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Sepsis and Adrenal Insufficiency

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Abstract

In sepsis, dysregulation of the hypothalamic–pituitary–adrenal axis, alterations in cortisol metabolism, and tissue resistance to glucocorticoids can all result in relative adrenal insufficiency or critical illness-related corticosteroid insufficiency (CIRCI). The symptoms and signs of CIRCI during sepsis are nonspecific, generally including decreased mental status, unexplained fever, or hypotension refractory to fluids, and the requirement of vasopressor therapy to maintain adequate blood pressure. While we have been aware of this syndrome for over a decade, it remains a poorly understood condition, challenging to diagnose, and associated with significantly diverging practices among clinicians, particularly regarding the optimal dosing and duration of corticosteroid therapy. The existing literature on corticosteroid use in patients with sepsis and septic shock is vast with dozens of randomized controlled trials conducted across the past 4 decades. These studies have universally demonstrated reduced duration of shock, though the effects of corticosteroids on mortality have been inconsistent, and their use has been associated with adverse effects including hyperglycemia, neuromuscular weakness, and an increased risk of infection. In this article, we aim to provide a thorough, evidence-based, and practical review of the current recommendations for the diagnosis and management of patients with sepsis who develop CIRCI, explore the controversies surrounding this topic, and highlight what lies on the horizon as new evidence continues to shape our practice.

Keywords

adrenal insufficiency, sepsis, septic shock, critical illness, corticosteroids, hydrocortisone

Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] An intact hypothalamic–pituitary–adrenal (HPA) axis is vital in the host response to sepsis.[2] In the late 1990s and early 2000s, the concept of *relative* (as contrasted with *absolute*) adrenal insufficiency arose to describe patients in septic shock whose HPA reserve was thought outmatched by the stress of the latter condition, resulting in blunted adrenal corticosteroid production.[3] The true incidence of adrenal insufficiency among patients with sepsis and septic shock has been difficult to determine. Historically, as with shifting paradigms, consensus regarding appropriate laboratory testing and parameters for its diagnosis has been hard to reach. Annane et al[3] found that more than half (54%) of 189 patients with septic shock had adrenal insufficiency as determined by a short cosyntropin stimulation test. Similarly, another study reported that approximately half of the patients with sepsis had concomitant adrenal insufficiency by either baseline cortisol levels or cosyntropin testing.[4] More recently, a study examining the co-occurrence of sepsis and adrenal insufficiency (as determined by cosyntropin testing) found that in 25% of patients, the 2 conditions overlapped.[5] Another study found a co-occurrence rate of 36.6% (using serum cortisol).[6]

In 2008, an international task force convened by the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) coined the phrase critical illness-related corticosteroid insufficiency (CIRCI) to more fully describe the impairment of the HPA axis during critical illness.[7] CIRCI was defined as inadequate cellular corticosteroid activity for the severity of the patient's critical illness. Although we have been aware of this clinical syndrome for over a decade, it remains a poorly understood condition, challenging to diagnose, and associated with significant variation among clinicians regarding the optimal dose and duration of corticosteroid treatment.[8]

In this article, our goal is to provide a thorough, evidence-based, and practical review of the current recommendations for the diagnosis and management of patients with sepsis who develop CIRCI, explore the controversies surrounding this topic, and highlight what lies on the horizon regarding this quotidian clinical entity. Management of critically ill patients on

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chronic steroid therapy is beyond the scope of this review article.

Pathophysiology

The Normal HPA Axis

When stressed, humans have developed a response to sustain life.[9,10] The HPA axis is a central actor in this response, comprised of the hypothalamic paraventricular nucleus (PVN), the anterior pituitary gland, and the adrenal glands. In the hypothalamus, the PVN is responsible for secreting corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), which synergistically incite the release of adrenocorticotropic hormone (ACTH) into the circulation.[11] ACTH is secreted both in a basal and pulsatile manner. In the physiologic state, this pulsatility is determined primarily by the circadian rhythm with peak levels of cortisol in the morning that decline throughout the day.[12,13] In the adrenal cortex, ACTH induces glucocorticoid synthesis. Most cortisol remains attached to cortisol-binding globulin (CBG), although an unbound fraction will remain lipophilic, able to traverse cellular membranes and bind to cytoplasmic glucocorticoid receptors (GRs), of which GRα and GRβ are particularly crucial in mediating the stress response.[14,15] Free cortisol achieves varied and powerful immunological and cardiovascular effects through the binding of GRα. In fact, the cortisol-GRα dimer can induce expression or repression of up to 20% of the human genome.[16] These effects are directly opposed by GRβ, and ultimately free cortisol inhibits the secretion of both CRH and ACTH through negative feedback, framing the HPA axis in a state of autoregulation.[9,10]

The HPA Axis During Critical Illness and Sepsis

During critical illness such as sepsis, the usual organization of the HPA axis is upset and replaced by a complex matrix of axis-independent regulators (Figure 1).[17-19] Firstly, it is characterized by an excessive increase in circulating free cortisol which correlates with the severity of the insult.[20] Secondly, the degree of hypercortisolemia is disproportionate to any increase in cortisol secretion and is completely dissociated from ACTH levels (ACTH-cortisol dissociation).[21,22] Instead, both ACTH and CBG levels fall sharply and see their binding activity hampered by the hostile environment of critical illness, both mechanisms increasing the fraction of free cortisol.[23]

Levels of proopiomelanocortin (POMC), the precursor molecule of ACTH, are elevated in sepsis through CRH/AVP-driven POMC expression and impaired processing into ACTH, contributing to adrenocortical steroidogenesis and the ACTH-cortisol dissociation.[24,25] Additionally, the enzymes involved in the breakdown of cortisol in the liver (α-ring reductases) and kidney (11β-hydroxysteroid dehydrogenase 2) are suppressed in response to inflammation.[26] Part of this suppression is driven by the accumulation of bile acids, which inhibit the activity of these enzymes through negative feedback.[27] The overall impact of these changes is modulated and amplified by the hepatic GRs through a mechanism that is not fully understood. This complex interplay of abnormal interactions favors a model of hypercortisolemia in critical illness secondary to reduced clearance of cortisol, rather than what was presumed to be upregulated production. Furthermore, critical illness is associated with a shift in GR expression from GRα-dominant to one in which GRβ transcription is increased, which has been associated with a blunted response to endogenous glucocorticoids referred to as "tissue resistance."

In both sepsis and acute respiratory distress syndrome (ARDS), downregulated GRα activity has been hypothesized and linked, both ex vivo and in vivo, to worsening glucocorticoid resistance, morbidity, and mortality. In some experimental models, the use of exogenous glucocorticoids has been associated with restored GRα expression, function, and resolution of inflammation, which may potentially translate into an improved clinical trajectory in the appropriate setting. However, emerging evidence (largely from murine studies) indicates a disparity among different tissues' GR profiles and their response to glucocorticoids, which clouds the interpretation of a generalized "tissue resistance" and suggests that the above changes of GR expression observed in the septic model may be adaptive and protective.[2,28]

Clinical Manifestations of CIRCI During Sepsis

The symptoms and signs of CIRCI during sepsis are nonspecific and generally include decreased mental status, unexplained fever, hypotension refractory to fluids, and the requirement of vasopressor therapy to maintain adequate blood pressure. While hyponatremia, hyperkalemia, hypoglycemia, and eosinophilia may be observed, these are generally uncommon, and their presence may be masked by routine intensive care unit (ICU) care such as fluid administration and close electrolyte management.

Other Confounding States With Abnormal Activation of HPA Axis

Several known and emerging therapies have been associated with disorders of the HPA axis. Perhaps the most well-known of these is the sedative etomidate, which inhibits 11β-hydroxylase and, therefore, the synthesis of cortisol. Though other sedatives can have this effect, it is only etomidate which is now limited to use as a single preintubation induction dose instead of a continuous infusion for sedation.[29] While the one-time use of this agent has not been definitively linked to increased mortality, retrospective analyses have shown an excess risk of poor outcomes in the critically ill. One possible reason for this is the variable effects of this drug. The sedative effects of etomidate have an onset of action within 15-20 s with a duration of action of approximately 2 to 3 min and a favorable hemodynamic profile in comparison to other sedatives used in the ICU such as propofol or midazolam. However, its effect on the adrenal cortex is much more potent, with a single dose of etomidate leading to a suppression of cortisol

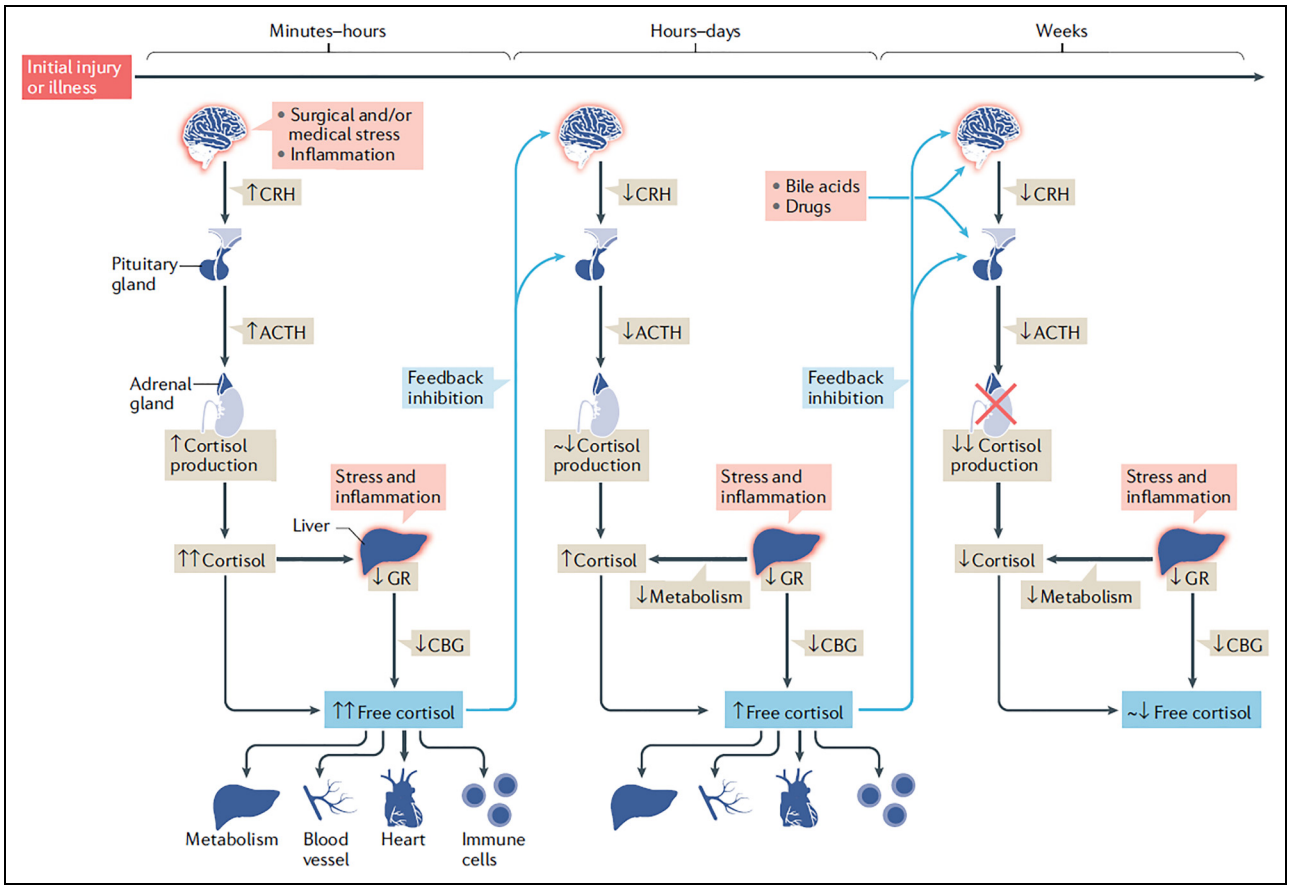


Figure 1. A newly proposed conceptual framework for adrenocortical function and dysfunction during critical illness.[17] Shown here are the central and peripheral drivers of increased cortisol availability during the acute, subacute, and chronic phases of critical illness. The acute phase, occurring within minutes to hours after the initial insult, is mostly characterized by a central, ACTH-driven rise in cortisol and a peripherally driven (by decreases in cortisol binding to cortisol binding proteins, in addition to GR-driven effects) further rise in free cortisol. By contrast, the subacute phase (occurring hours to days after the initial insult) is marked by a central suppression driven by feedback inhibition with sustained peripherally driven elevated total cortisol and free cortisol. During the prolonged phase, extending beyond several weeks of critical illness, the sustained central suppression of the HPA axis caused by feedback inhibition driven by sustained elevation of free cortisol and by elevated bile acids and/or drugs could lead to central hypoadrenalism.

Abbreviations: ACTH, adrenocorticotropic hormone; GR, glucocorticoid receptor; CBG, cortisol-binding globulin; CRH, corticotropin-releasing hormone; HPA, hypothalamic–pituitary–adrenal.

synthesis for up to 72 h. Additionally, it can interfere with other steroid-mediated processes.[2] The mixed results of several meta-analyses investigating this agent have left the debate over its use in the critically ill ultimately unresolved.[30]

Immune checkpoint inhibitor (ICI) regimens and cellular therapies, which modulate T-cell function to fight cancer cells, can also ignite immune-related adverse events including hypophysitis (inflammation of the pituitary gland), which can lead to a central (or "secondary") inhibition of ACTH release, and primary adrenal insufficiency, in which the synthesis of glucocorticoids by the adrenal glands is inhibited. Given the increased utilization of ICIs worldwide, it is important for intensivists to be aware of these possible mimics or confounding pathologies of CIRCI. A recent study showed that particular ICI combinations may result in relatively high rates of adrenal insufficiency (almost one-third of patients with nivolumab/ipilimumab combination therapy).[31] The use of ICIs may also result in a syndrome requiring long-term corticosteroid therapy in contrast to the rapidly tapering regimens often used for CIRCI.[32] Another novel cancer treatment associated with a sepsis-like presentation is chimeric antigen receptor (CAR)-T cell therapy. CAR-T can induce a hyperinflammatory state known as cytokine release syndrome (CRS), which can be difficult to distinguish from sepsis, with fever and hypotension being hallmarks of the condition. Current management of CRS relies on suppression of the powerful inflammatory response this therapy engenders, usually with specific cytokine antagonists (eg, tocilizumab and interleukin-6 receptor antagonist) and often alongside high doses of glucocorticoids.[33,34]

Laboratory Testing

Patients with CIRCI typically have normal or low plasma total cortisol levels and normal to low plasma ACTH. However, there is no single test that can reliably diagnose CIRCI in patients

with sepsis. The 2008 CIRCI guidelines suggested that the diagnosis of CIRCI is best made by an increase in total serum cortisol of <9 μg/dL after i.v. cosyntropin (synthetic ACTH) 250 μg administration or a random total cortisol of <10 μg/dL.[7] ACTH stimulation testing likely has limited applicability in critically ill patients, and the 2017 task force could not reach a consensus on whether the test was superior to random cortisol.[19] It is important to note that ACTH stimulation testing only tests adrenal responsiveness to ACTH and is not a test of the HPA axis.[35] The 2017 task force was not in favor of using plasma-free cortisol or salivary gland cortisol level over plasma total cortisol level as the evidence for this was of poor quality (low-quality observational studies with inconsistent findings). Similarly, assessing the hemodynamic response to hydrocortisone to diagnose CIRCI was not recommended. Although the low-dose (1 μg) ACTH stimulation test may have similar diagnostic accuracy and accuracy in predicting vasopressor dependency and clinical outcomes in septic patients, it requires some preparation and offers no advantage over the high-dose ACTH test.[36]

Treatment With Corticosteroids: Who, When, and How to Treat?

Over the past 4 decades, numerous randomized controlled trials (RCTs) have been conducted evaluating the role of corticosteroids in a wide variety of patients with sepsis and septic shock. These include adult, pregnant, and pediatric patients with and without ARDS who were treated with varying doses, dosing strategies, formulations, and durations of corticosteroid therapy. In the 1980s, RCTs using high-dose corticosteroid regimens (>400 mg/day hydrocortisone or equivalent for <3 days) in patients with septic shock demonstrated no beneficial treatment effect and even suggested that treatment may increase mortality.[37] Use of lower dose corticosteroids (referred to as "stress dose" steroids) was revived in the late 1990s when 2 small-sized RCTs showed faster reversal of shock and improved mortality.[38,39]

While different glucocorticoid agents have been trialed in sepsis and septic shock, a recent systematic review and meta-analysis of glucocorticoid therapy in septic shock compared 18 studies using hydrocortisone, 2 that used methylprednisolone ($n = 158$ patients) and 1 with dexamethasone ($n = 29$ patients).[40-43] As the greater part of the evidence examining corticosteroid use in sepsis is derived from trials that utilized hydrocortisone, our recommendations and those of the professional societies involve the use of this agent.

Table 1 lists the 4 landmark RCTs addressing the efficacy and safety of corticosteroids in patients with sepsis and septic shock over the past 20 years. Studies that included steroids as part of combination therapy with nonsteroidal agents (eg, vitamin C with hydrocortisone) were not included. In addition to appreciating the nuances of each RCT, it is worth appreciating that this body of literature represents some of the most robust data gathered in the critical care population across 3 continents.

For most of these landmark studies, IV hydrocortisone was used (with or without fludrocortisone) at a dose of 200 mg daily in divided doses (50 mg IV every 6 h) or continuous infusion for at least 7 days without a taper schedule. It is notable that only the RCTs that used a combination of hydrocortisone and fludrocortisone showed a mortality benefit.[44,46]

Though each of these RCTs differed in various ways, the primary outcome under consideration was 28- or 90-day mortality, and a secondary outcome that they all investigated was time to shock reversal. Some studies also evaluated days on mechanical ventilation (MV), the occurrence of superinfection, recurrent shock, gastrointestinal (GI) bleeding, neuromuscular weakness, and ICU and hospital length of stay. While these landmark studies did not concur on the benefit of corticosteroids regarding mortality benefit, they all found a shorter time to shock reversal with corticosteroid therapy. In fact, the largest study (ADRENAL)[47] also noted a shorter time to ICU discharge. Considering the volume of patients admitted to the ICU with sepsis, if this carries over into day-to-day ICU care, it might have a beneficial impact on ICU staffing and workflow in addition to patient-level outcomes.

One way to make sense of these studies at the bedside is to compare and contrast them. The 2 studies conducted in France (Annane's original study in 2002 and APROCCHSS in 2018) both used a combination of hydrocortisone with fludrocortisone in contrast to CORTICUS[45] and ADRENAL. Additionally, only the 2 French studies demonstrated a survival benefit with the coadministration of hydrocortisone plus fludrocortisone. This coincidence has led to the hypothesis of fludrocortisone coadministration being instrumental in these 2 studies' intervention arms securing a survival advantage, though this seems unlikely, as the mineralocorticoid effect that might be anticipated from 50 μg of fludrocortisone is already readily achieved by 200 mg of hydrocortisone (regardless of the enteral bioavailability of fludrocortisone in the vasopressor-dependent, critically ill patient).[17] Another hypothesis to explain the outcome discrepancy between the 2 Annane studies and the CORTICUS/ADRENAL trials notes the French trials had higher acuity patients (mortality among patients randomized in APROCCHSS was almost double that of ADRENAL). Importantly, all 4 studies showed a shorter time to reversal of shock. However, this alone (discontinuation of vasopressor therapy) cannot be seen as a meaningful patient-centered outcome. We can contrast this with the decreased use of blood transfusions and shorter time on the ventilator identified by the ADRENAL trial.

The use of corticosteroids in sepsis and septic shock is not without risk. The CORTICUS trial showed that patients treated with corticosteroids had an increased risk of superinfection and recurrent septic shock. Both of these findings may have significant downstream effects on patients. Finally, all of the landmark trials found that corticosteroid therapy increased the risk of hyperglycemia, a known risk factor for increased morbidity and mortality in the critically ill.[48] How, then, can we interpret this data in the face of uncertain and at times conflicting findings? It seems most appropriate to consider these studies

Table 1. Four Landmark RCTs Addressing the Efficacy and Safety of Corticosteroids in Patients With Sepsis and Septic Shock Over the Past 20 Years.

Study (year)	Country(s)	Population	Intervention	Controls	Primary outcome(s)	Secondary outcome(s)	Results	Adverse effects
Annane et al (2002)[44]	France	299 adult septic shock patients on MV with documented/ suspected infection and signs of shock	Hydrocortisone 50 mg i.v. q.6 h + fludrocortisone 50 μg p.o. q.24 h for 7 days	Placebo	28-day mortality in patients with relative adrenal insufficiency (cortisol level increase of ≤9 μg/ dL in corticotropin test)	ICU and hospital mortality, 1-year mortality, between patients with/ without response to corticotropin tests and time to shock reversal	Mortality (28-day, ICU, and hospital) lower and shorter time to shock reversal in the intervention arm	Similar risk of superinfection, GI bleeding, and psychiatric disturbance between arms
CORTICUS Sprung et al (2008)[45]	Austria, Belgium, France, Germany, Israel, Italy, Netherlands, Portugal, and the United Kingdom	499 adult patients, with evidence of infection, 2/4 SIRS criteria, and shock within the previous 72 h primarily with septic shock	Hydrocortisone 50 mg i.v. q 6 h for 5 days, then tapered over 6 days	Placebo	28-day mortality	ICU and hospital mortality, 1-year mortality, time to shock reversal	No mortality difference, a shorter time to shock reversal in the intervention arm	Increased risk of superinfection, hyperglycemia, hypernatremia, and weakness in the intervention arm
APROCCHSS Annane et al (2018)[46]	France	1241 adult patients with proven/ probable septic shock ≤ 24 h prior to enrollment	Hydrocortisone 50 mg i.v. q 6 h + fludrocortisone 50 μg p.o. q. 24 h for 7 days	Placebo	90-day mortality	Time to shock reversal, time to weaning from MV	Mortality is lower and shorter time to shock reversal in the intervention arm	Increased risk of hyperglycemia in the intervention arm, similar risk of GI bleeding, and superinfection
ADRENAL Venkatesh et al (2018)[47]	Australia, New Zealand, United Kingdom, Denmark, and Saudi Arabia	3658 adult septic shock patients on MV with documented/ suspected infection, 2/4 SIRS criteria, ≥4 h of vasopressors	Hydrocortisone 200 mg i.v. q 24 h continuously infused for 7 days (or to ICU discharge if shorter)	Placebo	90-day mortality	28-day mortality, time to shock reversal/ recurrence, time to wean from MV, hospital and ICU LOS, new infection	No mortality difference, shorter time to shock reversal, and ICU discharge in the intervention arm	Increased risk of hyperglycemia, hypernatremia, encephalopathy, and myopathy, similar risk of new bacteremia

Abbreviations: RCT, randomized controlled trial; MV, mechanical ventilation; ICU, intensive care unit; GI, gastrointestinal; MI, myocardial infarction; LOS, length of stay.

in the context of the existing meta-analyses and national society practice guidelines.

A systematic review with meta-analysis and trial sequential analysis of 22 RCTs including 7297 participants concluded that in adult patients with septic shock treated with corticosteroids in a dose of <500 mg per day of hydrocortisone (or equivalent) compared to placebo or usual care, there was a reduced duration of shock, MV, and ICU stay, but no significant change in short- and longer-term mortality, and an increased rate of adverse events.[40] Similarly, an updated systematic review and meta-analysis of 42 RCTs including 10 194 patients concluded that corticosteroids possibly result in a small reduction in mortality (2% absolute risk reduction) and hospital and ICU length of stay, but at the expense of increased rates of hyperglycemia, hypernatremia, and neuromuscular weakness.[49] Certainly, the increased risk of neuromuscular weakness may have an outsize effect on the patient's quality of life.

Given the volume of unclear and conflicting evidence, it is vital to know what our professional organizations recommend to clinicians at the bedside. The 2017 SCCM/ESICM guidelines suggested the use of <400 mg/day of IV hydrocortisone for ≥3 days at full dose in adult patients with septic shock that is not responsive to fluid and moderate- to high-dose vasopressor therapy.[19] Most recently, the 2021 Surviving Sepsis Guidelines suggested using IV corticosteroids (IV hydrocortisone 200 mg/day given as 50 mg IV every 6 h or as a continuous infusion) for adults with septic shock and an ongoing requirement for vasopressor therapy (≥0.25 mcg/kg/min of norepinephrine or epinephrine for at least 4 h), based on moderate quality evidence.[50] Coadministration of fludrocortisone was not addressed. On the basis of the evidence reviewed, professional consensus, and our own practice, we recommend the administration of 200 mg/day of hydrocortisone IV in divided doses (or by infusion) to patients with ongoing vasopressor requirement outlined in the Surviving Sepsis Guidelines, for at least 3 to 5 days with or without taper. A recent retrospective study showed that abrupt discontinuation of corticosteroids was associated with a lower likelihood of vasopressor reinitiation when compared with taper discontinuation.[51] In the event of shock recrudescence, the decision to reinstitute hydrocortisone should be tailored to the specific clinical circumstances. Our recommendations regarding corticosteroid administration in various systemic inflammatory processes are summarized in Table 2.

Adverse Effects of Corticosteroids

Hyperglycemia

Most landmark trials examining the use of adjunctive glucocorticoids in sepsis and septic shock showed an excess of hyperglycemia events in the corticosteroid arm. This occurs through several mechanisms, such as glucocorticoids' promotion of gluconeogenesis, inhibition of insulin secretion and glucose uptake, and increased protein degradation.[58] If this dysregulation is not appropriately managed, hyperglycemia has been clearly associated with increased ICU mortality.

Weakness

Sepsis and other forms of critical illness requiring ICU admission are associated with profound deconditioning in survivors. This is secondary to the marked catabolism of the critically ill state, with an approximate loss of muscle mass of 2% to 4% per day of ICU stay,[59] but also the toll of therapies used to combat this state. Glucocorticoids potentiate protein degradation and loss of lean muscle mass,[60] and prolonged use may increase the risk and severity of post-ICU syndrome with its attendant negative effects on quality of life.[61] However, a review article found that while many case reports and series in the 1970s and 1980s reported weakness in patients after receiving high-dose corticosteroids, this finding was not replicated in prospective studies, nor in contemporary randomized trials that utilized lower doses of corticosteroids and improved glycemic control.[62] Corticosteroids were not associated with increased duration of mechanical ventilatory support, one of the most significant side effects of weakness in the critically ill.[62]

Delirium

Glucocorticoid use may be associated with hyperarousal and sleep disturbance, behavioral changes, delirium, and frank psychosis.[63] As with hyperglycemia, ICU delirium is a well-established independent risk factor for morbidity and mortality in critically ill patients.[64] However, among the landmark RCTs, only the ADRENAL trial showed an increased rate of encephalopathy in septic patients who received IV hydrocortisone.[47] More broadly, the biological underpinnings of delirium have yet to be fully understood, much less the role of endogenous cortisol in this process. Exogenous corticosteroids have been associated with both decreased and increased risk of delirium. The Hydrocortisone for Prevention of Septic Shock (HYPRESS) study unexpectedly found lower rates of delirium in patients treated with hydrocortisone than in those who received a placebo.[65] Thus, the current literature does not support a clearly positive or negative association between glucocorticoid use and delirium.[64]

Infection

Concern for promoting infection risk has long been a theoretical detractor to the use of corticosteroids in patients with sepsis and septic shock. However, only the CORTICUS study found increased rates of superinfection among the septic patients who received IV hydrocortisone.[45]

GI Bleeding

As with the risk of infection, the inhibition of gastroprotective prostaglandins and the risk of GI hemorrhage in already-predisposed critically ill patients has been of concern with glucocorticoid use in sepsis for decades. In aggregate, hospitalized patients receiving glucocorticoids have been found to have a

Table 2. Administration of Corticosteroids to Patients With Various Systemic Inflammatory Processes and Sepsis (Who, When, and How?).

Patient	Dose	Duration	Notes
Inpatients with SIRS Inpatients with sepsis	Do not treat		
Inpatients with meningitis	Dexamethasone 0.15 mg/kg q.6h beginning shortly before or at the same time as the initiation of antibiotics [52]	4 days	Early, adjuvant glucocorticoids in bacterial meningitis improve morbidity and mortality (primarily *Salmonella pneumoniae*), particularly in developed regions, as opposed to those developing[53,54]
Inpatients with CAP	Treat for severe CAP; however, there are no consensus statements regarding the dose	There is no consensus statement regarding the duration	The 2019 ATS and IDSA guidelines recommend against adjunctive glucocorticoids[55] A 2021 systematic review and meta-analysis showed a lower incidence in need for MV[56] A 2023 RCT showed decreased 28-day mortality in ICU patients with severe CAP who received IV hydrocortisone 200 mg daily for either 4 or 8 days depending on clinical improvement followed by tapering for a total of 8 or 14 days compared to placebo[57]
Inpatients with early non-COVID-19 ARDS requiring invasive MV	Dexamethasone 20 mg IV daily tapered to 10 mg IV daily	5 days up to 10 days unless extubated	In unresolving ARDS (7-21 days)[18]
	Methylprednisolone 1 mg/kg IV bolus followed by 1 mg/kg/day followed by slow taper	Up to 3 days or 28 days	Methylprednisolone 2 mg/kg IV bolus, then • Day 1-14: 2 mg/kg/day divided q. 6h • Day 15-21: 1 mg/kg/day • Day 22-28: 0.5 mg/kg/day • Day 29-30: 0.25 mg/kg/day • Day 31-32: 0.125 mg/kg/day If extubated prior to day 14, then advanced to day 15 of regimen drug therapy
Critically ill patients with septic shock	Hydrocortisone 200 mg IV daily as a continuous infusion or 50 mg q.6h		After >4 h of requiring norepinephrine or epinephrine $\geq$0.25 mcg/kg/min[50]

Abbreviations: CAP, community-acquired pneumonia; ARDS, acute respiratory distress syndrome; MV, mechanical ventilation; ICU, intensive care unit.

higher risk of GI bleed and perforation, but the same meta-analysis found the subset receiving corticosteroids for sepsis or septic shock not to have an increased risk of GI bleeding.[66] More importantly, at the commonly prescribed dose of glucocorticoids for septic shock, no major trials have established a direct link between steroid use and increased risk of GI bleeding.

Future Research Directions

As regards ongoing investigation into how best to manage critically ill patients with sepsis, a phase II, multicenter RCT[67] is currently underway to address one of the least understood aspects of corticosteroid therapy—the use of mineralocorticoids. In this study, the 200 mg IV daily dose of hydrocortisone will be compared to 3 different doses of fludrocortisone to identify the possible impact of this combination therapy on a variety of primary and secondary outcomes including mortality, length of stay, shock recurrence, and ventilator-free days.

A way to reframe the adrenal insufficiency in the sepsis narrative is to consider whether there may exist different phenotypes of adrenal response to sepsis. Various strategies of genome analysis have been proposed to categorize the human response to sepsis. Among these is the endotype A/B schema, which refers to differing patterns of genes expressed.[68] Adults with endotype A1 had a 5-fold increased mortality between the ages of 18 and 40 years, although these differences diminished by age 60. Other ways to characterize these patients have been investigated, including stratification by proteomics and transcriptomics.[69,70] One small study has suggested that there may be a group of critically ill patients with sepsis who are harmed by the administration of steroids. A post hoc analysis of the Vasopressin versus Norepinephrine as Initial Therapy in Septic Shock (VANISH) RCT,[71] which enrolled patients in shock and randomized them to receive norepinephrine or vasopressin followed by hydrocortisone or placebo was enlightening.[72] It identified 2 transcriptomic sepsis response signatures (SRSs), one relatively immune-suppressed (SRS1) and the other, immuno-competent (SRS2) with different outcomes after corticosteroid therapy. Patients with the immunocompetent SRS2 endotype who were treated with corticosteroids had higher mortality than those who were given a placebo but not those with the SRS1 endotype. While these findings are promising, further validation studies are needed, and it is too early to consider them useful when managing patients at the bedside.

Another novel multicenter study currently recruiting patients in France has the goal of enrolling patients with sepsis and septic shock, identifying the particular biomarker profile or phenotype they express, and randomizing them to receive either hydrocortisone and fludrocortisone or placebo. The goal of this study will be to identify any subsets of patients who may benefit or be harmed by treatment with corticosteroids. The primary outcome is mortality at 90 days or persistent organ dysfunction, and secondary outcomes will include vasopressor-free days. Enrollment is expected to be completed by 2025.[73]

Finally, as with any other study involving the critically ill, it is important that we consider our research goals. The most investigated outcomes of critical care trials are mortality, infection-related outcomes, and ventilation-related outcomes.[74] It is worth considering whether alternative patient-centered outcomes such as discharge home or to a skilled nursing facility or measures of functional status may be more meaningful to most clinicians and their patients.

Conclusions

Relative adrenal insufficiency or CIRCI occurs frequently in patients with sepsis due to dysregulation of the HPA axis, alterations in cortisol metabolism, and tissue resistance to glucocorticoids. Several large meta-analyses of RCTs have demonstrated that administration of corticosteroids results in reduced duration of septic shock, although the effects on mortality have been inconsistent, and their use is associated with potential adverse effects, most notably hyperglycemia. The optimal dose, timing of initiation, and duration of corticosteroid therapy for septic shock remain uncertain. The majority of critical care clinicians typically administer 200 mg/day of hydrocortisone IV in divided doses (or by infusion) for at least 3 to 5 days or until the vasopressor dose starts decreasing or is weaned off. Some clinicians may consider adding fludrocortisone at 0.05 mg (50 μg) orally once daily. In the near future, we can look forward to updated guidelines from the SCCM for more comprehensive guidance on dosing and duration of corticosteroid therapy in patients with septic shock.

Authors Contribution

All authors contributed to the conception and design, acquisition, analysis, and interpretation of data for the work and final approval of the revised manuscript.

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