti-inflammatory therapy with corticosteroids is recommended. This therapy is recommended before starting anti-parasitic medicines, with a strong to moderate recommendation. (18). For subarachnoid neurocysticercosis, high-dose steroids are recommended along with extensive antiparasitic treatment, and, in some instances, surgery is required. Although dosages are not entirely standardized, administering dexamethasone at 0.2 mg/kg/day is recommended (19).

Myxedema Coma and Thyroid Storm

Myxedema coma is treated mainly with thyroid hormones. (20). For the management of myxedema coma, corticosteroids should be administered intravenously at suitable stress doses before

levothyroxine is given. (21). It is important to emphasise that this suggestion lacks evidence from controlled clinical studies. To treat thyroid storm, start with a loading dose of 300 milligrams of hydrocortisone and then continue to 100 milligrams every 8 hours. (22). However, the data supporting this suggestion comes from something other than large-scale clinical research. A countrywide retrospective investigation found that corticosteroids do not increase

survival in thyroid storm individuals. Furthermore, they cause glycemic instability and an increased requirement for insulin. (23).

Alcoholic Hepatitis

A comprehensive review and meta-analysis found that corticosteroid treatment (prednisolone 40 milligrams for a period of 28 days) significantly lowered death rates when compared with placebo (OR=0.58; 95% CI, 0.34-0.98; P=0.04) (24).

Table 2: Corticosteroid use and doses in multiple diseases

Disease	Dose
CNS tumor	Dexamethasone 6-24mg q/24hr
Bacterial meningitis	0.4-0.6mg/kg/day qid
Tuberculous meningitis	0.4mg/kg/day for the first week, then a reduction of 0.1mg/kg/week
Cysticercosis	Dexamethasone 0.2mg/kg/day
Exacerbated COPD	Prednisolone 40mg every day for five days
Exacerbated Asthma	Prednisolone 40 to 50 mg every day for 5 -7 days
Diffuse alveolar hemorrhage	Methylprednisolone 30mg per kg per day for 3 to 5 days
Septic shock	Start when norepinephrine dose is >0.25mcg/kg/min - Hydrocortisone 50mg every six hours for seven days - Fludrocortisone 50mcg per oral every day
Alcoholic hepatitis	Prednisolone 40mg every day for 28 days
Myxedema coma	Hydrocortisone loading dose of 300mg followed by 100mg every eight hourly
Post-extubation laryngeal edema	Methylprednisolone 4 doses of 20mg over 12 hourly
Community-acquired pneumonia	Hydrocortisone 200 mg daily for 5-7 days
Pneumocystis jiroveci pneumonia	Prednisolone 40mg every 12 hours for five days, followed by 40 mg every day for five days, then 20mg every day for 11 days.
Covid 19 pneumonia	Dexamethasone 6mg every day for ten days
Adrenal crisis	Hydrocortisone, 100mg bolus, followed by 200mg every 24-hour
HELLP syndrome	- No significant betterment in clinical results for both mother and baby - Improvement in platelet count by betamethasone 12mg every 12 hours for two days
Fetal lung maturation in women at risk of pre-term birth	Betamethasone 12 mg IM every day for two days OR Dexamethasone 6mg IM every six hours for one day

Central Nervous System Tumors

Dexamethasone is currently used for the management of malignant brain tumours. It treats peritumoral oedema and symptoms associated with intracranial hypertension. Doses of four milligrams every six hours for 8 to 19 days have been shown to reduce peritumoral oedema volume by 26% on average. (25). A treatment plan of four milligrams per 6 hours for seven days, then a maintenance dosage of 4 mg/day till the patient underwent surgery or radiation, resulted in a 56% decrease in oedema volume (26).

Diffuse Alveolar Hemorrhage

Diffuse alveolar haemorrhage (DAH) is a severe pulmonary complication of autoimmune diseases like systemic lupus erythematosus, vasculitis with antineutrophil cytoplasmic antibodies (ANCA), antiphospholipid syndrome, and anti-glomerular basement membrane syndrome. (27). Corticosteroids are indicated in around 98% of cases. Corticosteroids are primarily used to alleviate acute inflammation in the alveolar endothelial cells. (28). However, current treatment recommendations are founded on retrospective research and anecdotal findings. After the administration of high-dose corticosteroids, death rates still reach 50% (29).

HELLP Syndrome

According to a meta-analysis, there is no noticeable difference in clinical results for pregnant women and neonates suffering from HELLP syndrome. (30). Betamethasone at a dose of 12 mg per 24 hours for two days significantly improved platelet count compared to a placebo group. (31).

Fetal Lung Maturity in Women at Risk of Preterm Birth

Prenatal administration of steroids decreases the likelihood of respiratory distress (OR 0.66; 95% CI 0.54 to 0.82; p<0.001), mortality (OR 0.64; 95% CI 0.50 to 0.81; p<0.001), intraventricular haemorrhage (OR 0.67; 95% CI 0.54 to 0.83; p<0.001),

periventricular leukomalacia (OR 0.65; 95% CI 0.47 to 0.92; p<0.001), and necrotising enterocolitis when compared to unexposed premature babies. Corticosteroids are most beneficial when used before one to seven days of a suspected high risk of premature birth. If administered less than 24 hours before delivery, their effects may be inadequate. (32). Betamethasone has been demonstrated to reduce intraventricular haemorrhage significantly. Treatment involves administering intramuscular betamethasone 12 mg every 24 hours for two doses or dexamethasone six milligrams every 6 hours for four sessions. (33). An alternative approach is to provide 500 mg of hydrocortisone intravenously every 6 hours.

CONCLUSION

Corticosteroids are beneficial in treating numerous diseases in the ICU (Table 2). However, research studies are needed to determine the appropriate dosage and duration for autoimmune and endocrine problems.

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Data Availability statement

All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department concerned.

Consent for publication

Approved

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Not applicable

CONFLICT OF INTEREST

The authors declared the absence of a conflict of interest.

AUTHOR CONTRIBUTION

AHMED HOSSAMELDIN AHMED AWAD

Study Design, Review of Literature.

Conception of Study, Development of Research Methodology Design,

Study Design, Review of manuscript, final approval of manuscript.

AHMED MOHAMMED ABDELBAKY

Conception of Study, Final approval of manuscript.

Manuscript revisions, critical input.

MOHAMMED IBRAHIM SHOAI B

Data entry and data analysis, as well as drafting the article.

Coordination of collaborative efforts.

WAEEL GHALY ELMASRY

Study Design, Review of Literature.

Manuscript revisions, critical input.

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