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Steroids in the acutely ill: Evolving recommendations and practice

ABSTRACT

Critical illness-related corticosteroid insufficiency (CIRCI) is a state of systemic inflammation involving dysregulation of the hypothalamic-pituitary-adrenal axis, altered cortisol metabolism, and tissue resistance to corticosteroids. Many conditions may be associated with CIRCI, including sepsis, septic shock, acute respiratory distress syndrome, and severe community-acquired pneumonia. Recommendations and practice for diagnosing and treating this condition have evolved as information has emerged. Here, the author reviews the current thinking.

KEY POINTS

- Guidelines suggest giving intravenous (IV) hydrocortisone 200 mg/day (50 mg IV every 6 hours or as a continuous infusion) to patients who have septic shock and ongoing need for vasopressor therapy to maintain adequate blood pressure, but not to those who have sepsis without septic shock.
- Guidelines suggest giving IV methylprednisolone 1 mg/kg/day or dexamethasone 20 mg/day to those with acute respiratory distress syndrome, provided it is early (within 72 hours of onset) and severe (with a PaO_2/FiO_2 ratio < 200).
- Dexamethasone 6 mg IV once daily for up to 10 days is recommended for hospitalized patients with COVID-19 who require supplemental oxygen, noninvasive respiratory support, or invasive mechanical ventilation.
- Using and tapering steroids should always be guided by clinical response and side effects.

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The term CIRCI, or critical illness-related corticosteroid insufficency, was coined in 2008 by an international multidisciplinary task force of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine when they released the guidelines for the diagnosis and treatment of CIRCI.[1] The guidelines were updated in 2017[2,3] and are being updated for publication in 2023.

Recommendations have evolved as new information has been generated with regards to what causes CIRCI, how to diagnose it, who should receive corticosteroid treatment, and what regimens to use.

THREE MAIN MECHANISMS

In 2008, we described CIRCI as a syndrome of inadequate corticosteroid activity for the severity of the patient's illness, that may occur with a decrease in adrenal steroid production (adrenal insufficiency) or from tissue resistance to glucocorticoids with or without adrenal insufficiency. To these mechanisms we now add alterations in cortisol metabolism.

During critical illness, production of adrenocorticotropic hormone (ACTH) is often low, while cortisol levels tend to be normal or, usually, high. The diurnal rhythm in cortisol levels (normally lower in the evening and higher in the morning) is also lost.

More than 90% of circulating cortisol is bound to corticosteroid-binding globulin, which tends to fall during critical illness. Only 5% to 10% of cortisol is free and biologically active.

Normal total cortisol levels are between 5 and 24 µg/dL.

Cortisol is a lipophilic hormone that enters cells passively and binds to specific glucocorticoid receptors in the cytoplasm, or to membrane sites. Cortisol is metabolized primarily in the liver by 5 alpha/beta-reductases and in the kidneys by the 11-beta-hydroxysteroid dehydrogenase (11-beta-HSD) type 2 enzyme. During severe stress states, the expression and activity of these enzyme systems is reduced, leading to decreased clearance of cortisol. Upon binding of glucocorticoid, the glucocorticoid receptor undergoes a conformational change, dissociates from the chaperone proteins, and enters the nucleus and mitochondria, where it binds to positive (transactivation) or negative (cis-repression) specific DNA regions termed glucocorticoid responsive elements to regulate transcription and translation of target genes in a cell- and gene-specific manner. Nuclear factor kappa B is the major transcription protein that glucocorticoids inhibit, and this inhibition is responsible for downregulating the actions of proinflammatory cytokines such as tumor necrosis factor-alpha, interleukin 1, and interleukin 6. Glucocorticoids also act through a nongenomic pathway.

CIRCI IS COMMON

The incidence of CIRCI varies widely, depending on the population studied and the diagnostic criteria used: 20% to 60% of patients with septic shock in a medical intensive care unit, 21% to 75% of patients with human immunodeficiency virus infection who are critically ill, and 15% to 50% of patients with traumatic brain injury.[4,5]

The common clinical features are hemodynamic instability despite adequate fluid resuscitation, and fever and inflammation without an obvious source of infection that does not respond to empiric antimicrobial therapy. Other, nonspecific signs and symptoms can include altered mental status, gastrointestinal symptoms, hypoglycemia, eosinophilia, hyponatremia, and hyperkalemia. Hyponatremia and hyperkalemia are less common than in patients with primary adrenal insufficiency, in whom they may be more prominent.

Many conditions can be associated with CIRCI: sepsis, septic shock, acute respiratory distress syndrome (ARDS), major trauma, severe bacterial pneumonia, bacterial meningitis, and nonseptic shock states, such as in patients with cardiopulmonary bypass, post cardiac arrest, cardiogenic shock, and burns.

NO SINGLE TEST CAN RELIABLY DIAGNOSE CIRCI

In 2008, the Corticosteroid Guideline Task Force recommended two ways of testing for CIRCI in the critically ill:

- The cosyntropin stimulation test (an increase in the total serum cortisol from baseline of less than 9 µg/dL 60 minutes after giving an intravenous (IV) 250-µg dose of cosyntropin, a synthetic formulation of natural ACTH)
- A random total plasma cortisol level (of less than 10 µg/dL).

However in 2017, we concluded that no single test can reliably diagnose the syndrome, and we could not reach a consensus (> 80% agreement) on whether the ACTH stimulation test is superior to random cortisol for the routine diagnosis of CIRCI.

If the ACTH stimulation test is used, we recommend that the high dose of cosyntropin (250 µg IV) be used for testing rather than the low dose (1 µg), because the latter has mediocre sensitivity in critically ill patients. This was a weak recommendation based on low-quality evidence.

We advised against measuring plasma free cortisol. We found no randomized trial that compared serum total vs free cortisol levels to diagnose CIRCI. A prospective study of 112 critically ill adults with treatment-insensitive hypotension, published after the 2008 recommendations, found a good correlation between serum concentrations of free and total cortisol before and after 250 µg ACTH stimulation testing.[6] Measurement of free cortisol is cumbersome to perform and may not be widely available in hospital laboratories, and so for practical purposes we felt that measurement of total cortisol would be preferable for most clinicians.

We also suggested against the use of salivary cortisol levels, as it would not be cost-effective, practical, or feasible given that it is tested by enzyme immunoassay, which may not be routinely available at most centers.

Most importantly, we emphasized that if corticosteroids are clinically indicated in acutely ill or critically ill patients, there is no need to do a cosyntropin stimulation test.

Patients already on steroids (ie, ≥ 5 mg of prednisone or 20 mg of hydrocortisone per day for at least 3 weeks) are at risk of hypothalamic-pituitary-adrenal axis suppression. Cosyntropin stimulation testing is recommended only for those who are more likely to develop either permanent, secondary adrenal insufficiency or CIRCI, to confirm or deny need for perma-

nent replacement therapy or to monitor their recovery during the final phases when tapering the corticosteroid. Dexamethasone does not interfere with the cortisol response or with the cortisol assay. However, if someone is taking hydrocortisone, it should be discontinued the evening before stimulation testing.

DIFFERENT GLUCOCORTICOID PREPARATIONS

The biologic rationale for glucorticoid use in acutely ill patients relates to its potent anti-inflammatory effects and to its effects on cardiovascular tone, including enhanced vasoconstrictor response to exogenous catecholamines and inhibition of cyclo-oxygenase-2 and inducible nitric oxide synthase. Hydrocortisone tends to be preferred as replacement therapy, as it has a short duration of action which allows the hypothalamic-pituitary-adrenal axis to recover between doses. However, prednisone, dexamethasone, and methylprednisolone are the agents we generally use, particularly in those with severe inflammation including bacterial pneumonia and ARDS.

SIDE EFFECTS

Steroids are not benign drugs. They can be associated with several side effects, most notably hyperglycemia, but also hypernatremia, neuromuscular weakness, myopathy, superinfections, upper gastrointestinal bleeds, arrhythmias, and steroid-induced psychosis.

STEROIDS TO TREAT SEPTIC SHOCK

Corticosteroids have been used in septic shock for nearly 6 decades, and practice has changed as information has emerged.

1976—Schumer[7] performs the first randomized controlled trial, using very large doses of steroids, ie, dexamethasone 3 mg/ kg or methylprednisolone in doses of nearly 2 g daily, in 172 patients with clinical septic shock and finds a reduction in mortality.

1980s—Bone et al[8] and Sprung et al[9] find that high-dose methylprednisolone (30 mg/kg daily) does not increase survival, and it induces superinfections in many patients. For the next 15 years, steroids are avoided in patients with septic shock.

2002—Annane et al[10] find that the combination of hydrocortisone 50 mg IV every 6 hours plus fludrocortisone 50 µg enterally daily is associated with a lower mortality rate, especially in those who do not respond to the cosyntropin stimulation test. However, patients who do respond derive no benefit. In the next few years, cosyntropin stimulation testing becomes popular, and nonresponders get hydrocortisone plus fludrocortisone.

2008—The Corticosteroid Therapy of Septic Shock (CORTICUS) trial[11] finds no benefit to the use of hydrocortisone 50 mg IV every 6 hours in terms of survival, but shock reversal is faster. Response to the cosyntropin stimulation test does not seem to matter. Many clinicians begin to abandon the stimulation test in patients deemed to already have an indication for corticosteroids, ie, refractory septic shock.

2016—The Hydrocortisone for Prevention of Septic Shock (HYPRESS) trial,[12] with 380 patients, finds that hydrocortisone 200 mg/day IV for 5 days does not prevent progression from sepsis to septic shock, indicating steroids should not be used for patients with sepsis who are not in refractory shock.

2018—The Adjunctive Corticosteroid Treatment in Critically Ill Patients With Septic Shock (ADRENAL) trial,[13] in 3,800 patients, finds that hydrocortisone 200 mg by IV infusion for 7 days compared with placebo was not associated with survival benefit, but shock reversal is faster, duration of mechanical ventilation is shorter, and fewer blood transfusions are needed, with relatively few side effects, mainly hyperglycemia.

2018—The Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial,[14] in 1,241 patients, uses the combination of hydrocortisone 200 mg IV in divided doses (50 mg IV every 6 hours) and fludrocortisone 50 µg enterally daily for 7 days. At 90 days, fewer patients in the steroid group had died, shock reversal was faster, and the steroid regimen was found to be safe; hyperglycemia was the most common adverse reaction. At 180 days, the survival benefit remained.

2019—A Cochrane meta-analysis[15] finds that corticosteroid therapy "probably" reduces hospital mortality (by about 9%), and results in large reductions in length of stay in the intensive care unit (by about 1 day) and in the hospital (by about 1 and one-half days). Corticosteroid therapy was associated with increased risk of hyperglycemia, hypernatremia, and muscle weakness but no increased risk of superinfection and little or no difference in gastrointestinal bleeding, neuropsychiatric, stroke, or cardiac events.

2020—Enter artificial intelligence. Pirracchio et al[16] enter data from about 2,500 patients from 4 septic shock clinical trials into an artificial intelligence program to attempt to more precisely determine who should receive corticosteroids, based on multiple

patient variables. This seems to be where the future lies. They found that strategies to treat all patients with corticosteroids or to treat no one were associated with a worse outcome. In contrast, an individual estimation-based treatment strategy always yielded a positive net benefit.

2017 guidelines

The 2017 guidelines[3] were issued just before the results of the ADRENAL and APROCCHSS trials were published. Our suggestions at that time were as follows:

Consider the use of IV hydrocortisone less than 400 mg/day for at least 3 days in patients in septic shock who already got adequate fluid resuscitation and still need moderate to high-dose vasopressor therapy (conditional recommendation, low quality of evidence).

Do not use corticosteroids in adult patients with sepsis who are not in refractory shock (conditional recommendation, moderate quality of evidence).

Steroid use should always be guided by clinical response and tapered slowly to avoid the rebound phenomenon

Surviving Sepsis Campaign guidelines 2021

Recommendations from the Surviving Sepsis campaign[17] published in 2021 are similar, suggesting intravenous corticosteroids (eg, hydrocortisone 200 mg per day in divided doses or as continuous infusion) for adult patients in septic shock who continue to need vasopressor therapy (norepinephrine or epinephrine ≥ 0.25 µg/kg/minute at least 4 hours after initiation) (weak recommendation; moderate-quality evidence).

Stopping steroids

If the patient no longer needs vasopressor therapy, is out of shock, and is maintaining adequate blood pressure for at least 12 to 24 hours, it is probably time to consider tapering or discontinuing steroids.

An exception is in patients who have an underlying endocrine disorder or indication for using corticosteroids: in those patients you have to taper the corticosteroids back to their usual dose. This has to be done carefully. One recommendation is to decrease by 10 to 20 mg over several days to weeks, depending on how much they required for maintenance therapy.

Steroid use should always be guided by clinical response and tapered slowly to avoid the rebound phenomenon.

STEROID USE IN ACUTE LUNG INJURY AND ARDS

The ARDS Network study[18] showed that corticosteroids should not be used in patients in the late phase of ARDS, ie, after 2 weeks on a ventilator. But what about early?

Meduri et al[19] performed a randomized, double-blind placebo-controlled trial in 91 patients with severe early ARDS (within 72 hours), 66% of whom had sepsis. They randomized these patients in a 2:1 ratio to methylprednisolone infusion 1 mg/ kg/day vs placebo. They tapered the steroid slowly, keeping the same dose for 14 days, cutting it in half on day 15 to day 21, in half again from day 21 to 28, and then stopping. More importantly, they did surveillance with frequent bronchoscopies to rule out infection, and they avoided neuromuscular blockade so as not to accentuate neuromuscular weakness, a side effect of steroids.

The primary outcome was a reduction in the Lung Injury Score or successful extubation by day 7, both of which were achieved. There were also significant reductions in the duration of mechanical ventilation, length of stay in the intensive care unit, and mortality.

The 2017 guidelines[3] gave a weak recommendation for the use of methylprednisolone 1 mg/kg/day in patients with ARDS, specifically patients receiving at least 50% FiO_2 on mechanical ventilation with positive end-expiratory pressure of 10 cm H_2O or more who have a PaO_2/FiO_2 ratio under 200. The tradeoff is hyperglycemia. We felt there was no increased risk of neuromuscular weakness, gastrointestinal bleeding, or nosocomial infection.

Villar et al[20] performed a study in 277 patients who had moderate to severe ARDS, with PaO_2/FiO_2 ratios less than 200 despite lung-protective ventilation and other strategies to optimize them on mechanical ventilation; 77% of these patients had either pneumonia- or sepsis-associated ARDS. They randomized the patients to dexamethasone 20 mg/day for 5 days, and then 10 mg/day on days 6 to 10, and then stopped the steroid shortly after that in most patients. The study was conducted over 5 years. The trial was stopped by the Data and Safety Monitoring Board due to low enrollment rate after enrolling nearly 90% of the planned sample size. The investigators found significant benefits with dexamethasone in terms of ventilator-free days, all-cause mortality at day 60, and duration of mechanical ventilation.

STEROIDS IN SEVERE BACTERIAL PNEUMONIA

In 2017, we suggested using corticosteroids in hospitalized patients with severe community-acquired

pneumonia who required mechanical ventilation or vasopressor therapy (conditional recommendation, moderate quality of evidence).[21]

This was largely based on a trial by Torres et al,[22] published in 2015, in patients with severe community-acquired pneumonia and a high systemic inflammatory response, with C-reactive protein levels greater than 15 mg/L, requiring mechanical ventilation or vasopressor therapy. Corticosteroid therapy was associated with improvement in survival. Hyperglycemia was the most common adverse effect.

A Cochrane review[23] in 2017 looked at 17 randomized controlled trials involving 2,264 patients and showed corticosteroids to significantly reduce mortality and morbidity rates in patients with severe community-acquired pneumonia, but not in those with nonsevere community-acquired pneumonia.

COVID-19

The initial flulike symptoms of COVID-19 are usually associated with bioreplication, and by the time the patients come to the hospital with respiratory symptoms they usually are already at risk with a severe inflammatory response that can progress to ARDS and the need for invasive mechanical ventilation. These patients have elevations in proinflammatory markers and inflammatory cytokines such as C-reactive protein, IL-6, and IL-1.

In April 2020, we argued in favor of corticosteroid therapy in patients with severe COVID-19-associated ARDS based on available observational evidence at that time and the extremely high mortality associated with the disease, and in favor of not waiting for the results of the randomized controlled trials.[24]

The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial[25] published its results a few months later. It was large, with 6,425 patients, of whom 2,104 received dexamethasone 6 mg IV daily for up to 10 days, and the rest usual care. Dexamethasone reduced mortality by one-third in those who required mechanical ventilation and by one-fifth in those receiving supplemental oxygen. However, there was no benefit in patients who were not receiving respiratory support, and there was even the suggestion of harm that could not be excluded.

A meta-analysis conducted by the World Health Organization Rapid Evidence Appraisal for COVID-19 Therapies Working Group[26] showed that the mortality rate at 28 days was significantly lower in patients with COVID-19 pneumonia and ARDS who got corticosteroid therapy, compared with those who did not receive corticosteroids (32.7% vs 41.5%, respectively).

Is viral shedding a problem?

In the influenza H1N1 and SARS epidemics, when steroids were given very early, they were associated with adverse outcomes. However, by the time patients with COVID-19 come to the hospital and need supplemental oxygen or mechanical ventilation, they are usually in a very proinflammatory phase, and at that point there is probably already less likelihood of delay in SARS-CoV-2 viral clearance.

Cano et al[27] reviewed 73 studies involving 21,350 patients, which showed there was clearly a benefit of using corticosteroids in terms of mortality in very sick patients with COVID-19. They did not find any significant impact on viral shedding.

The mortality rate is significantly lower in severely ill patients with COVID-19 who receive dexamethasone

Low vs high dose of dexamethasone in COVID-19

Why not use a higher dose of dexamethasone? Dexamethasone 6 mg is equivalent to only about 30 mg of methylprednisolone. Would 12 mg be better than 6 mg?

Two randomized controlled trials[28,29] did not show a statistically significant benefit in terms of survival at 28 days in patients who received 12 mg compared with those who received 6 mg. Therefore, 6 mg of dexamethasone is still most commonly given. In my own practice, I occasionally either double the dose if patients are on 6 mg and not clinically responding and remain very hypoxic, or switch to methylprednisolone 1 mg/kg/day, and see if they respond. You can double it up to 2 mg per kg depending on inflammatory markers if they have ARDS.

Comparing dexamethasone and methylprednisolone, I favor methylprednisolone because it resides longer in the lung and is more potent as an anti-inflammatory agent, but always start with 6 mg of dexamethasone and then move from there depending on how sick the patient is.

The National Institutes of Health guidelines[30] recommend the following:

- Remdesivir, dexamethasone, or both for hospitalized patients who require supplemental oxygen
- Dexamethasone with or without remdesivir for patients who require oxygen through a high-flow nasal cannula or noninvasive ventilation (plus either baricitinib or IV tocilizumab for patients with

rapidly increasing oxygen needs and systemic inflammation)
- Dexamethasone for those requiring mechanical ventilation or extracorporeal membrane oxygenation (plus IV tocilizumab for those within 24 hours of admission to the intensive care unit).

Chaudhuri et al[31] did a systematic review and meta-analysis of 2,826 patients treated with steroids for COVID-19 and non-COVID-19 ARDS in 18 randomized controlled trials. They concluded the use of corticosteroids "probably" reduces mortality in patients with ARDS of any etiology, and patients who got a longer course of corticosteroids (more than 7 days) had higher rates of survival than those who got a shorter course. ■

DISCLOSURES

Dr. Pastores has disclosed serving as advisor or review panel participant for AbbVie Pharmaceuticals, as research investigator with bioMerieux, Eisai, and Revimmune, receiving royalty fees as textbook editor for McGraw-Hill.

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