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Review Article

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Adrenal Insufficiency in Critically Ill Patients: Conceptual Evolution, Pathophysiology, Diagnosis, and Therapeutic Recommendations.

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ABSTRACT

Corticosteroid insufficiency associated with critical illness (CIRCI) represents a dysfunction in the hypothalamic-pituitary-adrenal (HPA) axis that adapts to stress in patients suffering from severe conditions. This condition is different from a complete lack of cortisol and is marked by changes in cortisol metabolism, such as decreased levels of carrier globulin, central inhibition of the HPA axis, and peripheral resistance through glucocorticoid receptors. This review encapsulates experimental, translational, and clinical research concerning HPA axis regulation, cortisol availability, receptor signaling, and both diagnostic and therapeutic aspects of CIRCI. It highlights the adaptive nature of endocrine responses while also noting the possible inadequacies of total cortisol as a biomarker. In cases of severe illness, free cortisol levels may rise despite low ACTH due to reduced clearance rates and transporter protein functionality. Research indicates a weak correlation between standard testing methods and clinical outcomes. Hydrocortisone has been shown to alleviate shock and decrease reliance on vasopressors in septic shock scenarios, although its effects on mortality are varied. Lastly, assessing CIRCI necessitates consideration of a wider array of clinical and functional indicators beyond merely biochemical thresholds.

Keywords: Critical Illness, Adrenal Insufficiency, CIRCI, Hydrocortisone, Sepsis, HPA Axis, Intensive Care

Introduction

Cortisol as a Stress Hormone

Cortisol, the principal endogenous glucocorticoid, is pivotal in maintaining energy balance, regulating blood pressure and immune and vascular homeostasis [1]. Its secretion is tightly regulated by the hypothalamic-pituitary-adrenal (HPA) axis, maintaining time signature, a morning acrophase and adaptive amplification within acute stress, when serum levels could rise as much as fivefold above its baseline [2,3,4]. Physiologically, cortisol is produced in the fasciculate zone of the adrenal cortex in response to anterior pituitary-derived adrenocorticotropic hormone (ACTH) release [5,4]. ACTH release is controlled and regulated by corticotropin-releasing hormone (CRH) and arginine-vasopressin (AVP), which act synergistically on corticotropic cells (Figure 1). Under stress, noradrenergic modulation of the locus coeruleus enhances the excitability of CRH-dependent neurons and potentiates the activation of the HPA axis [6,4]. Additionally, peripheral inflammatory signals mediated by DAMPs (damage-associated molecular patterns) and PAMPs (pathogen-associated molecular patterns) drive inflammatory neuroendocrine and immunomodulatory activity, thereby inducing adrenal hormone production via Toll-like receptors without the effect of ACTH [7]. Collectively, the adaptive response of the HPA axis (Figure 2) accounts for the central and peripheral signaling, resulting in negative cortisol feedback on inflammation, metabolism, and vascular tone [8-12].

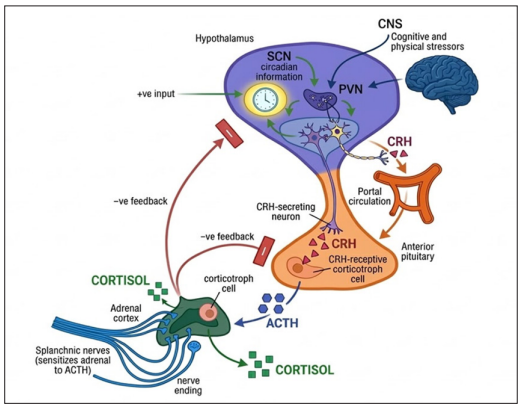

Figure 1: Central Adjustment of the HPA axis

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CNS: Central Nervous System, PVN: Paraventricular Nucleus of the Hypothalamus, SCN: Suprachiasmatic Nucleus of the Hypothalamus, CRH: Corticotropin-releasing Hormone, ACTH: Adrenocorticotropic Hormone, HPA Axis: Hypothalamic-Pituitary-Adrenal axis, +ve: Positive stimulation (green arrows), –ve: Negative feedback inhibition.

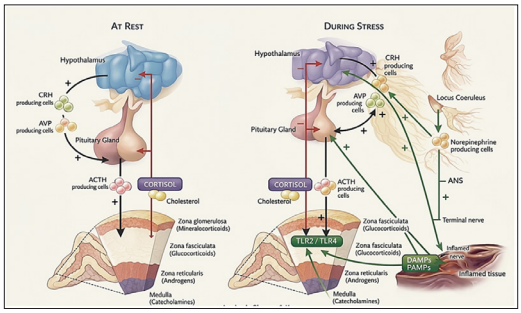

Figure 2: Glucocorticoid synthesis at rest and under external stress

Academic Glossary & Key: HPA: Hypothalamic–Pituitary–Adrenal, CRH: Corticotropin-Releasing Hormone, AVP: Arginine Vasopressin, ACTH: Adrenocorticotropic Hormone, TLR2/TLR4: Toll-like Receptors 2 and 4, DAMPs: Damage-Associated Molecular Patterns, PAMPs: Pathogen-Associated Molecular Patterns, PAMPs: Damage-Associated Molecular Patterns, ANS: Autonomic Nervous System, Arrow key: Positive stimulation (+), Negative inhibition (-), and directional flow (solid line with arrow)

Cognitive and Pathological Alterations in Cortisol Responses in Critical Disease

Serum cortisol is frequently raised in critically ill patients. Despite this improvement in hormone release, glucocorticoid signaling is frequently dysregulated at various levels—notably through reduced hypothalamic inhibition mediated by proinflammatory cytokines [13] to decreased sensitivity of tissues to glucocorticoids in target organs [14,15]. Increased systemic cortisol bioavailability in critical illness is also ascribed to reduced circulating transporters, reduced binding affinity of these proteins, and suppression of cortisol metabolism and clearance [16-19]. This stimulation of circulating free cortisol by peripheral mechanisms contributes to detrimental feedback of the hypothalamic-pituitary-adrenal axis, leading to low adrenocorticotropic hormone (ACTH) levels in many patients with serious illness [16,20,21]. Long-term suppression of ACTH levels has damaging effects on the structure and function of the adrenal cortex. Because the ACTH stimulation test is sensitive to decreases in the volume of cortisol distribution in the blood, its utility for evaluating adrenal function in critical illness is limited [17,22]. According to Vaidya et al. [4], however, adrenal insufficiency is a systemic pathophysiological disorder that has important implications for clinical outcomes in people with severe critical illness. Unlike classic primary or secondary adrenal insufficiency, CIRCI is a dysfunction of the HPA axis—the HPA axis is usually transient—that impairs the ability to respond effectively when acute physiological stress such as sepsis, trauma, surgery, and shock occurs, thus leading to an inappropriate adaptation to stress and leading to augmented morbidity and mortality. The plot below illustrates (Figure 3) normal biology for the HPA axis and a stress-induced activation of the axis.

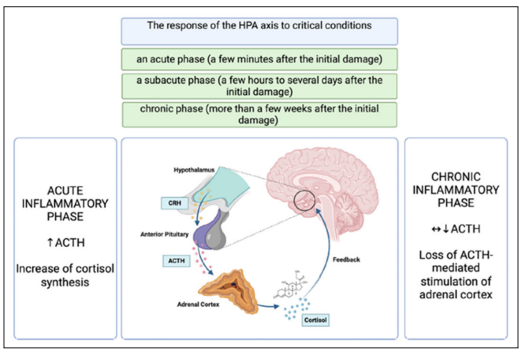

Figure 3: Response of the Hypothalamic-Pituitary-Adrenal Axis in the Context of Severe Disease (figure created by biorender.com).

Pathophysiology of CIRCI: What are the Biological Mechanisms to Control the Elevation of Systemic Cortisol in Acute Illness?

In critical disease, elevation of circulating cortisol is not only an indication of stress-resilient adrenal activation but also represents a radical and dynamic reorganization of its metabolism, bioavailability, and tissue signaling. More than the general rise in cortisol secretion, the endocrine system in the critically ill patient is largely controlled by peripheral mechanisms that extend half-lives and modify the biological action of cortisol. [23]. The liver and kidneys are the primary loci of clearance of cortisol [24,23]. In physiological conditions, inactivation is predominantly mediated by hepatic 5α/β-reductases and renal 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) [14]. In systemic inflammation, the activity of these enzymes is reduced, and, in turn, cortisol metabolism declines, thereby promoting cortisol accumulation [24,25]. Conversely, circulating cortisone that is inactive is locally converted into an active cortisol dose in extrarenal tissues such as liver, muscle, and adipose tissue by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) and mediated by pro-inflammatory cytokines including TNF-α and IL-1β [25,26]. This increased intracellular availability of cortisol may make tissue responses to stress heterogeneous [26]. Interestingly, hypercortisolemia does not lead to efficient glucocorticoid signaling because the condition coexists.

Systemic inflammation modifies cell sensitivity by lowering the glucocorticoid receptor [24]. The peripheral circulatory GRα, which mediates the metabolic, hemodynamic, and immunomodulatory properties of cortisol, in septic patients is lowered, and the functionally antagonistic GRβ isoform is typically elevated, leading to a GRα/GRβ imbalance with accompanying tissue resistance to glucocorticoids [14,27-29]. Indeed, translational data have shown that neutrophils contribute significantly to the loss of GRα expression during sepsis, whereas other tissues retain signaling, which explains the clinical variability observed in the response to hydrocortisone [14,27].

The following figures summarize the mechanisms that increase the systemic availability of endogenous cortisol in acute conditions (Figures 4 and 5).

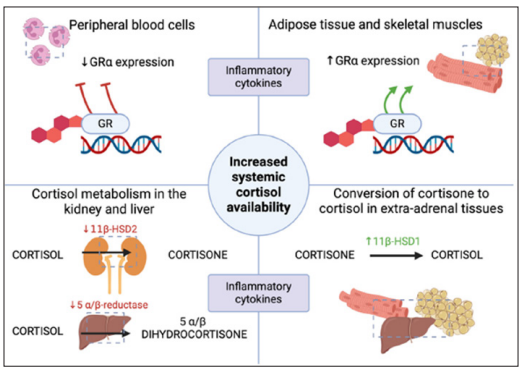

Figure 4: These Mechanisms Increase Systemic Cortisol Availability in Acute Conditions. (Figure created in BioRender.com). Abbreviations. GR: Glucocorticoid Receptor; 11β-HSD1: 11β-Hydroxysteroid Dehydrogenase Type 1; 11β-HSD2 :11β-Hydroxysteroid Dehydrogenase Type 2.

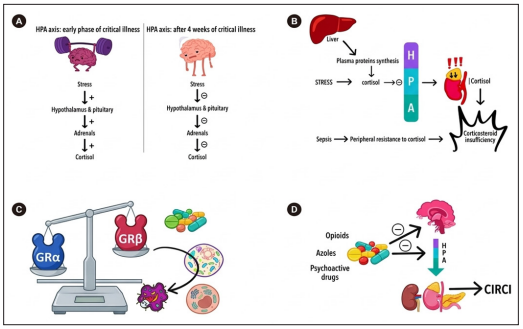

Figure 5: Pathophysiology of Critical Corticosteroid Deficiency Related to Disease (CIRCI). (A) Variation in the response of the hypothalamic-pituitary-adrenal (HPA) axis during critical illness. (B) Impaired cortisol metabolism, inhibition of the HPA axis, and peripheral cortisol resistance. (C) Resistance of tissues to corticosteroids. (D) Drug-Induced CIRCI. (Source: Acute and Critical Care, Ang 2024; 39(3):331–340). Abbreviations. GRα: glucocorticoid receptor alpha; GRβ: beta glucocorticoid receptor.

Temporal Dynamics of the HPA Axis in Critical Illness

Changes in the hypothalamic-pituitary-adrenal (HPA) axis in critical illness arise from the convergence of central and peripheral activities that time-dependently regulate the bioavailability and function of cortisol during the periods of acute, subacute and prolonged phases [30-32]. In the early phase (minutes to hours post-event), cortisol rises rapidly by the direct activation of the hypothalamic-pituitary-adrenal (HPA) axis and the release of ACTH. In tandem, the free fraction of cortisol is elevated due to decreased carrier proteins and altered receptor signaling, which, in turn, transiently enhances the peripheral glucocorticoid response. [17,33,32]. In the subacute phase, which lasts from hours to several days, a negative feedback mechanism of high free cortisol lowers ACTH release. Central inhibition does not fully counterbalance an elevated peripheral cortisol concentration, as peripheral cortisol clearance is less and its bioavailability is modified by tissue [17,33,32]. The sustained cortisol exposure elicits central HPA axis suppression during the prolonged phase, with a prolonged period for weeks.

Additional factors, including bile acid buildup, drug use, and chronic activation of central glucocorticoid receptors, help sustain feedback inhibition and result in functional central hypoadrenalism [17,33,32]. This temporally determined reorganization of the HPA axis is summarized, and the finding presented in Figure 6 reveals that critical illness is beyond the early stages of hormonal activation to evolve further toward a progressively dysfunctional endocrine adaptation with an immediate relevance to hemodynamic balance and resiliency to de novo stress in the critically ill patient [32].

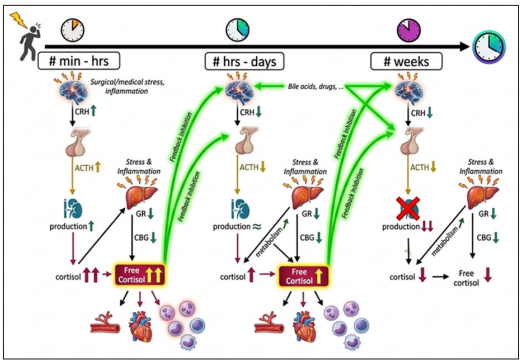

Figure 6: A Temporal Model of Neuroendocrine and Metabolic Responses to Critical Illness and Stress. (Based on conceptual work by Téblick et al., with concepts adapted from Nature Reviews Endocrinology 2019 [79].)

Time-Dependent Changes in ACTH and Cortisol Concentrations Across Critical Illness

In a chronologically mediated fashion, ACTH and cortisol levels are dynamic during critical disease. In the prospective study by Peeters et al. [34], low or normal ACTH levels were recorded on day 7 of admission, and total and free cortisol were higher than in healthy controls. More extended stays (> 4 weeks) showed more pronounced decreases in ACTH (P=0.09) and an elevation of free cortisol (P=0.002). ACTH or cortisol were similarly unaffected upon inhalation of glucocorticoids [34]. Though ACTH gradually recovered during the evolution and free cortisol decreased, relative central suppression remained, with no compensatory elevation of ACTH seen if free cortisol normalized [34,35].

Corticosteroid binding globulin (CBG) and albumin were lower compared to controls (increased cortisol-free fraction) [36,34]. On discharge from the ICU, a “rebound” was noted, with significant elevations of ACTH and cortisol, consistent with reversal of the suppression of the hypothalamic-pituitary-adrenal axis. [35-40]. Together, these findings suggest that free hypercortisolemia in critical illness does not reflect adrenal overproduction but instead results from a combination of central ACTH inhibition, reduced binding to carrier proteins, and decreased cortisol metabolism. Free cortisol normalization without parallel recovery of ACTH following prolonged illness further suggests enduring mechanisms of central inhibition that are hallmark of CIRCI [36-38,34-40].

Clinical Perspective on Adrenal Insufficiency in Critical Illness (CIRCI)

The concept of adrenal insufficiency in the critically ill patient has evolved from a dichotomy of “low cortisol levels” to a more integrated model that considers not only tissue resistance to glucocorticoids, changes in hormone bioavailability, and other enzymatic alterations that regulate biologically active free cortisol [36,41-42].

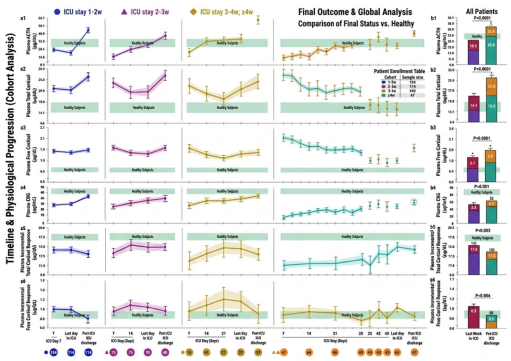

Figure 7: Physiological Evolution and Post-ICU Outcomes in Glucocorticoid-Free

(a) Simplified timeline and trend lines show the average evolution of adrenocortical function parameters for four distinct ICU length-of-stay cohorts from Day 7 to Post-Discharge, set against a 'Healthy Control Range' (shaded green). Shaded areas represent ± SEM over the timeline. Note the simplified representative days (7, 21, Last Day, Post-ICU 7d).

(b) Stacked bar charts provide a clear final comparison of 'All Patients' (n=347) across the six parameters, contrasting 'Last Week' and 'Post-ICU 7d' status. Bold value labels and legible P-values indicate statistical significance of these transitions with the control group. This re-visualization transforms complex raw data into clear, narrative trends for enhanced didactic value.

(Source: Intensive Care Med (2018), 44:1720–1729, page 1724 [80].

Biochemical Assessment of Adrenal Insufficiency (CIRCI)

The commonly used diagnostic marker for critical illness was total serum cortisol, and the system was stimulated with 250 µg cosyntropin (ACTH) [44]. However, the SCCM/ESICM consensus guideline 2008 [58] recommended that when the basal cortisol level is <10 µg/dL or the cortisol delta (post-ACTH level - basal cortisol) of the CIRCI is <9 µg/dL, the CIRCI should be determined [44,45].

Nevertheless, an inconsistency between hormone production from total cortisol and the amount of hormone active in metabolism was reported in patients with hypoalbuminemia, sepsis, or liver disease [17,46,47,22]. The deficiency has sparked new approaches [24,48,46]

a) Look into the so-called bioactive component of the hormone cortisol -- free cortisol.
b) Measure cortisol-binding globulin and serum albumin.
c) To use the hemodynamic response to corticosteroids as a functional marker of adrenal reserve. But there are significant diagnostic limitations:

- Binding-protein concentrations affect total cortisol [46,47,15].
- Most ICUs do not have free cortisol assays [48,46].
- There is a lack of agreement between the expression of affective and clinical response to ACTH stimulation and corticosteroids [17,48].
- At present, no single gold standard for CIRCI diagnosis is widespread [44, 48].

Why is the Diagnosis of CIRCI Complicated by Clinical and Hormonal Factors?

Clinical and endocrine diagnosis of CIRCI is difficult due to nonuniform disease pathology, heterogeneous symptom presentation, and limited access to diagnostic tools [17,44,49,50]. While classic adrenal insufficiency involves an absolute adrenal cortisol deficiency, CIRCI comprises an insufficient or suboptimal HPA axis signaling [17,44,43-49]. Hemodynamic phenotype-based clinical judgment (i.e., refractory shock with no detectable, reversible pathology) should be the primary diagnostic criterion in an assumed CIRCI diagnosis. The latest clinical guidelines, supported by a growing body of evidence, also advocate triage based on clinical grounds when assessing the potential usefulness of hormone replacement in suspected corticosteroid deficiency among people with critical illness, rather than relying on isolated biochemical markers [17,44-63]. Large randomized trials in septic shock support a phenotype-directed therapeutic approach: hydrocortisone may not reduce long-term mortality but may accelerate return to normotension during shock and ICU discharge, suggesting its greatest benefit lies in catecholamine-dependent shock control rather than in ACTH-guided intervention. [62-67]. Recent reviews indicate that biochemical assessment has significant limitations, including the heterogeneity of binding proteins, assay availability, and poor correlation with steroid reactivity; therefore, clinical context and therapeutic response must be integrated into the decision-making process. [17,63,64]. Clinically, a suspected CIRCI patient commonly presents:

(a) hypotension resistant to fluids and/or vasopressors [44,33,48];
(b) persistent (or recurrent) shock that is not clearly identified [44,33,48];
(c) unexplained hypoglycemia or resistant hyponatremia [34];
(d) multiorgan dysfunction with no identifiable alternate etiology [44,63].

While these findings are not diagnostic on their own, they are crucial for sustaining a high level of clinical suspicion and for conducting early, targeted assessment and treatment [4,65,64,51,52].

A Review of the Literature on CIRCI Therapy: What to use, When to Use it, How to Treat it, and What is Needed to use for CIRCI Patients

In the past twenty years, several randomized clinical trials have guided the therapeutic use of corticosteroids in critically ill patients with corticosteroid insufficiency related to critical illness (CIRCI) [44,67-98]. Although systemic corticosteroids are a cornerstone of therapy, the timing of initiation, dosing schedule, duration of therapy, and specific clinical targets remain contentious [67,98].

When to Start Treatment?

The guidelines outlined by the SCCM/ESICM [45], as well as guidelines that were confirmed through multicenter studies and the APROCCHSS and ADRENAL trials [65,66], recommend corticosteroid therapy on at least the following patients: a) persistent septic shock that is refractory to appropriate resuscitation with fluids and vasopressors [44,67-98], b) unexplained hypotension in critically ill patients threatened by adrenal dysfunction [44-98], c) hemodynamic instability in patients with mechanical ventilation and cardiovascular maladaptation and d) certain situations including major surgery, severe trauma, necrotizing pancreatitis [64].

For sepsis/multiorgan failure patients, routine corticosteroid drug treatment with no clear clinical indication is not feasible [26,36]. The APROCCHSS trial demonstrated that administering hydrocortisone and fludrocortisone reduced mortality in septic shock [66,98]. In contrast, the ADRENAL study did not show a benefit on overall mortality but did show faster shock reversal and a reduced need for vasopressors. [66-68]. The inappropriate or continued use of corticosteroids causes hyperglycemia, neuromuscular weakness, and bacterial or fungal infections [48,68].

What Corticosteroid Should be Administered and to What Amount?

Treatment should be initiated first and foremost on clinical and hemodynamic criteria, not solely on single biochemical characteristics [44,94]. In critically ill patients with elevated clinical suspicion and severe clinical suspicion for CIRCI, empirical therapy may be indicated after discarding pharmacological agents that depress the HPA axis. Hydrocortisone is the drug of choice as it is a glucocorticoid and a mineralocorticoid. Normally, the patient responds to a 200 mg/day IV infusion, either continuous or fractionated, or to 50 mg every 6 hours, used to maintain hemodynamic stability. Patients progress through clinical recovery from hours to days. Therapy should be refocused in the absence of hemodynamic improvement. The dose of corticosteroid agents should be slowly reduced until they show improvement on clinical assessments, normally when patients are within a 5-to-7-day recovery period, and then stopped to prevent an inflammatory response [44,48,67]. The recommendation is stringent, and a procedure has been established for the therapeutic management of critically ill patients with suspected or established CIRCI, including dose-dependent control measures. Even though its application is life-threatening, as already mentioned in the case of refractory shock, exposure to high doses, either by overtreatment or long treatments, is usually accompanied by metabolic, neuromuscular, and infectious complications [69]. Treatment is carefully escalated and de-escalated gradually and in a well-controlled setting. Given this, vasopressors should be gradually reduced or discontinued once hemodynamic control is achieved and clinical improvement is evident; consequently, the hydrocortisone dose should be reduced accordingly. The present strategy is expected to ward off the abrupt cessation of the hypothalamic-pituitary-adrenal (HPA) axis, which is responsible for transient secondary adrenal insufficiency [70]. Secondly, to prevent adrenal crisis related to iatrogenic glucocorticoid dependence among critically ill patients and, ultimately, to confirm clinical stability without continuous hormonal intervention [71]. We discontinue corticosteroids primarily based on clinical and hemodynamic progress.

Cosyntropin stimulation testing is not currently recommended to aid in weaning, except in cases of clinical relapse and ongoing suspicion of hypoadrenalism related to cessation of treatment [70-72].

Risks of Prolonged Corticosteroid Treatment in Critically ill Individuals

However, a risk profile of significant adverse events has been linked with chronic use of systemic corticosteroids in critically ill patients, especially when the duration of therapy is > 7-10 days without a sequential dose reduction. Such complications can range from persistent hyperglycemia with a greater need for insulin to immunosuppression that increases risk for nosocomial infections, from invasive mycoses to critically ill myopathy, glucocorticoid-induced neuropsychiatric problems, to inhibition of the hypothalamic-pituitary-adrenal (HPA) axis, limiting response to new physiological stimulation, as is the case with many other pharmacological agents [69,71]. Post-discharge follow-up from ICU.

Endocrinology's evaluation of patients with the presence of persistent fatigue, orthostatic hypotension, or after-discharge hypoglycemia after receiving corticosteroids for > seven days in the ICU should rule out iatrogenic secondary adrenal insufficiency [69,70,72]. The follow-up aims are: (1) to exclude persistent secondary adrenal insufficiency; (2) to capture the functional recovery of the HPA axis by dynamic testing; and (3) to delineate temporary steroid coverage plans in situations of new physiological stress. Dynamic HPA axis functional testing, such as cosyntropin stimulation tests (1 μg or 250 μg), total or free cortisol measurement, and baseline ACTH measurement, can also be performed when appropriate, and outpatient follow-up should include these [71,72]. It is also important to prepare for the possibility of transient glucocorticoid therapy during any stress conditions, particularly before procedures.

CIRCI Patient-Centered Decision Algorithm

Care for critically ill-related corticosteroid insufficiency (CIRCI) patients has been described as an integrated approach that uses clinical status, selected laboratory measures, and patient response to available treatment [44,73].

The following algorithm briefly describes the diagnostic and therapeutic strategy for critically ill patients with suspected CIRCI (Figure 8):

The clinical algorithm can help both clinical and intensive care teams make informed, individualized decisions that are sensitive to the pathophysiology of CIRCI. Its use can reduce mortality from refractory shock and complications arising from inappropriate use of glucocorticoids.

New Biomarkers for CIRCI: a Diagnostic Revolution?

Notably, the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) updated their guidelines in 2024 to prevent the indiscriminate use of corticosteroids and to recommend their use only in judicious clinical settings [44,73] a diagnostic revolution for new biomarkers for CIRCI. Classically, the diagnosis of critically ill-related corticosteroid insufficiency (CIRCI) has been derived from the measurement of serum total cortisol. It is challenging to apply this approach to severely ill patients; carrier status, stress-response variability, peripheral metabolic changes, and the mismatch with reality have all been reported to have serious drawbacks [74-79].

Therefore, alternative biomarkers are proposed for enhancing diagnostic accuracy and pathophysiological investigation of the hypothalamic-pituitary-adrenal (HPA) axis. Plasma cortisol, salivary cortisol, is released. Free cortisol consists of a biologically active fraction unbound from cortisol binding globulin (CBG) or albumin and can exhibit dissimilar characteristics from total cortisol in critically ill patients [78,80]. An equilibrium dialysis

or ultrafiltration-derived quantification correlates more strongly with clinical severity and HPA axis functional state [4]. Unaffected by clinical features of open-airway insufficiency or disease, salivary cortisol, as an indirect measure of free cortisol, is limited in intubated patients with mucositis or hyposalivation [6]. However, this test has the advantage of greater physiological fidelity to real hormone activity. But it suffers from several limitations, including a lack of methodological standardization, restricted availability, and long processing times adrenocorticotropic hormone (ACTH) [80]. ACTH differentiates between primary adrenal insufficiency (elevated levels of ACTH) and secondary or tertiary forms (low or inappropriately normal levels of ACTH). However, its diagnostic utility in the ICU setting is limited by circadian irregularities, cytokine-mediated suppression, Drug-Induced variability, and essential stress [91,78]. Cortisol/albumin, and cortisol/CBG ratio.

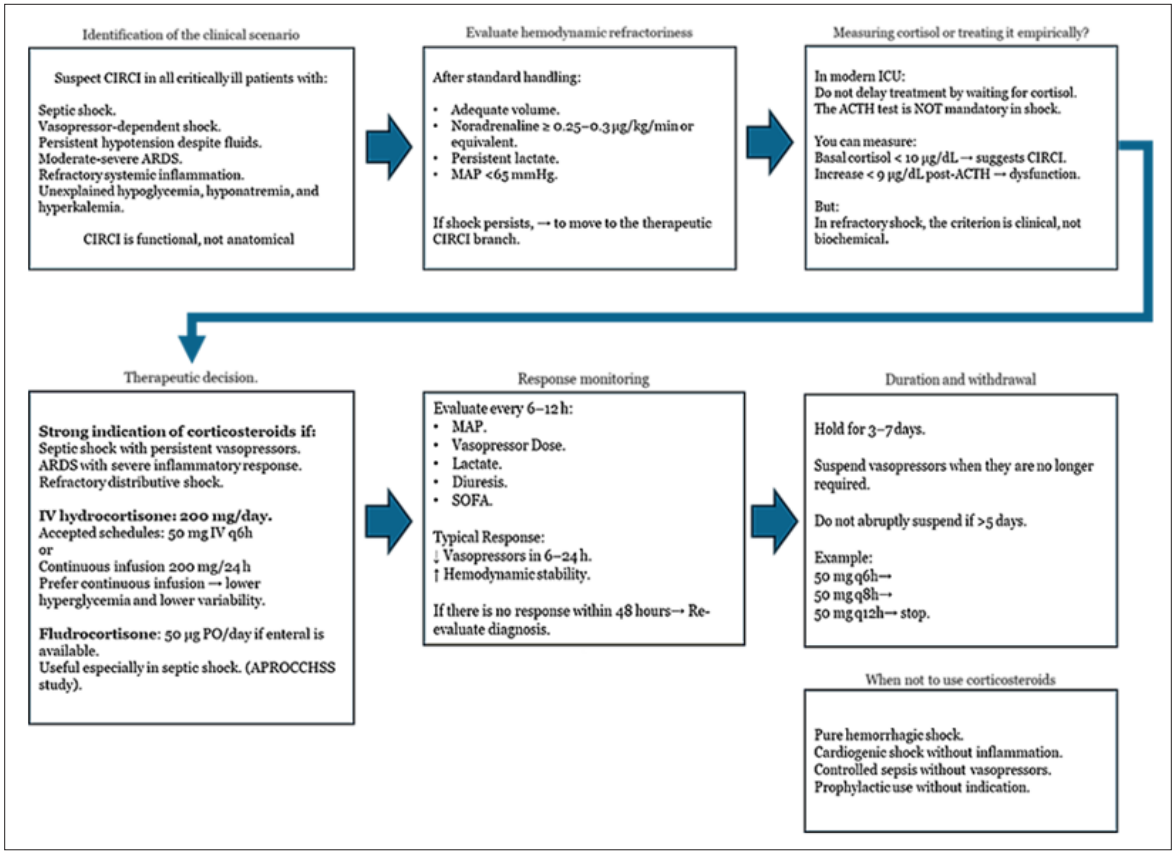

Figure 8: Clinical decision algorithm for treating CIRCI in the ICU (graph created by Rafael Reaño, MD).

While there are no established cut-points, the cortisol/albumin and cortisol/CBG ratios provide a simplified estimate of the biological fraction by integrating total cortisol with its corresponding carrier proteins [80]. Some studies have shown that a low cortisol/albumin ratio is associated with worse prognosis in sepsis.

In critical illness, indirect biomarker research has shown promise in characterizing HPA axis dysregulation along with glucocorticoid resistance. The most-published ones are: (a) interleukin-6 (IL-6), a signal of systemic inflammation and associated peripheral resistance to glucocorticoids; (b) copeptin, a stable peptide derived from the precursor of AVP, which indicates neuroendocrine activation and functional integrity of the HPA axis and (c) glucocorticoid resistance indices, as determined by expression ratios of glucocorticoid receptor isoforms (GRα/GRβ) alone or by ex vivo functional tests evaluating the potential of cortisol to suppress inflammation in immune cells. Although these markers provide complementary assessment of function to serum cortisol, they remain under prospective validation for clinical applicability [78,81]. However promising they are, these biomarkers have not yet been incorporated into primary diagnostic algorithms and applied in a systematic clinical setting; multicenter prospective validation is essential as a first step. CIRCI in common clinical settings. Early diagnosis of CIRCI is based on both pathophysiology and a high index of clinical suspicion, particularly in settings with high prevalence. In these contexts, glucocorticoid therapy should be used primarily on the basis of clinical and hemodynamic criteria [44,92-95,73,85].

Practical Clinical Settings for CIRCI.

Early diagnosis depends on understanding CIRCI pathophysiology and clinical suspicion, particularly in high-prevalence settings. In these situations, glucocorticoid therapy is indicated based on clinical and hemodynamic criteria [44,92-95,73,85]. Severe sepsis and septic shock. It is the most studied scenario.

In septic shock, CIRCI can occur in 25%-40% of patients, especially if hypotension remains despite adequate resuscitation with adequate fluids and vasopressors, with persistent lactic acidosis and poor hemodynamic response. Therapeutic recommendations: intravenous hydrocortisone 200 mg/day in refractory shock, with possible other benefits of fludrocortisone in a few studies [58,59,67-97,73].

Severe polytrauma. Traumatic brain injury, massive hemorrhage, and multiple fractures can elicit transient HPA axis dysfunction secondary to bilateral adrenal hemorrhage or post-traumatic

pituitary injury leading to acute adrenal insufficiency [40-82]: major surgery and complex recovery post-operation. Heavy surgery like liver transplantation, heart surgery with heart-lung circulation, laparotomies for abdominal sepsis, and the resulting physiological stress level can be overwhelming.

Suspicion of CIRCI should be raised if hemodynamic insufficiency persists, by preferring clinical examination over isolated cortisol readings [26,69,99] prolonged mechanical ventilation or challenging weaning. A prolonged ICU stay is associated with central suppression of the HPA axis and changes in cortisol bioavailability, which are linked to ICU-acquired weakness and respiratory distress [54,79,82]. Axis dysfunction should be considered when unexplained diaphragmatic fatigue, post-extubation hypotension, or critical myopathy with generalized weakness are present. Severe COVID-19 and Hyperinflammation. In severe cases of COVID-19, dexamethasone (6 mg/day) has been demonstrated to lower mortality in patients on oxygen or mechanical ventilation. WHO clinical guidelines recommend corticosteroids in severe or critical cases but not in mild disease [51,53,55,77,100]. These circumstances emphasize the vital need to supplement biochemical indices with clinical context, hemodynamic evolution, and clinical response. Clinical targeted suspicion is essential to the development of early interventions to both prevent mortality and optimize functional results, and, in the present age population, is one of the potential strategies for reducing overall patient mortality

Conclusión

- The hypothalamic-pituitary-adrenal axis plays a pivotal role in the body's ability to adapt to stress. Its malfunction in an acute condition can disturb cardiovascular, metabolic, and immune homeostasis.
- Thus, CIRCI is not commonly manifested as low levels of total cortisol but as insufficient production of hormones due to stress and tissue resistance to glucocorticoids.
- Consider the condition of CIRCI in patients with septic shock who do not respond to fluids or vasopressors, particularly if no correctable cause is recognized.
- Diagnosis is still clinical and contextual; specifically, patients with refractory hypotension, sustained septic shock, and unexplained multi-organ failure should be identified.
- Do not rely on total basal cortisol alone in decision-making. It integrates clinical data, hemodynamic responses, and, where available, free or corrected cortisol levels.
- When indicated, you should use an intravenous hydrocortisone (either bolus or infusion) as standard treatment, without having to use additional fludrocortisone.
- See treatment-related complications, including hyperglycemia, secondary infections, and muscle weakness.
- Conventional hormone testing (total cortisol and cosyntropin test) is limited; new techniques based on free cortisol, ACTH, or corrected indices are being studied.
- Intravenous hydrocortisone therapy does improve hemodynamic status in particular patients yet should be used cautiously and avoided for prolonged periods of time without clear indications.
- Progressive de-escalation and follow-up in the ICU are necessary for preventing iatrogenic adrenal insufficiency or steroid withdrawal syndrome.
- Gradually decrease the steroid dose between the 5th and 7th day with clinical improvement.
- Refer to endocrinology any patient who receives over 7 days of corticosteroids or presents with signs and symptoms of secondary adrenal insufficiency after discharge.
- We need more prospective studies and functional diagnostic tools to assess the subgroups of patients who benefit from corticosteroid therapy.

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Conflict of Interest

The author declares that he has no conflicts of interest.

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