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Corticosteroids in the Intensive Care Unit: Evidence-Based Recommendations

Corticosteroids are commonly used drugs in multiple diseases and conditions of critically ill patients. In this article, we review the pharmacology of corticosteroids and provide recommendations for their use in the ICU based on the best available evidence.

Corticosteroids: Pharmacology and General Aspects

Corticosteroids are hormones synthesised in the adrenal cortex from cholesterol. They are classified into mineralocorticoids and glucocorticoids. Their functions include maintaining water and electrolyte balance, anti-inflammatory effects, regulation of blood pressure, immunosuppression, glycaemic control, and other metabolic pathways (Young and Marsh 2018). Exogenous or synthetic corticosteroids exhibit glucocorticoid and mineralocorticoid properties to varying degrees (**Table 1**). Most circulating steroids bind to plasma proteins such as corticosteroid-binding globulin (CBG), albumin, and alpha-1 acid glycoprotein. In critically ill patients (e.g., sepsis, severe burns, or acute myocardial infarction), CBG rapidly decreases its plasma concentration, increasing the amount of free glucocorticoids that can control the inflammatory response, gluconeogenesis, and stress (Gardill et al. 2012). The effect of cortisol may be insufficient due to adrenal dysfunction and corticosteroid resistance to counteract an exaggerated and prolonged inflammatory response (Keh 2016). Exogenous corticosteroids enter cells by binding to the glucocorticoid receptor, exerting their action in the nucleus, where they bind to DNA, generating down-regulation of the release of inflammatory substances (Barnes 2011). Side effects at moderate or high doses may be associated with an increased infection rate, longer ICU stay, more ventilator days, and a tendency towards higher mortality (Britt et al. 2006), as well as myopathies, gastrointestinal bleeding, fluid retention, and

psychotic reactions (Yasir et al. 2023).

In this article, we review the pharmacology of corticosteroids and provide recommendations for their use in the ICU based on the best available evidence.

Septic Shock

Corticosteroids have been under evaluation as adjunctive therapy for septic shock for over 50 years. In the latest meta-analysis, the relative risk (RR) for 90-day mortality in patients with septic shock, comparing hydrocortisone to placebo, was 0.93 (95% CI, 0.82 to 1.04; $p=0.22$). This value was 0.86 (95% CI, 0.79 to 0.92) for the combination of hydrocortisone and fludrocortisone and 0.96 (95% CI, 0.82 to 1.12) without fludrocortisone (Pirrachio 2023). It is recommended to initiate corticosteroids when a norepinephrine dose of 0.25 mcg/kg/min is reached.

Community-Acquired Pneumonia and *Pneumocystis jirovecii* Pneumonia

A randomised controlled study demonstrated a decrease in mortality among patients with severe community-acquired pneumonia (CAP), defined as the initiation of invasive mechanical ventilation (IMV) or non-invasive mechanical ventilation with at least 5 cm H₂O of PEEP, administration of high-flow nasal cannulas, PaO₂/FiO₂ less than 300, and PORT PSI of at least 130 points. The study found a reduction in mortality in patients who were administered hydrocortisone compared to placebo



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Agent	Potency		Dose		PB	Metabolism	Indications
	GC	MC	Equivalent	Length			
Glucocorticoids							
Short action							
Hydrocortisone	1	1	100	8-12 h	>90%	CYP3A4/GP	Septic shock, adrenal crisis, myxoedema coma
Inhaled Budesonide	ND	ND	ND	2-4 h	85-90%	CYP3A4	Asthma exacerbation
Intermediate action							
Methylprednisolone	5	0.25	20	12-36 h	76.8%	CYP3A3	ARDS, postextubation laryngeal oedema
Prednisone	4	0.6	25	12-36 h	70-90%	CYP3A4	COPD exacerbation, alcoholic hepatitis, <i>Pneumocystis jirovecii</i> pneumonia
Long action							
Dexamethasone	25	0	3.75	36-72 h	77%	CYP3A4/GP	COVID-19 pneumonia, bacterial meningitis, CNS tumours
Betamethasone	25	0	3.75	36-72 h	64%	CYP3A4	Foetal lung maturation
Mineralocorticoids							
Fludrocortisone	10	125	ND	12-36 h	70-80%	CYP3A4	Septic shock

Table 1. Drugs dosage, mechanism of action, and indications of corticosteroids

GC: glucocorticoid, MC: mineralocorticoid, GP: glycoprotein P, PB: protein binding, PJP: *Pneumocystis jirovecii* pneumonia *Hydrocortisone equivalent dose

(absolute difference, -5.6%, 95% CI, -9.6 to -1.7; $p=0.006$), a decrease in intubations (HR, 0.59; 95% CI, 0.40 to 0.86), and a reduction in the use of vasopressors (HR, 0.59; 95% CI, 0.43 to 0.82) (Dequin et al. 2023). A systematic review with meta-analysis demonstrated that the use of corticosteroids reduced the risk of all-cause mortality in CAP (RR: 0.69, 95% CI: 0.53-0.89), especially in younger patients (Cheema et al. 2024; Chaudhuri et al. 2024).

In patients with *pneumocystis jirovecii* pneumonia, a systematic review and meta-analysis showed a decrease in mortality associated with the administration of 40 mg of prednisone twice daily for five consecutive days, followed by 40 mg once daily for the next five days and 20 mg once daily for the remaining 11 days (21 days) (RR 0.59, 95% CI, 0.41 to 0.85) (Hannah et al. 2015).

COVID-19 Pneumonia

In the RECOVERY study on COVID-19, the administration of 6 mg of dexamethasone per day to patients receiving supplementary oxygen or respiratory support was associated with a reduction in 28-day mortality in those undergoing IMV (RR 0.64; 95% CI, 0.51 to 0.81) and those receiving oxygen therapy (RR 0.82; 95% CI, 0.72 to 0.94) (RECOVERY Collaborative Group 2021). A systematic review and meta-analysis on the use of corticosteroids in patients with COVID-19 pneumonia demonstrated a decrease in mortality with the use of corticosteroids (OR 0.72, 95% CI 0.57-0.87). Viral clearance, superinfections, and the use of antibiotics were more common in this cohort (van Paassen et al. 2020).

Acute Respiratory Distress Syndrome

The use of corticosteroids in patients with acute respiratory distress syndrome (ARDS) is reserved for the following causes: CAP, COVID-19, *pneumocystis jirovecii* and diffuse alveolar haemorrhage (lack of evidence). Initiating corticosteroids after 14 days of IMV is not recommended, and adverse effects should be monitored, including immunosuppression, bacterial, fungal, parasitic, or mycobacterial infections (Qadir et al. 2024).

Postextubation Laryngeal Oedema

In patients who have failed the cuff leak test but are otherwise deemed ready for extubation based on other assessments, it is recommended to administer corticosteroid therapy at least four

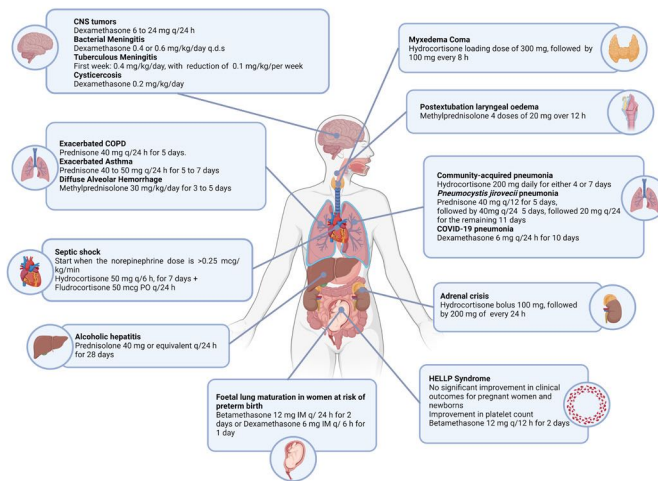


Figure 1. Use of corticosteroids in multiple pathologies

hours before extubation. It is suggested to give four doses of 20 mg of methylprednisolone over 12 hours, which reduces the incidence of postextubation laryngeal oedema (3% vs 22%, $p < 0.0001$), the overall incidence of reintubations (4% vs 8%, $p = 0.02$), and the proportion of reintubations secondary to laryngeal oedema (8% vs 54%, $p = 0.005$) (Francois et al. 2007).

Exacerbated COPD

According to the GOLD 2024 guidelines, the use of systemic corticosteroids is recommended during COPD exacerbations, with a maximum duration of five days and a daily dose of 40 mg of prednisone (or equivalent). This treatment approach is found to be equally effective through enteral or parenteral administration (GOLD 2024). Corticosteroids have been shown to reduce recurrence rates and the need for hospitalisation in patients experiencing COPD exacerbations. There is a significant improvement in lung function test results and a decrease in the risk of treatment failure in both outpatient and hospitalised patients when compared to placebo (OR 0.48; 95% CI 0.35, 0.67), without a significant difference in mortality (Walters et al. 2014).

Exacerbated Asthma

It is recommended to use inhaled corticosteroids for the treatment of exacerbated asthma. The benefits of this approach include acute relief of symptoms, a reduction in the risk of severe asthma attacks, a lower likelihood of hospitalisation, and the avoidance of initiating oral corticosteroids (Global Initiative for Asthma 2023). Oral corticosteroids are recommended for patients who, despite using inhaled corticosteroids for 2-3 days, fail to improve their symptoms during an asthma attack. The recommended dose is 40-50 mg/day of prednisone for 5 to 7 days (Normansell et al. 2016). In patients presenting to the emergency department with asthma exacerbation, the administration of corticosteroids via any route (IV, oral, IM, or inhaled) is recommended within the first hour of admission. This measure has been shown to reduce the probability of requiring hospitalisation by 50% (0.50 95% CI 0.31-0.81 $p=0.004$) (Rowe et al. 2001).

Adrenal Crisis

Adrenal crisis or insufficiency is defined as an acute deterioration in health associated with absolute hypotension (systolic blood pressure <100 mmHg), with characteristics resolving after the parenteral administration of glucocorticoids (demonstrated by a marked resolution of hypotension within one hour and improvement of clinical symptoms within two hours) (Rushworth et al. 2019). There are no controlled clinical trials regarding the treatment. The use of parenteral hydrocortisone is suggested. It is administered through a bolus injection of 100 mg IV or IM (while awaiting IV access). This bolus should be followed by 200 mg of hydrocortisone every 24 hours, either through continuous IV infusion or, alternatively, in doses of 50 mg of hydrocortisone per IV/IM injection every six hours (Arlt 2016).

Bacterial Meningitis

A systematic review and meta-analysis of randomised controlled trials on bacterial meningitis found that patients administered dexamethasone versus placebo had significantly lower rates of severe hearing loss (RR 0.67; 95% CI: 0.51 to 0.88), a decrease

in the incidence of any hearing loss (RR 0.74; 95% CI), and neurological sequelae (RR 0.83; 95% CI: 0.69 to 1.00; $p=0.05$). An analysis focused on different bacteria causing meningitis demonstrated that patients with *Streptococcus pneumoniae* meningitis treated with corticosteroids had a lower mortality rate (RR 0.84; 95% CI: 0.72 to 0.98). Most studies utilised a four-day regimen of dexamethasone (0.4 or 0.6 mg/kg/day) administered in four daily doses (Brouwer et al. 2015).

Tuberculous Meningitis

A systematic review and meta-analysis of randomised controlled trials on tuberculous meningitis demonstrated that corticosteroids reduce the risk of death by 25% between two months and two years after initiating treatment (RR 0.75; 95% CI 0.65 to 0.87). In most studies, a dexamethasone dose reduction regimen was employed over the course of one month, distributed as follows: in week 1, 0.4 mg/kg/day for 7 days; in week 2, 0.3 mg/kg/day for 7 days; in week 3, 0.3 mg/kg/day for 7 days; and in week 4, 0.1 mg/kg/day for 7 days (Prasad et al. 2016).

Cysticercosis

In cases of viable intraparenchymal neurocysticercosis with multiple enhanced lesions, the use of anti-inflammatory therapy with corticosteroids is suggested to manage diffuse cerebral oedema. This therapy should be administered before initiating treatment with antiparasitic drugs, with a strong-moderate recommendation. In the case of subarachnoid neurocysticercosis, chronic use of high-dose steroids is advised, in addition to requiring intensive antiparasitic therapy and, in some cases, surgical intervention. Although the doses are not fully standardised, the administration of dexamethasone at 0.2 mg/kg/day may be considered, according to the strong-moderate recommendation. For patients with spinal neurocysticercosis and spinal cord dysfunction, such as paraparesis or incontinence, the use of corticosteroids is suggested as part of adjunctive management along with antiparasitic therapy, with a strong-moderate recommendation (White et al. 2017).

Myxoedema Coma and Thyroid Storm

The treatment of myxoedema coma primarily revolves around the use of thyroid hormones (Ylli et al. 2019). The administration of corticosteroids is recommended as part of the initial treatment for myxoedema coma, involving intravenous administration at appropriate stress doses before levothyroxine administration (Jonklaas et al. 2014). It is essential to note that this recommendation lacks support from controlled clinical trials. In cases of thyroid storm, a loading dose of 300 mg of hydrocortisone is suggested, followed by 100 mg every 8 hours (ATA guidelines 2016). However, it is important to acknowledge that the supportive evidence for this recommendation is not derived from large-scale clinical trials (Ross et al. 2016). A nationwide retrospective study indicated that corticosteroids do not improve survival in patients with thyroid storm. Moreover, they also induce glycaemic dysregulation and an increased need for insulin (Senda et al. 2020).

Alcoholic Hepatitis

A systematic review and meta-analysis revealed that corticosteroid monotherapy (prednisolone 40 mg or equivalent for 28 days) significantly reduced mortality compared to placebo (OR=0.58; 95% CI, 0.34-0.98; P=0.04) (Sung-Lee 2017).

Central Nervous System Tumours

Dexamethasone has been used for malignant brain tumours. It is employed to manage peritumoral oedema and alleviate symptoms related to intracranial hypertension. For the treatment of peritumoral oedema, described doses include 4 mg every 6 hours for 8 to 19 days, resulting in an average reduction in oedema volume (26%). Another regimen involves 4 mg every 6 hours for

7 days, followed by a maintenance dose of 4 mg/day until surgical intervention or radiotherapy, leading to an average reduction in oedema volume (56%). The following regimen is proposed based on symptom relief (Ly et al. 2017): initial one-time dose of 10 mg, followed by 4 mg every 6 hours

Diffuse Alveolar Haemorrhage

Diffuse alveolar haemorrhage (DAH) is a severe pulmonary complication that can occur in certain autoimmune diseases such as systemic lupus erythematosus, vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA), antiphospholipid syndrome, and anti-glomerular basement membrane syndrome (Al-Adhoubi and Bystrom 2020). Corticosteroids are recommended in up to 98% of all cases. Their primary goal is to reduce the acute inflammatory response of the alveolar endothelium (Ednalino et al. 2015); however, to date, therapeutic recommendations for corticosteroids are based on retrospective trials and anecdotal reports. Despite the use of high-dose corticosteroids, mortality exceeds 50% (Park 2021).

HELLP Syndrome

A systematic review with meta-analysis (Sun et al. 2023) found no significant improvement in clinical outcomes for pregnant women and newborns with HELLP syndrome. However, the platelet count showed improvement after the administration of betamethasone at a dosage of 12 mg every 24 hours for two days (81.2%, 95% CI [43%, 533%]) compared to a placebo group (94.5%, 95% CI [24%, 627%]); there was no statistically significant difference between the two groups (p=0.23) (Ozer et al. 2009).

Foetal Lung Maturation in Women at Risk of Preterm Birth

Prenatal corticosteroid treatment in women at risk of preterm birth reduces the risk 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), leukomalacia periventricular (OR 0.65; 95% CI 0.47 to 0.92; p<0.001) and necrotising enterocolitis compared to unexposed premature newborns. Corticosteroids should be initiated when a high risk of preterm birth is anticipated within the next one to seven days to achieve its effectiveness; if administered less than 24 hours before delivery, the effectiveness is incomplete. Betamethasone has shown a greater reduction in intraventricular haemorrhage. A course of therapy consists of intramuscular betamethasone 12 mg doses every 24 hours for two doses, or intramuscular dexamethasone 6 mg doses every 6 hours for four doses. An alternative is intravenous hydrocortisone 500 mg every 6 hours. (Dongkin et al. 2021).

Conclusion

The use of corticosteroids has demonstrated effectiveness in multiple pathologies in the ICU (**Figure 1**); however, clinical trials are needed to establish dosage and treatment duration for autoimmune and endocrine disorders.

Conflict of Interest

None.

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