Review Article

CIRMI—a new term for a concept worthy of further exploration: a narrative review

Gladness Dakalo Nethathe[1,2,3]^, Jeffrey Lipman[3,4,5]^, Ronald Anderson[6]^, Charles Feldman[1]^

[1]School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [2]Department of Anaesthesia and Perioperative Medicine, Royal Brisbane and Women's Hospital, Queensland, Australia; [3]Faculty of Medicine, The University of Queensland, Queensland, Australia; [4]Intensive Care Services and Jamieson Trauma Institute, Royal Brisbane and Women's Hospital, Butterfield Street, Herston, Brisbane, Queensland, Australia; [5]Scientific Consultant, Nimes University Hospital, University of Montpellier, Nimes, France; [6]Department of Immunology, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa

Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: GD Nethathe; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Gladness Dakalo Nethathe. Staff Specialist, Department of Anaesthesia and Perioperative Medicine, Level 4, Ned Hanlon Building, Royal Brisbane and Women's Hospital, Butterfield Street, Herston, Brisbane, 4029, Queensland, Australia. Email: gladness.nethathe@wits.ac.za.

Background and Objective: Critical illness-related corticosteroid insufficiency (CIRCI) describes hypothalamic-pituitary-axis impairment during critical illness associated with three major pathophysiological events; dysregulation of the hypothalamic-pituitary-axis, altered cortisol metabolism, and tissue corticosteroid resistance. Similar changes are evident with regard to mineralocorticoid dysfunction in critical illness. Hyperreninemic hypoaldosteronism describes a sub-population of critically ill patients with an impaired adrenal aldosterone response to increased levels of renin. In the light of the recent demonstration of significant mortality improvements associated with adjunctive glucocorticoid treatment in combination with fludrocortisone in septic shock, and the suggestion that angiotensin II is effective in treating vasodilatory shock, the clinical relevance of mineralocorticoid dysfunction in critical illness requires further exploration. This interpretative review considers hyperreninemic hypoaldosteronism, a concept worth re-examining in the light of the potential mortality benefit of mineralocorticoid supplementation in critical illness. We compare the pathophysiological and clinical characteristics of CIRCI and hyperreninemic hypoaldosteronism, two syndromes that represent corticosteroid and mineralocorticoid dysfunction in critical illness. We highlight gaps in the literature and give novel insights into the limitations of assessment, diagnosis and treatment.

Methods: English language abstracts and articles published before June 2021 were identified through PubMed and Google Scholar. Randomized trials, observational studies, basic sciences studies, systematic and narrative reviews were considered. Reference lists of articles were searched for further relevant material.

Key Content and Findings: Difficulties are encountered in interpreting measures of gluco- and mineralocorticoid activity in critical illness. Aldosterone levels, like cortisol, have been shown to be increased in sepsis and hemorrhagic shock. The finding of hyperreninemia and hyperaldosteronism with an aldosterone/plasma renin activity ratio below 2 should prompt consideration of hyperreninemic hypoaldosteronism, a finding, which likely signifies the loss of negative feedback control of the renin-angiotensin-aldosterone system.

Conclusions: As there is evidence to suggest that in acute critical illness, hyperreninemic hypoaldosteronism, is associated with poor outcomes, co-administration of hydrocortisone with fludrocortisone in patients with septic shock should be considered. In keeping with the concept of CIRCI, we suggest the term critical illness-related mineralocorticoid insufficiency as a more appropriate description

^ ORCID: Gladness Dakalo Nethathe, 0000-0001-6875-8422; Jeffrey Lipman, 0000-0002-5965-9876; Ronald Anderson, 0000-0002-5925-6452; Charles Feldman, 0000-0002-6881-8314.

of the impaired aldosterone response to increased levels of renin seen in this group of patients.

Keywords: Adrenal insufficiency; critical illness; glucocorticoids; mineralocorticoids; corticosteroid insufficiency

Submitted Oct 28, 2021. Accepted for publication Apr 09, 2022.
doi: 10.21037/atm-21-5572
View this article at: https://dx.doi.org/10.21037/atm-21-5572

Background

Critical illness-related corticosteroid insufficiency (CIRCI) describes hypothalamic-pituitary-axis impairment during critical illness, arising from a concern that global tissue availability of cortisol is altered, which influences outcomes in the critically ill (1-4). A recent task team has described three major pathophysiological events in CIRCI; dysregulation of the hypothalamic-pituitary-axis, altered cortisol metabolism, and tissue corticosteroid resistance (1). Although there is no single test that can reliably diagnose CIRCI, a delta cortisol (change in baseline cortisol at 60 min of <9 µg/dL) after intravenous cosyntropin (250 µg) and a random plasma cortisol of <10 µg/dL may be used (5). Similar changes are evident regarding mineralocorticoid dysfunction in critical illness (6,7). One such aldosterone dysfunction syndrome is selective hypoaldosteronism, which describes a sub-population of critically ill patients with an impaired adrenal aldosterone response to increased levels of renin, and is defined by the finding of hyperreninemia and hyperaldosteronism with an aldosterone/plasma renin activity (ALDO/PRA) ratio below 2. Alternatively termed hyperreninemic hypoaldosteronism, selective hypoaldosteronism has been described in both hemodynamically unstable critically ill adult and pediatric patients with severe trauma and septic shock (8-11). Aldosterone deficiency/dysfunction syndromes have, however, not been well characterized in critical illness, and like corticosteroid replacement in CIRCI, the indication for mineralocorticoid replacement or modulation of the renin-angiotensin-aldosterone system in this group remains controversial.

In this interpretative review, we consider hyperreninemic hypoaldosteronism, a concept worth re-examining given the recent demonstration of significant mortality improvements associated with adjunctive glucocorticoid treatment in combination with fludrocortisone in septic shock (12). The suggestion that angiotensin II is effective in treating vasodilatory shock further highlights the potential role of therapeutic approaches targeting the renin-angiotensin-aldosterone system in septic shock (13).

Objective

We summarise and compare the pathophysiological and clinical characteristics of CIRCI and hyperreninemic hypoaldosteronism, two syndromes that represent glucocorticoid and mineralocorticoid dysfunction in critical illness. We explore diagnostic challenges encountered in interpreting measures of glucocorticoid and mineralocorticoid activity in the critically ill. Current gaps in the literature are highlighted and novel insights into the limitations of assessment, diagnosis and treatment are presented (11).

Furthermore, the term CIRCI is well established despite the associated diagnostic challenges. In keeping with the concept of CIRCI, we thus suggest the term critical illness-related mineralocorticoid insufficiency (CIRMI) as a more appropriate description of the impaired aldosterone response to increased levels of renin seen in this group of patients. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-21-5572/rc).

Methods

We identified source references through searches of PubMed and Google Scholar for English language abstracts and articles published before June 2021. Randomized trials, observational studies, basic sciences studies and systematic and narrative reviews were considered. We focused on mineralocorticoid dysfunction and critical illness. The keywords used include: the terms “adrenal”, “adrenal insufficiency”, “mineralocorticoid insufficiency”, “critical illness”, “aldosterone”, “critical illness corticosteroid insufficiency”, “stress response”, “renin-angiotensin-aldosterone-system”, “hyperreninaemia”, “hypoaldosteronism”, “hyperreninaemic hypoaldosteronism”, “glucocorticoid receptors” and “mineralocorticoid

Table 1 The search strategy summary

Items	Specification
Date of Search	The initial search was conducted on 12/10/2017
Databases and other sources searched	Google Scholar, PubMed
Search terms used	Terms used included "adrenal", "adrenal insufficiency", "mineralocorticoid insufficiency", "critical illness", "aldosterone", "critical illness corticosteroid insufficiency", "stress response", "renin-angiotensin-aldosterone-system", "hyperreninaemia", "hypoaldosteronism", "hyperreninaemic hypoaldosteronism", "glucocorticoid receptors" and "mineralocorticoid receptors"
Timeframe	English language abstracts and articles published before June, 2021
Inclusion and exclusion criteria	English language abstracts and articles
Selection process	GDN identified source references. Randomized trials, observational studies, basic sciences studies and systematic and narrative reviews were considered. Reference lists of original articles, narrative reviews, clinical guidelines, and previous systematic reviews and meta-analyses were searched for further relevant material. Citations from articles identified in these searches were also reviewed and included, where appropriate

receptors". These keywords were used as single search terms and in combinations. Reference lists of original articles, narrative reviews, clinical guidelines, and previous systematic reviews and meta-analyses were searched for further relevant material. Citations from articles identified in these searches were also reviewed and included, where appropriate. The search strategy summary is presented in *Table 1*.

Selected basic physiology

Challenges to the concept of adrenal functional zonation

The standard description of the mammalian adrenal is that of a gland that consists of a cortex and medulla (14). The adrenal cortex consists of the zona fasciculata, zona reticularis and zona glomerulosa. Each zone is understood to have a distinct role in secreting glucocorticoids, androgens and aldosterone respectively, an observation referred to as 'functional zonation' of the adrenal cortex (15,16). Such zonal differences in enzyme concentrations are generally understood to result in compartmentalization of enzymatic reactions (17). Individual zones are, however, not distinctly autonomous in their production of steroids (18,19). The zona glomerulosa; for instance, does not appear to have all the enzymes required for aldosterone biosynthesis (18). Aldosterone synthase expression is understood to be restricted to the zona glomerulosa; however, expression of the enzyme by a cell population of zona glomerulosa cells, as well as by the brain, blood vessels, and the heart, has been described (14,20-23). Such integrated functions imply that pathology affecting an adrenal zone such as that may occur in critical illness due to widespread inflammation, is more likely to have widespread effects affecting the entire adrenal cortex and its mediators, rather than be localised to one specific zone (18).

The zona reticularis, the innermost adrenal cortical layer, secretes androgens (dehydroepiandrosterone, dehydroepiandrosterone sulphate and androstenedione), which are not the focus of this review (24,25).

The stress response and steroid biosynthesis

Mechanisms involved in regulating the normal hypothalamic axis and the stress response in critical illness have been extensively reviewed (26-32). *Figure 1* illustrates the hypothalamic-pituitary-adrenal axis during acute critical illness.

Corticotrophin leads to increased synthesis of most steroidogenic pathway enzymes, and an increase in production and secretion of all adrenal steroids, a process termed steroidogenesis (3,36-38). With specific reference to aldosterone, aldosterone synthase (CYP11B2), primarily expressed in the zona glomerulosa, converts deoxycorticosterone to aldosterone through the intermediates, corticosterone and 18-hydroxycorticosterone (16,28,39,40). Further corticotrophin release is inhibited by a negative feedback mechanism (41-43). Adrenal stimulation through non-pituitary mechanisms occurs as a result of direct adrenal stimulation by cytokines, adipokines, neuropeptides and other mediators (42,43). Corticotrophin levels are typically low in acute critical illness due to factors

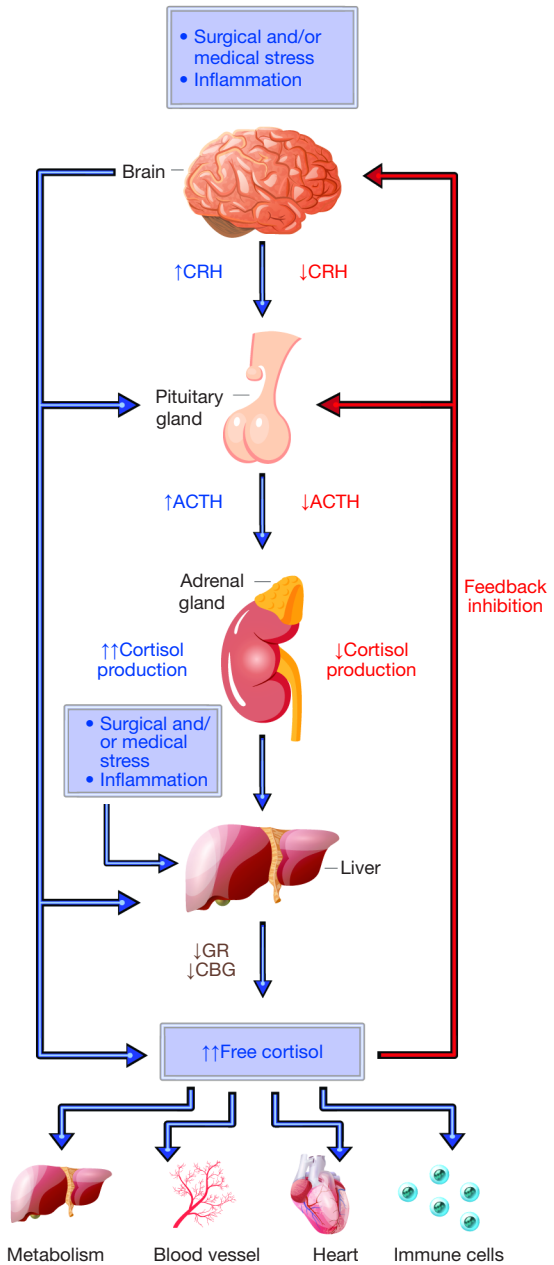

Figure 1 The hypothalamic-pituitary-adrenal axis during acute critical illness. CRH mediates the release of ACTH from the pituitary in response to stress and/or inflammation. ACTH, in turn, results in increased cortisol production from the adrenal gland. The increase in pro-inflammatory mediators during acute inflammation results in a reduction in CBG and plasma albumin and/or downregulation of hepatic GR, with a subsequent increase in free cortisol levels (33-35). CRH, Corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; CBG, cortisol binding globulin; GR, glucocorticoid receptors.

such as negative feedback inhibition because of high free cortisol levels seen in critical illness (44). This has been demonstrated up to day 28 of illness. Importantly in one study, even when cortisol levels begin to decrease if illness persists beyond 4 weeks, corticotrophin levels did not rise until later during recovery (44). The low corticotrophin seen in acute critical illness is of interest as experimental evidence suggests that corticotrophin is required for normal aldosterone production (45). Reduced levels of aldosterone have been shown in a pro-opiomelanocortin-knockout mouse model, suggesting a mechanism through which derangements in cortisol physiology are associated with derangements in aldosterone physiology during critical illness (45).

Chronically, the effects of corticotrophin on aldosterone secretion appear to oppose those of acute corticotrophin secretion (46). Plasma levels of aldosterone decline and, histologically, chronic corticotrophin (≥2 days) results in adrenal hyperplasia, increased conversion of zona glomerulosa cells to zona fasciculata cells, atrophy of the adrenal zona glomerulosa, and the resultant diversion of precursors from the mineralocorticoid pathway to the glucocorticoid pathway (28,46). The duration of the pathophysiological derangement should thus be taken into consideration if mineralocorticoid supplementation or antagonism is to be employed.

Regulation of aldosterone secretion, the mineralocorticoid receptor and mineralocorticoid activity

Classically, aldosterone, angiotensin II and renin regulate extracellular fluid balance, sodium and potassium (46,47). Other peptides and receptors have also been demonstrated to be involved in regulating aldosterone release (48,49). The regulation of the renin-angiotensin-aldosterone system is demonstrated in *Figure 2*. Variations in plasma/serum levels of aldosterone additionally occur within different populations, as well as across age and gender (7,22,47). Interestingly, corticotrophin does not appear to play as significant a role in regulating aldosterone secretion as it does in cortisol secretion (28,46,47,50). Additionally. pharmacological agents such as heparin, adrenaline and dopamine, as well as atrial natriuretic peptide, have been shown to modulate aldosterone secretion (21,46).

The mineralocorticoid receptor is co-expressed with the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) in epithelial tissue, and in certain types of non-epithelial tissue such as the human heart (51,52).

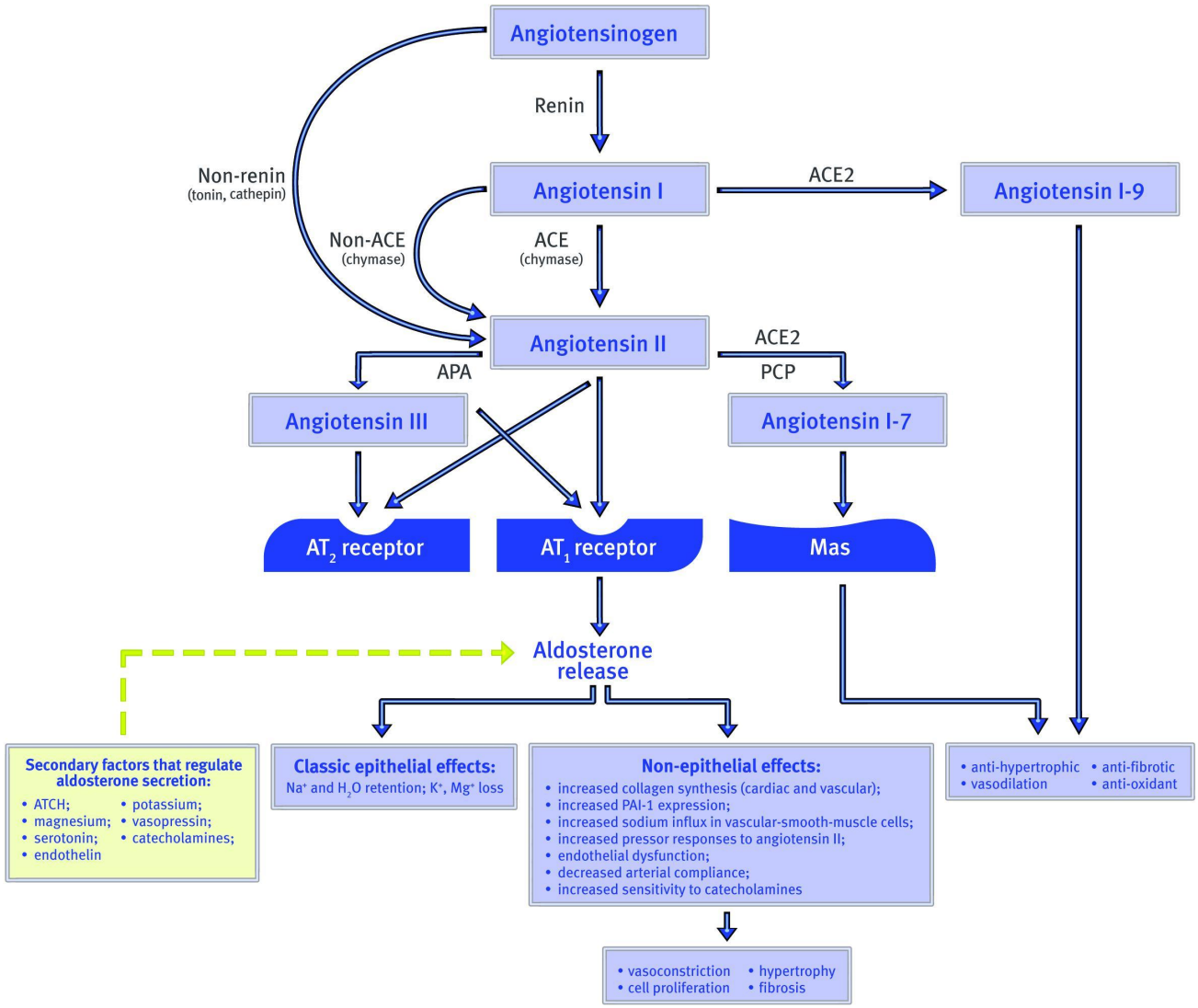

Figure 2 Renin Angiotensin Aldosterone System. Angiotensin I, a result of the conversion of angiotensinogen by the action of renin, is converted to angiotensin II through the action of angiotensin converting enzyme (ACE). Further peptides and receptors have since been demonstrated to be involved in the cascade that regulates aldosterone release. ACE, angiotensin converting enzyme; ADH, antidiuretic hormone; APA, aminopeptidase A; PCP, prolyl carboxypeptidase; Mas, mitochondrial assembly receptor; AT_1 receptor, angiotensin II type 1 receptor; AT_2 receptor, angiotensin II type 2 receptor; K^+, potassium; Mg^{2+}, magnesium.

The inhibition of 11β-HSD2, an intracellular isoenzyme, which converts cortisol to cortisone, allows cortisol to function as a mineralocorticoid receptor agonist (52,53). In aldosterone-selective tissues, 11β-HSD2, prevents cortisol binding to mineralocorticoid receptors, rendering mineralocorticoid-responsive tissues such as the kidney, sensitive to mineralocorticoids only (54-57). Defective 11β-HSD2 activity has been demonstrated in inflammatory states, and in the syndrome of apparent mineralocorticoid excess, signifying enhanced glucocorticoid activation of renal mineralocorticoid receptors (52,58,59). To the contrary, pro-inflammatory cytokines upregulate 11β-HSD1. This balance of reduced 11β-HSD2 activity with upregulated 11β-HSD1 activity is predicted to increase local glucocorticoid concentrations.

In contrast to cortisol, aldosterone is not bound to plasma proteins, rendering it less affected by alterations in protein binding and plasma protein concentrations that are observed

in critical illness (47). Effects of aldosterone are mediated through mineralocorticoid and non-mineralocorticoid receptors and are understood to be regulated by both genomic and non-genomic mechanisms (53,56,60). Genomic mechanisms were previously understood to be mediated exclusively through the nuclear pathways, translation and transcription, which take several hours to be effective and are mediated via the mineralocorticoid receptor (46,61). Rapid genomic mechanisms, that are activated within minutes, also exist (61,62). Aldosterone additionally operates via non-genomic mechanisms, activated by second messenger pathways (61,63).

Interestingly, aldosterone and estrogens, but not cortisol or corticosterone, have been shown to activate the transmembrane G-protein-coupled receptor 30 (GPR30 receptor), a receptor demonstrated to be involved in non-mineralocorticoid receptor-mediated rapid aldosterone actions (63-66). GPR30 has been postulated to result in the activation of phosphatidylinositol 3-kinase-dependent contraction and extracellular signal-regulated kinase activation in vascular smooth muscle cells (63) More recently, G-protein-coupled estrogen receptor-1 (GPER-1), as well as angiotensin receptor type 1 (AT1), have been demonstrated to play a role in aldosterone-mediated rapid effects (61). Thus aldosterone mediates its rapid actions through both mineralocorticoid and mineralocorticoid-independent pathways (61,63,66). Furthermore, there is evidence to suggest that rapid aldosterone actions are involved in the regulation of classical genomic actions (65). Genomic and non-genomic effects of aldosterone and cortisol are demonstrated in *Figure 3*.

Notably, aldosterone has been demonstrated to achieve greater transactivation than other ligands at the mineralocorticoid receptor (46). On the contrary, the effects of cortisol on the mineralocorticoid receptor depend on the underlying disease process. Cortisol can act as both an agonist and an antagonist at the mineralocorticoid receptor (67). Mineralocorticoid antagonistic effects, which are when cortisol binds to the mineralocorticoid receptor, but does not result in its activation, occur under physiological conditions. In conditions of high oxidant stress, cortisol acts as a mineralocorticoid receptor agonist (67). Therefore, although cortisol has similar affinity for mineralocorticoid receptors as aldosterone, the understanding that the resultant functions thus overlap may be inaccurate due to the molecular structural versatility of cortisol, the variable effects of cortisol at the mineralocorticoid receptor, and the differences in downward signalling, between the two ligands, aldosterone and cortisol, at the mineralocorticoid receptor (64). These variations in receptor utilisation support the need for further investigations on the additive beneficial role of fludrocortisone in combination with hydrocortisone in critical illness (68).

Changes in adrenal physiology with critical illness

Cortisol metabolism, tissue glucocorticoid activity and sensitivity in critical illness

The reduction in plasma albumin and corticosteroid binding globulin, altered protein binding, downregulation of hepatic glucocorticoid receptors, increased volume of distribution and altered 11β-HSD2 activity that occurs in critical illness, results in an increase in the free fraction and bio-availability of cortisol (53,64,69,70). Furthermore, a dissociation between total and free cortisol concentrations occurs over time in acute illness (70). Glucocorticoid tissue action is determined by a combination of tissue cortisol bioavailability, tissue glucocorticoid receptor density and glucocorticoid intracellular metabolism (59,71).

The glucocorticoid receptor is cytosolic in its unbound form, is expressed in almost every human cell and regulates genes that affect metabolism and the immune system (71). The receptor is involved in the adaptation to physiological stress, with the receptor-glucocorticoid complex regulating the expression of anti-inflammatory proteins in the nucleus or suppressing the expression of pro-inflammatory proteins in the cytosol. Inflammation and cytokines significantly affect glucocorticoid receptor number and function (72-74). A decrease in both binding activity and glucocorticoid receptor-mediated transcription, have been shown in acute respiratory distress syndrome (75). On the contrary, however, increased glucocorticoid receptor expression and binding capacity have been demonstrated in burn injury (73). The demonstration of reduced cortisol metabolism in sepsis implies increased exposure to cortisol at tissue level, suggesting that lower doses of hydrocortisone than previously advocated, may be sufficient if steroid supplementation is to be used (4,59,76). A mortality benefit of corticosteroid supplementation was not demonstrated, however, in the *Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock* (*ADRENAL*) trial (77). In this context, *in vitro* glucocorticoid sensitivity has been shown to be associated with disease severity and to be highly

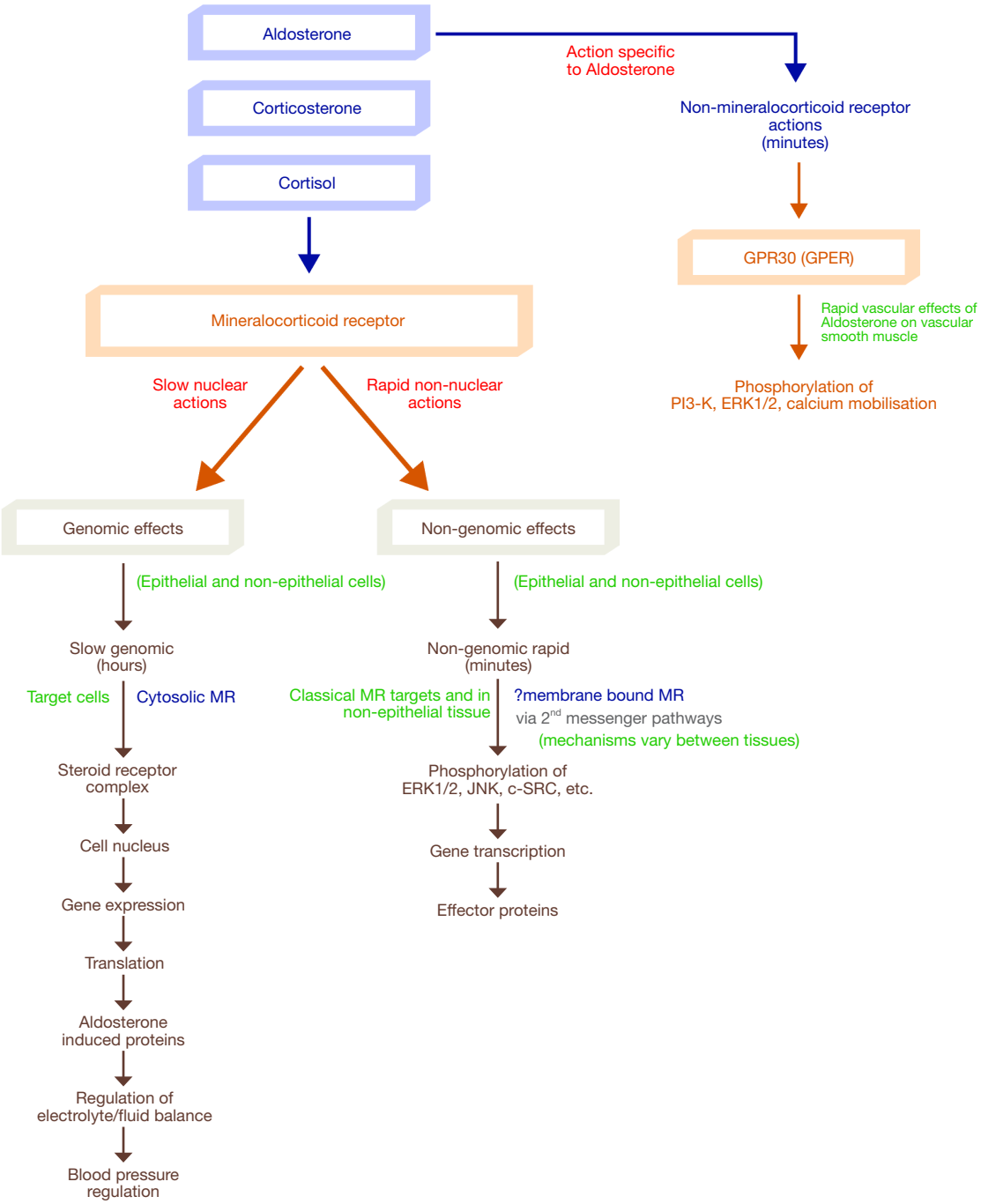

Figure 3 Aldosterone action; genomic and non-genomic effects of aldosterone and cortisol. Classical slow genomic actions mediated through the MR result in gene transcription and the production of effector proteins. Fast actions mediated through a surface receptor, which interact with the classic genomic actions, have been recently described to be mediated through the G-protein coupled receptor GPR30(GPER) and/or possibly through a membrane bound mineralocorticoid receptor. Aldosterone action through GPR30(GPER) is currently understood to be specific for aldosterone. GPR30, G protein-coupled receptor 30; PI3-K, Phosphatidylinositol 3-kinase; ERK1/2, extracellular-signal regulated kinase 1/2; JNK, c-Jun NH2-terminal kinase; c-SRC, non-receptor tyrosine kinase c-SRC protein; BP, blood pressure; MR, mineralocorticoid receptor.

variable in both healthy and critically ill individuals, being influenced by genetic and disease-related factors (78-83). The association of *in vitro* glucocorticoid sensitivity with clinical outcome has not yet been shown, however, regardless of whether glucocorticoid therapy has been employed.

Acute and chronic renin-angiotensin-aldosterone system activation and the role of aldosterone antagonism

A direct correlation between hyperaldosteronism and mortality has been demonstrated and is characteristic of congestive heart failure (84,85). The *Randomized Aldactone Evaluation Study*, was a double-blind randomized controlled trial, which enrolled 1,663 heart failure patients with ejection fraction <35%, New York Heart Association class III or IV, who were already on an angiotensin converting enzyme inhibitor, a loop diuretic, and, in most cases, digoxin therapy (86). In these patients, spironolactone, reduced the risk of death from any cause by 30% (relative risk 0.7, 95% CI: 0.6 to 0.82, P<0.001) and hospitalization from worsening heart failure by 35% (RR 0.65, 95% CI: 54 to 77, P<0.001) (86). Similarly, Pitt and colleagues conducted *The EPHESUS trial*, a large multicenter randomized controlled trial that included patients with an ejection fraction <40% with clinical features of heart failure or diabetes, who were randomized 3–14 days post-myocardial infarction to receive eplerenone or placebo (87). All-cause mortality (RR =0.85, 95% CI: 0.75 to 0.96, P=0.008) and the combined end-point of death from any cause or cardiac hospitalization were significantly reduced in the treatment group (relative risk =0.87, 95% CI: 0.79 to 0.95, P=0.002) (87). Similar and further evidence, linking aldosterone antagonism to mortality improvement in heart failure has led to the generalised assumption that aldosterone antagonism is associated with improved mortality outcomes in critical illness (84,86,88). Chronic mineralocorticoid excess has indeed been demonstrated to lead to hypertension, to promote pro-inflammatory, pro-atherogenic and pro-thrombotic mechanisms leading to cardiac and other visceral fibrosis, fluid retention and congestion (61,84,88,89). In contrast, the acute activation of the renin-angiotensin-aldosterone system as well as the aldosterone neurohormonal mechanisms, which are seen in the acute phase of septic or hemorrhagic shock, are compensatory components of the acute stress response (90-92).

Elevated plasma renin activity associated with relatively low aldosterone levels has been investigated as a marker of perfusion and prognosis (8,93-95). Such a state of selective hypoaldosteronism, featuring a reduction in plasma aldosterone levels, despite rising corticotrophin and renin levels, suggests a dissociation between plasma renin and aldosterone (90,96). Commonly associated with hypotension, hyperreninemic hypoaldosteronism is interpreted to represent a state of aldosterone deficiency (11,93,97).

The etiology of hyperreninemic hypoaldosteronism is hypothesised to be adrenal dysfunction in a subset of patients with CIRCI (11,93,97). As the zona glomerulosa does not appear to have all the enzymes required for aldosterone biosynthesis (18) substrates are likely diverted away from aldosterone production in the promotion of cortisol production during critical illness, with the hyperreninemia likely a subsequent result of relative hypoadrenalism. Proposed etiological mechanisms are discussed in relation to CIRCI. Currently available data from adult and pediatric populations are contrasted and critically synthesised and an interpretation of the findings offered in *Table 2*. Parallels with CIRCI are, however, apparent.

A comparison of critical illness-related corticosteroid insufficiency and hyperreninemic hypoaldosteronism

Altered regulation of cortisol and aldosterone

Dysregulation of the hypothalamic-pituitary-adrenal axis associated with variable cortisol levels, altered cortisol metabolism, and tissue resistance to glucocorticoids are considered the three major constituents of CIRCI (1,5,27). Altered cellular glucocorticoid metabolism and specifically reduced cortisol metabolism in sepsis have been well described elsewhere (1,4,58,99).

Hypoaldosteronism is classified as (I) defective stimulation of aldosterone secretion, (II) primary defects in adrenal synthesis or secretion of aldosterone, and (III) aldosterone resistance (100). Clinically, defective aldosterone action manifests as decreased effective blood volume, orthostatic hypotension and shock. Laboratory characteristics such as hyponatremia, hyperkalemia and metabolic acidosis are likely to be present. Patients with primary adrenal insufficiency exhibit low serum cortisol and aldosterone concentrations, but may have high plasma renin activity in the setting of concurrent volume depletion and/or hypotension.

With regards to hyperreninemic hypoaldosteronism, an impaired adrenal aldosterone response to elevated renin

Table 2 Summary of published data from adult and pediatric populations on hyperreninemic hypoaldosteronism in critical illness

Author, year	Subjects	Summary findings
Zipser *et al.*, 1981 (11).	Twenty-eight critically ill patients with persistent hypotension, hospitalised in a medical intensive care unit (11)	The first description of hyperreninemic hypoaldosteronism in hemodynamically-unstable, critically ill patients
		Plasma renin activity found to be elevated in all participants (21.6±7.2 ng/mL·h), with low plasma aldosterone (1–9 ng/dL) in a subset of 18 patients with septic shock
		A spectrum of aldosterone responsiveness in 18 patients with persistent hypotension and a higher mortality rate (78%) was described
		A defect at the level of the zona glomerulosa was suggested by the lack of an aldosterone response to angiotensin II or corticotrophin in this subset (11). The study is limited, by its small sample size. and the subsequent advancements that have occurred with regard to aldosterone and renin level measurement
Findling and colleagues, 1987	Eighty three critically ill patients	A dissociation between plasma renin and aldosterone levels was found in 24 patients (8). Mean aldosterone levels of 19±5 ng/dL were found in those with an impaired aldosterone response to renin. This, was in comparison to mean aldosterone levels of 48±6 ng/dL in those with an appropriate renin response to aldosterone (8)
		A dissociation between plasma renin and aldosterone levels associated with a higher mortality was found in 24 patients. This may represent adrenal adaptation aimed at promoting cortisol production
		Similar findings have been observed in pediatric patients with septic shock (9,10)
Lichtarowicz-Krynska and colleagues, 2004	Sixty critically ill patients (31 with acute meningococcal disease, 29 twenty-nine with other diagnoses, including major surgery and severe respiratory infection)	Plasma renin activity measured in 15 participants with meningococcal disease. Of these 80% (12 of the 15) had aldosterone/plasma renin activity ratios <2 on admission (9)
		Patients with meningococcal sepsis had mean plasma aldosterone levels of 427.5±88.1 pg/mL (96.7% of values within the normal healthy age range), with levels of 1,489.2±244.2 pg/mL (P<0.0001) for the group with other diagnoses (59.3% of values above the normal healthy age range) (9)
		Compared to the non-meningococcal sepsis group, the meningococcal sepsis group had higher levels of serum cortisol and a higher predicted risk of mortality (32.3% *vs.* 9.4%) (9)
		Low aldosterone levels observed in this pediatric setting
		Of interest, those with the highest plasma aldosterone levels had the lowest cortisol measurements on admission
Tolstoy and colleagues, 2013.	Thirty-two trauma patients with hemorrhagic shock. Prospective observational study aimed at investigating the prevalence and impact of mineralocorticoid deficiency following hemorrhagic shock	Study conducted in an urban level I trauma centre over a 6-month period
		Blood samples for measurement of plasma aldosterone (PA) and renin (PR) (radioimmunoassay) were obtained on admission and at 8, 16, 24, and 48 hours
		Mineralocorticoid deficiency was defined as a plasma aldosterone/PR of ≤2
		Mineralocorticoid deficiency, was observed on admission, in 48% of patients (10)
		Markedly elevated renin levels were observed in the mineralocorticoid deficient cohort (10). In this study, patients with mineralocorticoid deficiency were more likely to be hypotensive, required more blood products and crystalloids and were at higher risk of acute kidney injury (10)

Table 2 (*continued*)

Table 2 (*continued*)

Author, year	Subjects	Summary findings
Chung and colleagues, 2017	Hundred and five patients with septic shock evaluated and observed PRA as a useful prognostic biomarker of 28-day mortality (98)	Blood samples were analysed on days 1, 3, and 7 for plasma aldosterone concentration, PRA and plasma aldosterone concentration/PRA ratio, cortisol and C-reactive protein
		Participants were divided into survivors (n=59) and non-survivors (n=46), according to 28-day mortality
		Lower PRA, plasma aldosterone concentration, Acute Physiologic and Chronic Health Evaluation (APACHE) II scores, and Sequential Organ Failure Assessment (SOFA) scores were observed in the survivor group (all $P<0.05$)
		The group with PRA ≥3.5 $ng \cdot mL^{-1} \cdot h^{-1}$ on day 1 showed significantly higher mortality than the group with PRA <3.5 $ng \cdot mL^{-1} \cdot h^{-1}$ (log-rank test, $P<0.001$) (98)
		Hyperreninemic hypoaldosteronism found in 55.2% of patients with septic shock, was not observed to be correlated with clinical outcome (renal failure, ventilator-free days, ICU-free days, and 28-day mortality)
		Findings support evidence for prolonged plasma renin activation, as a potential prognostic indicator in septic shock (98)
		Failure of aldosterone levels to increase after angiotensin II or corticotrophin infusions suggests damage to the zona glomerulosa
		Changes have been observed to be reversible in survivors (11,97)

levels has been demonstrated in critically ill patients, but not low plasma levels of aldosterone *per se*, with no definitive link of clinical translation to poor outcomes as yet (8,9).

Normal aldosterone levels have been demonstrated in patients with and without mineralocorticoid deficiency, whereas, markedly raised renin levels have been demonstrated only in those that are mineralocorticoid deficient (defined by a PA/PRA ratio of less than 2) (10). In critical illness, hypoaldosteronism is not typically associated with prominent sodium wasting due to compensatory mechanisms that promote sodium retention such as the effect of angiotensin II and norepinephrine (101). The findings of both reduced and elevated plasma aldosterone levels, despite rising corticotrophin and renin levels as seen in hyperreninemic hypoaldosteronism, suggest that hyperreninemia may be a sign of inadequate aldosterone activity for the severity of illness (90,96). Damage to the zona glomerulosa, as suggested by the lack of an aldosterone response to angiotensin II or corticotrophin infusions, the apparent loss of negative feedback regulation and tissue mineralocorticoid resistance may also be contributory (11,47,97).

Clinical features of adrenal insufficiency are often non-specific, and those of mineralocorticoid insufficiency may overlap with those of cortisol insufficiency (18,102). Currently accepted clinical features of CIRCI include fever and asthenia, as well as refractory hypotension, neuromuscular dysfunction, electrolyte and metabolic abnormalities and gastrointestinal dysfunction, which manifests as anorexia and intolerance to enteral feeding (5). Similarly hyperreninemic hypoaldosteronism may manifest as part of hypoadrenalism with similar findings of fever, asthenia and fatigue, as well as orthostatic hypotension and shock, and electrolyte and metabolic abnormalities (10,93).

Clinical characteristics of CIRCI (5) and hyperreninemic hypoaldosteronism (CIRMI) likely reflect the current lack of definitive data and understanding of both of these conditions. The significant overlap that exists between these two conditions is apparent (5). Clinical features of hyperreninemic hypoaldosteronism (CIRMI) are presented in *Tables 2-4*.

Evidence of peripheral resistance

Both glucocorticoid and mineralocorticoid receptors are homologous, compete for the same ligands, form homodimers and heterodimers together, bind a number of the same hormone response elements on DNA, and share co-regulatory proteins required for efficient gene transcription (64). Splicing of the human glucocorticoid receptor gene results in the generation of two glucocorticoid

Table 3 Clinical features of hyperreninemic hypoaldosteronism

System	Recognised clinical features of hyperreninemic hypoaldosteronism
General features	Hypoaldosteronism may manifest as part of hypoadrenalism with findings such as fever and asthenia. Hyperpigmentation is a feature of chronic hypoaldosteronism
Cardiac	Decreased effective blood volume, Orthostatic hypotension and shock (10,93)
	Arrhythmia from hyperkalemia (103)
Electrolyte and Metabolic	Hyponatremia
	Hyperkalemia (102)
	Metabolic acidosis
Neuromuscular	Hypothalamic or pituitary gland necrosis or hemorrhage
	Weakness, muscle cramps and fatigue
Abdominal	Adrenal gland hemorrhage or necrosis
	May manifest as part of hypoadrenalism
	Abdominal discomfort and salt craving (102)

receptor isoforms, namely glucocorticoid receptor-α and glucocorticoid receptor-β. Glucocorticoid receptor-α, the classic glucocorticoid receptor, resides primarily in the cytoplasm where it is expressed ubiquitously. Glucocorticoid receptor-β is expressed ubiquitously, but does not bind glucocorticoid agonists (104). In sepsis, reduced glucocorticoid receptor-α and increased glucocorticoid receptor-β density and transcription in various tissues occurs. The upregulation of glucocorticoid receptor-α has been shown to augment glucocorticoid activity, while glucocorticoid receptor-β has been shown to inhibit glucocorticoid-α activity (105). Even with elevated plasma cortisol concentrations, inadequate tissue glucocorticoid receptor-α-mediated anti-inflammatory activity is postulated to lead to glucocorticoid resistance (5). However, separate mineralocorticoid and glucocorticoid effects exist and their primary ligands, aldosterone and cortisol (or corticosterone), are regulated differently and serve distinct purposes (64).

Little concordance exists between currently available methods of assessing glucocorticoid sensitivity, while inter-individual differences in glucocorticoid receptor sensitivity may be tissue specific (106). Moreover, although changes in cellular glucocorticoid metabolism, in particular decreased cortisol metabolism, have been observed in sepsis, (4) tissue corticosteroid bioavailability has not been consistently shown to predict clinical outcome in critical illness.

Similarly, concerning aldosterone, reduced adrenal aldosterone production and stress-induced hypersecretion of corticotrophin with activation of the renin-angiotensin aldosterone system has been demonstrated in shock (107). Additionally, up to 40% to 65% of critically ill patients have high-plasma renin activity and relatively low-plasma aldosterone concentrations. This dissociation between plasma renin and aldosterone levels is interpreted to represent relative aldosterone deficiency (8,11,27,97). A proposed schematic representation of the hypothalamic-pituitary axis and key mechanisms in hyperreninemic hypoaldosteronism are demonstrated in *Figure 4*.

Challenges with the confirmation of deficiency states

Challenges with the diagnosis of CIRCI, based on the administration of synthetic corticotrophin, have been detailed elsewhere (2,5). Briefly, as baseline total plasma cortisol levels are often variable in critical illness, currently accepted basal and stimulated cortisol levels, which were developed in healthy, non-stressed subjects pose difficulties (108). Thus, a single adrenocorticotropic hormone stimulation test does not reveal adrenal insufficiency in septic shock (109). Additionally, the decline in plasma binding protein that occurs may result in a decrease in total cortisol levels (70,99). Elevated serum cortisol levels in critical illness raise the concern that lack of a total cortisol response to corticotrophin may be an appropriate negative feedback response of a hypercortisolemic state (4,41). Furthermore, considerably

Table 4 Comparison between CIRCI and hyperreninemic hypoaldosteronism

Defining Characteristics	CIRCI	Hyperreninemic hypoaldosteronism-proposed CIRMI
Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis	Loss of negative feedback demonstrated. Reduced corticotropin levels demonstrated likely a result of central adrenocortical suppression	Stress-induced hypersecretion of corticotrophin demonstrated with activation of the renin-angiotensin aldosterone system in shock
		Dissociation of aldosterone and renin shown, implying loss of negative feedback or aldosterone resistance
		Inadequate comparative data
	Challenges of the definition of a deficiency state identified	Challenges of the definition of a deficiency state identified
Altered hormone metabolism	Variable levels of cortisol have been described in critical illness, in different populations and different critical illness diseases	Variable levels of aldosterone and renin action have been described in critical illness, in different populations and different critical illness diseases
	Altered cortisol metabolism has been demonstrated	Dissociation of aldosterone and renin shown, implying loss of negative feedback or aldosterone resistance
	Plasma clearance of cortisol has been shown to be markedly reduced during critical illness	Inadequate comparative data on altered aldosterone metabolism demonstrated
	Confirmatory/diagnostic testing is debatable and is not agreed upon	Confirmatory/diagnostic testing is debatable and is not agreed upon
Tissue resistance to glucocorticoids	Proof of cortisol resistance in critical illness exists- (Changes in glucocorticoid receptor-α and -β expression, decreased clearance of cortisol, 11-β hydroxysteroid dehydrogenase changes)	Minimal evidence of proof of aldosterone resistance in critical illness exists
		Dissociation of aldosterone and renin shown, implying loss of negative feedback or aldosterone resistance

CIRCI, critical illness-related corticosteroid insufficiency; CIRMI, critical illnessrelated mineralocorticoid insufficiency.

raised plasma cortisol levels are generally noted in non-survivors of critical illness and less so in survivors, a finding thought to be inconsistent with the concept of insufficiency (110-114). However, glucocorticoid resistance may be present despite high plasma cortisol levels, much like insulin resistance is tethered to hyperinsulinemia (5,115). Additionally, concerning cortisol measurement, ultra-high frequency tandem mass spectrometry may be more reliable, as variability exists in standard assays (116,117).

As with CIRCI, challenges exist regarding the diagnosis of mineralocorticoid dysfunction in critical illness. Critical illness-associated hyperreninemic hypoaldosteronism is defined by a PA/PRA ratio <2, a definition based on values used in non-critically ill patients with mineralocorticoid deficiency. This corresponds to the 98th percentile of the control population (93). Low aldosterone levels, relative to plasma renin levels, have been demonstrated in pediatric meningococcal septic shock (9). However, reference material and reporting units for both aldosterone and renin differ widely with internationally accepted standardized methodologies not yet in place (96,97,118). Additionally, the use of renin and aldosterone measurements using reference ranges obtained from non-critically ill populations, in the diagnosis of hypoaldosteronism poses a number of on angiotensin II synthesis (11,119). Further methodological concerns include the lack of validation of these tests for use in the critically ill, as well as implications of technical limitations in their performance (plasma renin activity and serum aldosterone measurements should be performed after three hours in the upright or seated position as this increases renin and aldosterone release) (120). Currently, no reference ranges exist for plasma renin activity in critical illness.

Difficulties with the consistent demonstration of hypoaldosteronism in critical illness are compounded by the methods used to measure aldosterone (11). Marked overestimation of aldosterone levels occurs in renal impairment with the use of homogenous immunoassays, likely because of antibody cross-reactivity with uncleared aldosterone metabolites (121). The lack of standard

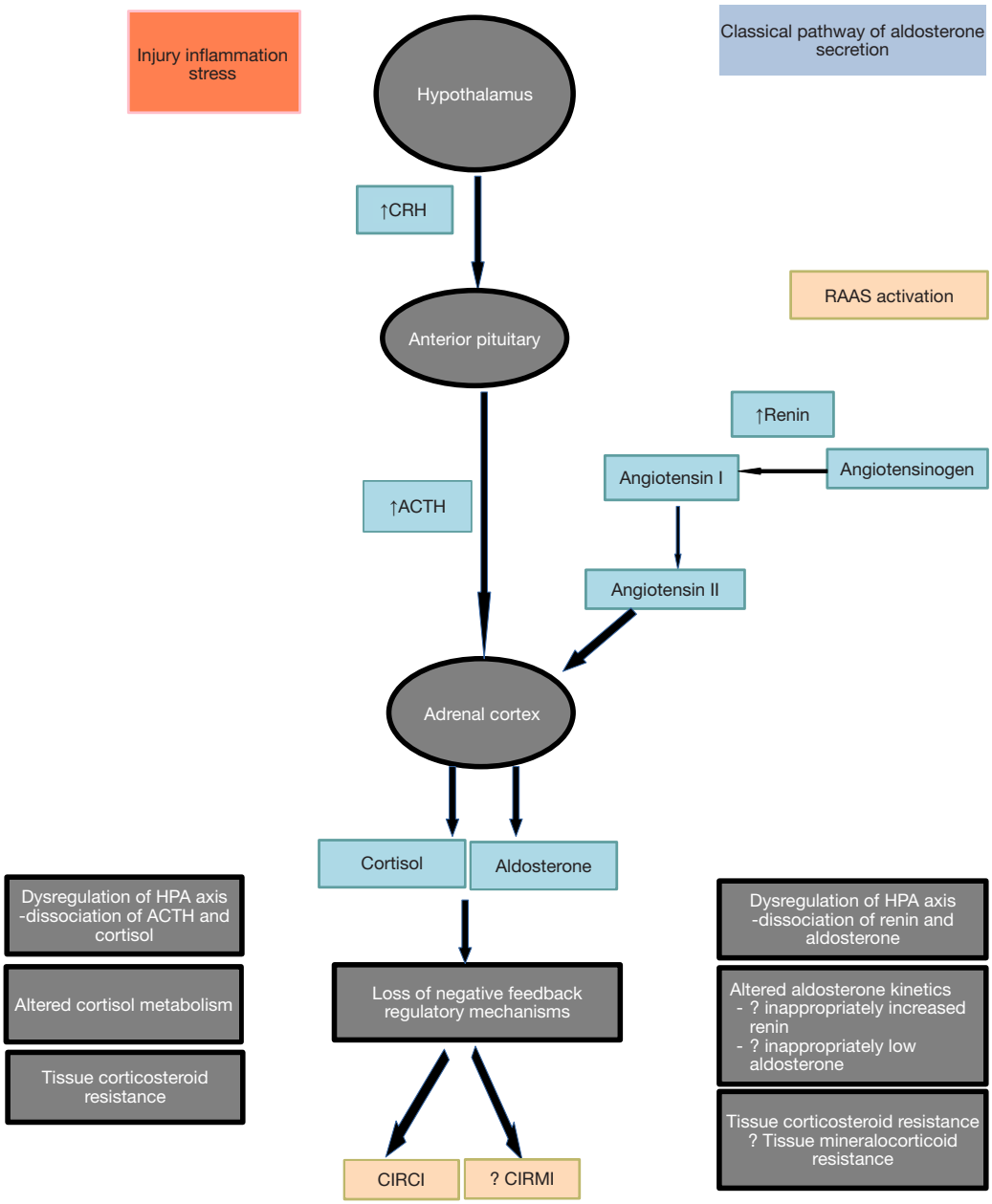

Figure 4 Proposed schematic representation of the hypothalamic-pituitary axis and key mechanisms in hyperreninemic hypoaldosteronism. Renin-angiotensin-aldosterone system activation occurs through the classical pathway of aldosterone secretion. Additional corticotrophin independent pathways include effects of cytokines and vasopressin, which trigger corticotrophin release, independent of hypothalamic control. Critical illness triggers release of corticotrophin-releasing hormone from the hypothalamus. Corticotrophin-releasing hormone stimulates the anterior pituitary to release adrenocorticotropic hormone, which stimulates the release of cortisol and to a lesser extent, aldosterone from the adrenal cortex. In a subset of critically ill patients, the loss of regulatory negative feedback mechanisms results in the dissociation of renin and aldosterone (hyperreninemic hypoaldosteronism) which is characterized by hyperreninemia in the face of inappropriately low aldosterone and is associated with a higher mortality. HPA, hypothalamic-pituitary-adrenal; ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; RAAS, renin-angiotensin-aldosterone system; CIRCI, critical illness-related corticosteroid insufficiency; CIRMI, critical illnessrelated mineralocorticoid insufficiency.

reference ranges for aldosterone across populations, as well as variations in assay procedures among laboratories further compounds aldosterone level assessments (122-124). High performance liquid chromatography and tandem mass spectrometry (LC-MS/MS) is a more accurate method of determining aldosterone levels, however, due to cost implications and technical demands associated with LC-MS/MS systems, radio-immunoassays remain the method of choice (125,126). Currently, no published standardized LC-MS/MS reference method or standard reference materials are available (121).

A comparison of therapeutic interventions

Evidence of an altered adrenal axis in septic shock, associated with a high mortality and characterized by organ dysfunction, and potentially improved by glucocorticoid supplementation, justifies therapy (37,110,111,127). Although the rationale for corticosteroid use in the management of patients with septic shock is well defined (128), there is uncertainty regarding the survival effect of adjunctive corticosteroid supplementation in severe sepsis and septic shock (128-130). Corticosteroids may not be beneficial or may lead to a small reduction in mortality with a possible increase in the risk of hyperglycemia and neuromuscular weakness (12,77,128,130,131).

Four large studies on the use of corticosteroids for the reversal of septic shock reported conflicting results. In the Ger-Inf-05 trial, hydrocortisone therapy in patients with septic shock and adrenal insufficiency was associated with improved survival (110). However, intravenous hydrocortisone did not reverse shock in patients with septic shock and was not associated with improved survival even in patients with adrenal insufficiency in another trial (111). Subsequently, two randomized controlled trials have shown trends in outcomes in favour of the cortisol group (12,77). In the *ADRENAL* trial, which included 3,800 mechanically ventilated patients with septic shock, a continuous infusion of 200 mg of hydrocortisone did not result in a lower 90-day mortality than placebo (27.9% *vs.* 28.8%; OR, 0.95; CI: 0.82 to 1.1; P=0.5) (77,128). Evidence of benefit was demonstrated with regard to time to shock resolution, duration of mechanical ventilation, length of ICU stay and reduced frequency of blood transfusions (77).

The *APROCCHSS* trial evaluated the effect of hydrocortisone, in combination with fludrocortisone, drotrecogin-alfa and respective placebos in 1,241 patients with septic shock. Mortality at intensive care and hospital discharge was significantly lower in the *hydrocortisone in combination with fludrocortisone* group (43.0% *vs.* 49.1%; P=0.03) (12,128). The RR of death in the hydrocortisone in combination with fludrocortisone group was 0.88 (95% CI: 0.78 to 0.99). The number of vasopressor-free days and organ-failure-free days was significantly higher in the hydrocortisone in combination with fludrocortisone group (14 *vs.* 12 days, P=0.003 and 17 *vs.* 15 days, P<0.001 respectively).

A recently suggested treatment strategy for septic shock is intravenous hydrocortisone at a maximum dose of 400 mg/day for at least 3 days in patients with septic shock that is not responsive to fluid and moderate- to high-dose vasopressor therapy (5). A lower dose, of 200 mg/day, for a more defined period of 7 days, commenced within 4 to 6 h of the initiation of vasopressor therapy in patients with persisting shock, has been recommended (128). A comparison of large randomized controlled trials of hydrocortisone therapy in septic shock is presented in *Table 5*.

The role of fludrocortisone, remains unclear. The only two trials demonstrating a decrease in mortality with steroid replacement therapy in septic shock included hydrocortisone in combination with fludrocortisone in the therapeutic group (12,110).

In *COIITSS*, a 2×2 factorial, randomized trial, a secondary objective assessed the benefit of fludrocortisone in septic shock patients who received hydrocortisone (132). Patients were randomly assigned to 1 of 4 groups: hydrocortisone with continuous intravenous insulin infusion, hydrocortisone in combination with fludrocortisone with continuous intravenous insulin infusion, hydrocortisone with conventional insulin therapy, or hydrocortisone in combination with fludrocortisone plus conventional insulin therapy (132). Hydrocortisone in combination with oral fludrocortisone did not result in a statistically significant improvement in in-hospital mortality, however there was a –3% absolute difference in hospital mortality rates in patients treated with hydrocortisone in combination with fludrocortisone (132). Although this result was not statistically significant, the study was not adequately powered to detect a relevant treatment effect (132).

The administration of fludrocortisone in septic shock in the Activated Protein C and Corticosteroids for Human Septic Shock trial was demonstrated to have a mortality benefit at 90 days (12,133). However, on the contrary, the use of renin-angiotensin-aldosterone system antagonism, namely angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, in the setting of sepsis has

Table 5 Comparison of randomized controlled trials investigating hydrocortisone therapy in septic shock

Study	Population	Intervention	Primary outcomes
Annane *et al.*, 2002, JAMA (110). *Ger-Inf-05 trial*	300 adults enrolled after undergoing a corticotropin test (250 µg)	Patients randomized to hydrocortisone 50 mg intravenous (IV) bolus 6 hourly and fludrocortisone 50 µg tablet once daily or placebo for 7 days	Improved survival [53% *vs.* 63% (OR 0.54; 95% CI: 0.31–0.97; P=0.04)]
Sprung *et al.*, 2008, NEJM (111). *CORTICUS*	499 adults within 72 hours of diagnosis of septic shock with hypoperfusion or organ dysfunction after. Enrolled undergoing a corticotrophin test (250 µg)	Patients randomized to hydrocortisone 50 mg IV 6 hourly for 5 days, 12 hourly for 3 days, 24 hourly for 3 days, then stopped or placebo	Intravenous hydrocortisone did not reverse shock in patients with septic shock [76% *vs.* 70.4% (P=0.41)] and was not associated with improved survival [34% *vs.* 32% (P=0.51)] even in patients with adrenal insufficiency
Venkatesh *et al.*, 2018, NEJM (77). *ADRENAL*	3,800 mechanically ventilated adults with septic shock	A continuous infusion of 200 mg of hydrocortisone or placebo daily for 7 days or ICU discharge or death	A continuous infusion of hydrocortisone did not result in a lower 90-day mortality than placebo (27.9% *vs.* 28.8%; OR, 0.95; CI: 0.82–1.1; P=0.5)
Annane, 2018, NEJM (12). *APROCCHSS*	1,241 adults with septic shock	2×2 factorial design: hydrocortisone 50 mg IV 6 hourly and fludrocortisone 50 µg through a nasogastric tube daily (or matching placebo) for 7 days Activated protein C 24 µg/kg/h for 96 hours or matching placebo) (Activated protein C arm discontinued as a result of activated protein C market withdrawal)	Improved survival. All-cause mortality at 90 days [49% *vs.* 43% (RR 0.88; 95% CI: 0.78–0.99; P=0.03)]

yielded conflicting results (92,134).

Fludrocortisone has been administered concurrently with high doses of hydrocortisone, doses purportedly high enough to have sufficient mineralocorticoid activity (12,110).

However, effects of fludrocortisone that are not mediated through the mineralocorticoid receptor should be considered (65,135,136). The implications of the differences in cellular downward signalling between the ligands, cortisol and fludrocortisone, acting on the mineralocorticoid receptor, require further clarification (133). Importantly, the bioavailability of oral fludrocortisone in critical illness requires elucidation (128,137,138).

The currently recruiting *Fludrocortisone Dose Response Relationship and Vascular Responsiveness in Septic Shock* (FluDRes) trial is a phase II, open label randomized controlled trial investigating the biological basis of vascular responsiveness in sepsis, as well as the pharmacokinetics and pharmacodynamics of fludrocortisone in septic shock (139). Results of this trial will, hopefully, help address the role of combination therapy with hydrocortisone and fludrocortisone in the critically ill.

Angiotensin II has recently emerged as a non-catecholamine vasopressor agent in the management of septic shock (13). In the *ATHOS-3* (*Angiotensin II for the Treatment of High-Output Shock*) trial, patients with refractory high output shock were randomised to receive infusions of angiotensin II or placebo within a 48-hour study period. The administration of angiotensin II was associated with a positive vasopressor response to mean arterial pressure at 3 hours when compared to placebo. [114 (69.9%) *vs.* 37 (23.4%) (OR 7.95, P<0.001)]. The measurement of renin levels was not part of the investigation in this trial. We hypothesize that in such populations hyperreninemic hypoaldosteronism may be concurrently present and we advocate for the assessment of hyperreninemic hypoaldosteronism in this population.

Indeed, Bellomo and colleagues recently used renin concentrations to identify patients that may benefit from angiotension II therapy (140). Serum samples from patients enrolled in the *ATHOS-3* trial were assessed for renin, angiotensin I, and angiotensin II concentrations before the start of administration of angiotensin II or placebo and after 3 hours. In those with renin concentrations above the study population median, angiotensin II significantly reduced 28-

day mortality to 28 of 55 (50.9%) patients compared with 51 of 73 patients (69.9%) of the placebo group (unstratified hazard ratio, 0.56; 95% confidence interval, 0.35 to 0.88; P=0.012) (P=0.048 for the interaction). A larger study assessing the response of aldosterone to angiotensin II along with renin measurements and with a patient centred outcome, such as duration of ICU stay or survival, would be of interest. Nonetheless, the finding, in this trial, that patients who had hyperreninemia were more likely to benefit from angiotensin II therapy highlights a population of catecholamine-resistant vasodilatory shock patients who have the potential to benefit from therapy modulating the renin-angiotensin-aldosterone system. As the maintenance of cardiovascular homeostasis is through multiple mechanisms, exploring the concept of synergy with regards to vasoactive medications in refractory vasodilatory shock, through the use of therapeutic approaches targeting both sympathetic tone and endocrine mechanisms, is a rational therapeutic approach.

Conclusion and future directions

Critical illness has been observed to be accompanied by variable degrees of cortisol secretion (33), increased free cortisol, glucocorticoid insensitivity, as well as disruption of glucocorticoid negative feedback. Both cortisol and aldosterone are of an adrenal source, and cortisol is capable of down-regulating both mineralocorticoid and glucocorticoid receptors (141). It is expected that such mechanisms affecting cortisol function in critical illness would be accompanied by a similar disruption in aldosterone function. Aldosterone levels, like cortisol, have been shown to be increased in sepsis and hemorrhagic shock. Furthermore, there is evidence to suggest that in acute critical illness, hyperreninemic hypoaldosteronism, a finding, which likely signifies the loss of negative feedback control of the renin-angiotensin-aldosterone system, is associated with poor outcomes. Indeed, there is evidence to suggest that there exists a population of catecholamine resistant vasodilatory shock patients with high renin levels who have the potential to benefit from therapy modulating the renin-angiotensin-aldosterone system, namely angiotensin II.

Evidence of improved outcomes with cortisol supplementation have been described. Although cortisol has mineralocorticoid activity, aldosterone has clinically relevant non-mineralocorticoid effects.

As with CIRCI, confident consideration and implementation of therapeutic interventions would require some clarifications.

An ALDO/PRA ratio below 2 has been defined as inappropriately low in previous studies and remains a criteria for definition until data from more recent studies becomes available (8). We suggest the assessment of hyperreninemic hypoaldosteronism through the assessment of ALDO/PRA ratio with the consideration of co-administration of hydrocortisone with fludrocortisone in patients with septic shock. Unlike the non-acute setting, cortisol levels are likely to be elevated in critical illness and they are of less diagnostic utility in the diagnosis of hyperreninemic hypoaldosteronism.

A number of questions remain:

(I) Is cortisol the only adrenal hormone with an outcome benefit that is affected in critical illness?

(II) Is there peripheral resistance to aldosterone in critical illness, much like that described with cortisol, and how can it be demonstrated? Peripheral resistance to cortisol has already been described;

(III) Do changes exist that affect the expression and activity of enzymes and receptors involved in aldosterone metabolism and the mineralocorticoid pathway as appears to be the case for cortisol?

(IV) Considering the methodological challenges and the lack of standardisation of diagnostic procedures, how can techniques that assess plasma renin activity, as well as the measurement of plasma aldosterone in the critically ill population, be improved?

(V) Lastly, if critical illness-related mineralocorticoid insufficiency is demonstrated, how should it be treated, as the bioavailability of the current form of fludrocortisone in critical illness is debatable?

In view of the conceptual similarities between the conditions hyperreninemic hypoaldosteronism and CIRCI, we suggest the term critical illness-related mineralocorticoid insufficiency (CIRMI) as a more appropriate description of the impaired aldosterone response to increased levels of renin seen in this group of patients.

Acknowledgments

Funding: This study was supported by funds from The National Research Foundation of South Africa, Pretoria, South Africa (to GDN) and The Discovery Foundation, Braamfontein, Johannesburg, South Africa (to GDN). The funds contribute towards research expenses for a PhD project. Funding sources have had no role in the writing of

this manuscript or decisions to submit any research outputs arising from the PhD project for publication.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-21-5572/rc

Peer Review File: Available at https://atm.amegroups.com/article/view/10.21037/atm-21-5572/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-21-5572/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Annane D, Pastores SM, Arlt W, et al. Critical illness-related corticosteroid insufficiency (CIRCI): a narrative review from a Multispecialty Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). Intensive Care Med 2017;43:1781-92.
2. Marik PE, Pastores SM, Annane D, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. Crit Care Med 2008;36:1937-49.
3. Boonen E, Van den Berghe G. Cortisol metabolism in critical illness: implications for clinical care. Curr Opin Endocrinol Diabetes Obes 2014;21:185-92.
4. Boonen E, Vervenne H, Meersseman P, et al. Reduced cortisol metabolism during critical illness. N Engl J Med 2013;368:1477-88.
5. Annane D, Pastores SM, Rochwerg B, et al. Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. Crit Care Med 2017;45:2078-88.
6. Corrêa TD, Takala J, Jakob SM. Angiotensin II in septic shock. Crit Care 2015;19:98.
7. Nethathe GD, Cohen J, Lipman J, et al. Mineralocorticoid Dysfunction during Critical Illness: A Review of the Evidence. Anesthesiology 2020;133:439-57.
8. Findling JW, Waters VO, Raff H. The dissociation of renin and aldosterone during critical illness. J Clin Endocrinol Metab 1987;64:592-5.
9. Lichtarowicz-Krynska EJ, Cole TJ, Camacho-Hubner C, et al. Circulating aldosterone levels are unexpectedly low in children with acute meningococcal disease. J Clin Endocrinol Metab 2004;89:1410-4.
10. Tolstoy NS, Aized M, McMonagle MP, et al. Mineralocorticoid deficiency in hemorrhagic shock. J Surg Res 2013;180:232-7.
11. Zipser RD, Davenport MW, Martin KL, et al. Hyperreninemic Hypoaldosteronism in the Critically ill: A New Entity. J Clin Endocrinol Metab 1981;53:867-73.
12. Annane D, Renault A, Brun-Buisson C, et al. Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. N Engl J Med 2018;378:809-18.
13. Khanna A, English SW, Wang XS, et al. Angiotensin II for the Treatment of Vasodilatory Shock. N Engl J Med 2017;377:419-30.
14. Nishimoto K, Nakagawa K, Li D, et al. Adrenocortical zonation in humans under normal and pathological conditions. J Clin Endocrinol Metab 2010;95:2296-305.
15. Gallo-Payet N, Martinez A, Lacroix A. Editorial: ACTH Action in the Adrenal Cortex: From Molecular Biology to Pathophysiology. Front Endocrinol (Lausanne) 2017;8:101.
16. Nishimoto K, Koga M, Seki T, et al. Immunohistochemistry of aldosterone synthase leads the way to the pathogenesis of primary aldosteronism. Mol Cell Endocrinol 2017;441:124-33.
17. White PC. Disorders of aldosterone biosynthesis and action. N Engl J Med 1994;331:250-8.
18. Vinson GP. Functional Zonation of the Adult Mammalian

Adrenal Cortex. Front Neurosci 2016;10:238.
19. Nishimoto K, Tomlins SA, Kuick R, et al. Aldosterone-stimulating somatic gene mutations are common in normal adrenal glands. Proc Natl Acad Sci U S A 2015;112:E4591-9.
20. Chong C, Hamid A, Yao T, et al. Regulation of aldosterone secretion by mineralocorticoid receptor-mediated signaling. J Endocrinol 2017;232:525-34.
21. Spät A, Hunyady L. Control of aldosterone secretion: a model for convergence in cellular signaling pathways. Physiol Rev 2004;84:489-539.
22. Aiba M, Fujibayashi M. Alteration of subcapsular adrenocortical zonation in humans with aging: the progenitor zone predominates over the previously well-developed zona glomerulosa after 40 years of age. J Histochem Cytochem 2011;59:557-64.
23. Hayashi T, Zhang Z, Al-Eyd G, et al. Expression of aldosterone synthase CYP11B2 was inversely correlated with longevity. J Steroid Biochem Mol Biol 2019;191:105361.
24. Endoh A, Kristiansen SB, Casson PR, et al. The zona reticularis is the site of biosynthesis of dehydroepiandrosterone and dehydroepiandrosterone sulfate in the adult human adrenal cortex resulting from its low expression of 3 beta-hydroxysteroid dehydrogenase. J Clin Endocrinol Metab 1996;81:3558-65.
25. Rainey WE, Nakamura Y. Regulation of the adrenal androgen biosynthesis. J Steroid Biochem Mol Biol 2008;108:281-6.
26. Desborough JP. The stress response to trauma and surgery. Br J Anaesth 2000;85:109-17.
27. Marik PE. Critical illness-related corticosteroid insufficiency. Chest 2009;135:181-93.
28. El Ghorayeb N, Bourdeau I, Lacroix A. Role of ACTH and Other Hormones in the Regulation of Aldosterone Production in Primary Aldosteronism. Front Endocrinol (Lausanne) 2016;7:72.
29. Stocco DM, Clark BJ. Regulation of the acute production of steroids in steroidogenic cells. Endocr Rev 1996;17:221-44.
30. Selvaraj V, Stocco DM, Clark BJ. Current knowledge on the acute regulation of steroidogenesis. Biol Reprod 2018;99:13-26.
31. Miller WL. Steroid hormone synthesis in mitochondria. Mol Cell Endocrinol 2013;379:62-73.
32. Manna PR, Stetson CL, Slominski AT, et al. Role of the steroidogenic acute regulatory protein in health and disease. Endocrine 2016;51:7-21.
33. Téblick A, Peeters B, Langouche L, et al. Adrenal function and dysfunction in critically ill patients. Nat Rev Endocrinol 2019;15:417-27.
34. Jenniskens M, Weckx R, Dufour T, et al. The Hepatic Glucocorticoid Receptor Is Crucial for Cortisol Homeostasis and Sepsis Survival in Humans and Male Mice. Endocrinology 2018;159:2790-802.
35. Charmandari E, Tsigos C, Chrousos G. Endocrinology of the stress response. Annu Rev Physiol 2005;67:259-84.
36. Preiser JC, Ichai C, Orban JC, et al. Metabolic response to the stress of critical illness. Br J Anaesth 2014;113:945-54.
37. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. N Engl J Med 2003;348:727-34.
38. Simpson ER, Waterman MR. Regulation of the synthesis of steroidogenic enzymes in adrenal cortical cells by ACTH. Annu Rev Physiol 1988;50:427-40.
39. Miller WL. Molecular biology of steroid hormone synthesis. Endocr Rev 1988;9:295-318.
40. Chung BC, Matteson KJ, Voutilainen R, et al. Human cholesterol side-chain cleavage enzyme, P450scc: cDNA cloning, assignment of the gene to chromosome 15, and expression in the placenta. Proc Natl Acad Sci U S A 1986;83:8962-6.
41. Peeters B, Meersseman P, Vander Perre S, et al. ACTH and cortisol responses to CRH in acute, subacute, and prolonged critical illness: a randomized, double-blind, placebo-controlled, crossover cohort study. Intensive Care Med 2018;44:2048-58.
42. Vermes I, Beishuizen A, Hampsink RM, et al. Dissociation of plasma adrenocorticotropin and cortisol levels in critically ill patients: possible role of endothelin and atrial natriuretic hormone. J Clin Endocrinol Metab 1995;80:1238-42.
43. Vassiliadi DA, Dimopoulou I, Tzanela M, et al. Longitudinal assessment of adrenal function in the early and prolonged phases of critical illness in septic patients: relations to cytokine levels and outcome. J Clin Endocrinol Metab 2014;99:4471-80.
44. Peeters B, Meersseman P, Vander Perre S, et al. Adrenocortical function during prolonged critical illness and beyond: a prospective observational study. Intensive Care Med 2018;44:1720-9.
45. Coll AP, Challis BG, Yeo GS, et al. The effects of proopiomelanocortin deficiency on murine adrenal development and responsiveness to adrenocorticotropin. Endocrinology 2004;145:4721-7.
46. Connell JM, Davies E. The new biology of aldosterone. J Endocrinol 2005;186:1-20.

47. Williams GH. Aldosterone biosynthesis, regulation, and classical mechanism of action. Heart Fail Rev 2005;10:7-13.
48. Zaman MA, Oparil S, Calhoun DA. Drugs targeting the renin-angiotensin-aldosterone system. Nat Rev Drug Discov 2002;1:621-36.
49. Patel VB, Zhong JC, Grant MB, et al. Role of the ACE2/Angiotensin 1-7 Axis of the Renin-Angiotensin System in Heart Failure. Circ Res 2016;118:1313-26.
50. Persson PB. Renin: origin, secretion and synthesis. J Physiol 2003;552:667-71.
51. Leftheris K, Zheng Y, Lala DS. Chapter 6 - Recent Advances in Mineralocorticoid Receptor Antagonists. In: Macor JE, editor. Annual Reports in Medicinal Chemistry [Internet]. Academic Press; 2011 [cited 2020 May 13]. p. 89-102. Available online: http://www.sciencedirect.com/science/article/pii/B9780123860095000217
52. Glorioso N, Filigheddu F, Parpaglia PP, et al. 11beta-Hydroxysteroid dehydrogenase type 2 activity is associated with left ventricular mass in essential hypertension. Eur Heart J 2005;26:498-504.
53. Fuller PJ, Young MJ. Mechanisms of mineralocorticoid action. Hypertension 2005;46:1227-35.
54. Annane D. Is There a Mineralocorticoid Deficiency in Critically Ill Patients? How Can It Be Diagnosed? Should It Be Treated? In: Evidence-Based Practice of Critical Care [Internet]. Philadelphia: Elsevier; 2010 [cited 2019 Jul 27]. p. 521-4. Available online: https://linkinghub.elsevier.com/retrieve/pii/B9781416054764000742
55. Funder JW. Aldosterone action. Annu Rev Physiol 1993;55:115-30.
56. Ngarmukos C, Grekin RJ. Nontraditional aspects of aldosterone physiology. Am J Physiol Endocrinol Metab 2001;281:E1122-7.
57. Gaeggeler HP, Gonzalez-Rodriguez E, Jaeger NF, et al. Mineralocorticoid versus glucocorticoid receptor occupancy mediating aldosterone-stimulated sodium transport in a novel renal cell line. J Am Soc Nephrol 2005;16:878-91.
58. Venkatesh B, Cohen J, Hickman I, et al. Evidence of altered cortisol metabolism in critically ill patients: a prospective study. Intensive Care Med 2007;33:1746-53.
59. Chapman K, Holmes M, Seckl J. 11β-hydroxysteroid dehydrogenases: intracellular gate-keepers of tissue glucocorticoid action. Physiol Rev 2013;93:1139-206.
60. Gotoh K, Shibata H. Aldosterone: History and Introduction. In: Singh AK, Williams GH, editors. Textbook of Nephro-Endocrinology (Second Edition) [Internet]. Second Edition. Academic Press; 2018. p. 465-76. Available online: http://www.sciencedirect.com/science/article/pii/B9780128032473000271
61. Hermidorff MM, de Assis LV, Isoldi MC. Genomic and rapid effects of aldosterone: what we know and do not know thus far. Heart Fail Rev 2017;22:65-89.
62. Falkenstein E, Christ M, Feuring M, et al. Specific nongenomic actions of aldosterone. Kidney Int 2000;57:1390-4.
63. Gros R, Ding Q, Sklar LA, et al. GPR30 expression is required for the mineralocorticoid receptor-independent rapid vascular effects of aldosterone. Hypertension 2011;57:442-51.
64. Gomez-Sanchez E, Gomez-Sanchez CE. The multifaceted mineralocorticoid receptor. Compr Physiol 2014;4:965-94.
65. Mihailidou AS, Tzakos AG, Ashton AW. Non-Genomic Effects of Aldosterone. In: Vitamins and Hormones [Internet]. Elsevier; 2019 [cited 2019 Jun 7]. p. 133-49. Available online: https://linkinghub.elsevier.com/retrieve/pii/S0083672918300839
66. Wendler A, Wehling M. Is GPR30 the membrane aldosterone receptor postulated 20 years ago? Hypertension 2011;57:e16; author reply e17.
67. Funder JW. Aldosterone and Mineralocorticoid Receptors-Physiology and Pathophysiology. Int J Mol Sci 2017;18:1032.
68. Laviolle B, Nesseler N, Massart C, et al. Fludrocortisone and hydrocortisone, alone or in combination, on in vivo hemodynamics and in vitro vascular reactivity in normal and endotoxemic rats: a randomized factorial design study. J Cardiovasc Pharmacol 2014;63:488-96.
69. Blot SI, Pea F, Lipman J. The effect of pathophysiology on pharmacokinetics in the critically ill patient--concepts appraised by the example of antimicrobial agents. Adv Drug Deliv Rev 2014;77:3-11.
70. Cohen J, Smith ML, Deans RV, et al. Serial changes in plasma total cortisol, plasma free cortisol, and tissue cortisol activity in patients with septic shock: an observational study. Shock 2012;37:28-33.
71. Chrousos GP, Kino T. Glucocorticoid action networks and complex psychiatric and/or somatic disorders. Stress 2007;10:213-9.
72. Bergquist M, Nurkkala M, Rylander C, et al. Expression of the glucocorticoid receptor is decreased in experimental Staphylococcus aureus sepsis. J Infect 2013;67:574-83.
73. Bergquist M, Jirholt P, Nurkkala M, et al. Glucocorticoid receptor function is decreased in neutrophils during endotoxic shock. J Infect 2014;69:113-22.
74. Bergquist M, Huss F, Hästbacka J, et al. Glucocorticoid

receptor expression and binding capacity in patients with burn injury. Acta Anaesthesiol Scand 2016;60:213-21.
75. Meduri GU, Muthiah MP, Carratu P, et al. Nuclear factor-kappaB- and glucocorticoid receptor alpha- mediated mechanisms in the regulation of systemic and pulmonary inflammation during sepsis and acute respiratory distress syndrome. Evidence for inflammation-induced target tissue resistance to glucocorticoids. Neuroimmunomodulation 2005;12:321-38.
76. Van den Berghe G. Non-thyroidal illness in the ICU: a syndrome with different faces. Thyroid 2014;24:1456-65.
77. Venkatesh B, Finfer S, Cohen J, et al. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. N Engl J Med 2018;378:797-808.
78. Cohen J, Pretorius CJ, Ungerer JP, et al. Glucocorticoid Sensitivity Is Highly Variable in Critically Ill Patients With Septic Shock and Is Associated With Disease Severity. Crit Care Med 2016;44:1034-41.
79. Quax RA, Manenschijn L, Koper JW, et al. Glucocorticoid sensitivity in health and disease. Nat Rev Endocrinol 2013;9:670-86.
80. Quax RA, Koper JW, de Jong PH, et al. In vitro glucocorticoid sensitivity is associated with clinical glucocorticoid therapy outcome in rheumatoid arthritis. Arthritis Res Ther 2012;14:R195.
81. van Oosten MJ, Dolhain RJ, Koper JW, et al. Polymorphisms in the glucocorticoid receptor gene that modulate glucocorticoid sensitivity are associated with rheumatoid arthritis. Arthritis Res Ther 2010;12:R159.
82. Syed AA, Redfern CP, Weaver JU. In vivo and in vitro glucocorticoid sensitivity in obese people with cushingoid appearance. Obesity (Silver Spring) 2008;16:2374-8.
83. van Winsen LM, Muris DF, Polman CH, et al. Sensitivity to glucocorticoids is decreased in relapsing remitting multiple sclerosis. J Clin Endocrinol Metab 2005;90:734-40.
84. Weber KT. Aldosterone in congestive heart failure. N Engl J Med 2001;345:1689-97.
85. Swedberg K, Eneroth P, Kjekshus J, et al. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial Study Group. Circulation 1990;82:1730-6.
86. Pitt B, Zannad F, Remme WJ, et al. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. N Engl J Med 1999;341:709-17.
87. Pitt B, Williams G, Remme W, et al. The EPHESUS trial: eplerenone in patients with heart failure due to systolic dysfunction complicating acute myocardial infarction. Eplerenone Post-AMI Heart Failure Efficacy and Survival Study. Cardiovasc Drugs Ther 2001;15:79-87.
88. Orsborne C, Chaggar PS, Shaw SM, et al. The renin-angiotensin-aldosterone system in heart failure for the non-specialist: the past, the present and the future. Postgrad Med J 2017;93:29-37.
89. Verbrugge FH, Tang WH, Mullens W. Renin-Angiotensin-aldosterone system activation during decongestion in acute heart failure: friend or foe? JACC Heart Fail 2015;3:108-11.
90. Aguilera G, Kiss A, Sunar-Akbasak B. Hyperreninemic hypoaldosteronism after chronic stress in the rat. J Clin Invest 1995;96:1512-9.
91. Fountain JH, Lappin SL. Physiology, Renin Angiotensin System. In: StatPearls [Internet] [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 [cited 2020 Mar 19]. Available online: http://www.ncbi.nlm.nih.gov/books/NBK470410/
92. Salgado DR, Rocco JR, Silva E, et al. Modulation of the renin-angiotensin-aldosterone system in sepsis: a new therapeutic approach? Expert Opin Ther Targets 2010;14:11-20.
93. Davenport MW, Zipser RD. Association of hypotension with hyperreninemic hypoaldosteronism in the critically ill patient. Arch Intern Med 1983;143:735-7.
94. du Cheyron D, Lesage A, Daubin C, et al. Hyperreninemic hypoaldosteronism: a possible etiological factor of septic shock-induced acute renal failure. Intensive Care Med 2003;29:1703-9.
95. du Cheyron D, Bouchet B, Cauquelin B, et al. Hyperreninemic hypoaldosteronism syndrome, plasma concentrations of interleukin-6 and outcome in critically ill patients with liver cirrhosis. Intensive Care Med 2008;34:116-24.
96. Raff H, Sandri RB, Segerson TP. Renin, ACTH, and adrenocortical function during hypoxia and hemorrhage in conscious rats. Am J Physiol 1986;250:R240-4.
97. Stern N, Beck FW, Sowers JR, et al. Plasma corticosteroids in hyperreninemic hypoaldosteronism: evidence for diffuse impairment of the zona glomerulosa. J Clin Endocrinol Metab 1983;57:217-20.
98. Chung KS, Song JH, Jung WJ, et al. Implications of Plasma Renin Activity and Plasma Aldosterone Concentration in Critically Ill Patients with Septic Shock. Korean J Crit Care Med 2017;32:142-53.
99. Cohen J, Pretorius C, Venkatesh B. Dismissal of the utility of free cortisol measurement is premature. Intensive Care

Med 2012;38:718; author reply 719-20.
100. Arai K, Chrousos GP. Aldosterone Deficiency and Resistance. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000.
101. DeFronzo RA. Hyperkalemia and hyporeninemic hypoaldosteronism. Kidney Int 1980;17:118-34.
102. Pazderska A, Pearce SH. Adrenal insufficiency - recognition and management. Clin Med (Lond) 2017;17:258-62.
103. Batlle D, Arruda J. Hyperkalemic Forms of Renal Tubular Acidosis: Clinical and Pathophysiological Aspects. Adv Chronic Kidney Dis 2018;25:321-33.
104. Kino T. Glucocorticoid Receptor. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000.
105. Torrego A, Pujols L, Roca-Ferrer J, et al. Glucocorticoid receptor isoforms alpha and beta in in vitro cytokine-induced glucocorticoid insensitivity. Am J Respir Crit Care Med 2004;170:420-5.
106. Ebrecht M, Buske-Kirschbaum A, Hellhammer D, et al. Tissue specificity of glucocorticoid sensitivity in healthy adults. J Clin Endocrinol Metab 2000;85:3733-9.
107. Braley LM, Adler GK, Mortensen RM, et al. Dose effect of adrenocorticotropin on aldosterone and cortisol biosynthesis in cultured bovine adrenal glomerulosa cells: in vitro correlate of hyperreninemic hypoaldosteronism. Endocrinology 1992;131:187-94.
108. Loriaux DL, Fleseriu M. Relative adrenal insufficiency. Curr Opin Endocrinol Diabetes Obes 2009;16:392-400.
109. Loisa P, Uusaro A, Ruokonen E. A single adrenocorticotropic hormone stimulation test does not reveal adrenal insufficiency in septic shock. Anesth Analg 2005;101:1792-8.
110. Annane D, Sébille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002;288:862-71.
111. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008;358:111-24.
112. Cohen J, Venkatesh B. Relative adrenal insufficiency in the intensive care population; background and critical appraisal of the evidence. Anaesth Intensive Care 2010;38:425-36.
113. Jurney TH, Cockrell JL Jr, Lindberg JS, et al. Spectrum of serum cortisol response to ACTH in ICU patients. Correlation with degree of illness and mortality. Chest 1987;92:292-5.
114. Span LF, Hermus AR, Bartelink AK, et al. Adrenocortical function: an indicator of severity of disease and survival in chronic critically ill patients. Intensive Care Med 1992;18:93-6.
115. Shanik MH, Xu Y, Skrha J, et al. Insulin resistance and hyperinsulinemia: is hyperinsulinemia the cart or the horse? Diabetes Care 2008;31 Suppl 2:S262-8.
116. McWhinney BC, Briscoe SE, Ungerer JP, et al. Measurement of cortisol, cortisone, prednisolone, dexamethasone and 11-deoxycortisol with ultra high performance liquid chromatography-tandem mass spectrometry: Application for plasma, plasma ultrafiltrate, urine and saliva in a routine laboratory. J Chromatogr B Analyt Technol Biomed Life Sci 2010;878:2863-9.
117. Cohen J, Ward G, Prins J, et al. Variability of cortisol assays can confound the diagnosis of adrenal insufficiency in the critically ill population. Intensive Care Med 2006;32:1901-5.
118. Bornstein SR, Licinio J, Tauchnitz R, et al. Plasma Leptin Levels Are Increased in Survivors of Acute Sepsis: Associated Loss of Diurnal Rhythm in Cortisol and Leptin Secretion. J Clin Endocrinol Metab 1998;83:280-3.
119. Dickson ME, Sigmund CD. Genetic basis of hypertension: revisiting angiotensinogen. Hypertension 2006;48:14-20.
120. Sealey JE. Plasma renin activity and plasma prorenin assays. Clin Chem 1991;37:1811-9.
121. Rehan M, Raizman JE, Cavalier E, et al. Laboratory challenges in primary aldosteronism screening and diagnosis. Clin Biochem 2015;48:377-87.
122. Kerstens MN, Kobold AC, Volmer M, et al. Reference values for aldosterone-renin ratios in normotensive individuals and effect of changes in dietary sodium consumption. Clin Chem 2011;57:1607-11.
123. Tiu SC, Choi CH, Shek CC, et al. The use of aldosterone-renin ratio as a diagnostic test for primary hyperaldosteronism and its test characteristics under different conditions of blood sampling. J Clin Endocrinol Metab 2005;90:72-8.
124. Hannemann A, Friedrich N, Lüdemann J, et al. Reference intervals for aldosterone, renin, and the aldosterone-to-renin ratio in the population-based Study of Health in Pomerania (SHIP-1). Horm Metab Res 2010;42:392-9.
125. Cawood ML. Measurement of Aldosterone in Blood. In: Wheeler MJ, Hutchinson JSM, editors. Hormone Assays in Biological Fluids [Internet]. Totowa, NJ: Humana Press; 2006 [cited 2019 Apr 19]. p. 177-85.
126. O'Shea PM, Griffin TP, Browne GA, et al. Screening for primary aldosteronism using the newly

developed IDS-iSYS® automated assay system. Pract Lab Med 2017;7:6-14.
127. Long B, Koyfman A. Controversies in Corticosteroid use for Sepsis. J Emerg Med 2017;53:653-61.
128. Cohen J, Venkatesh B. Adjunctive Corticosteroid Treatment in Septic Shock. Anesthesiology 2019;131:410-9.
129. Rochwerg B, Oczkowski S, Siemieniuk RA, et al. Corticosteroids in sepsis: an updated systematic review and meta-analysis (protocol). BMJ Open 2017;7:e016847.
130. Rochwerg B, Oczkowski SJ, Siemieniuk RAC, et al. Corticosteroids in Sepsis: An Updated Systematic Review and Meta-Analysis. Crit Care Med 2018;46:1411-20.
131. Keh D, Trips E, Marx G, et al. Effect of Hydrocortisone on Development of Shock Among Patients With Severe Sepsis: The HYPRESS Randomized Clinical Trial. JAMA 2016;316:1775-85.
132. COIITSS Study Investigators; Annane D, Cariou A, et al. Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. JAMA 2010;303:341-8.
133. Venkatesh B, Finfer S, Myburgh J, ADRENAL investigators. Glucocorticoids with or without Fludrocortisone in Septic Shock. N Engl J Med 2018;379:895.
134. Hsu WT, Galm BP, Schrank G, et al. Effect of Renin-Angiotensin-Aldosterone System Inhibitors on Short-Term Mortality After Sepsis: A Population-Based Cohort Study. Hypertension 2020;75:483-91.
135. Dooley R, Harvey BJ, Thomas W. Non-genomic actions of aldosterone: from receptors and signals to membrane targets. Mol Cell Endocrinol 2012;350:223-34.
136. Boldyreff B, Wehling M. Non-genomic actions of aldosterone: mechanisms and consequences in kidney cells. Nephrol Dial Transplant 2003;18:1693-5.
137. Fuller PJ, Yao Y, Yang J, et al. Mechanisms of ligand specificity of the mineralocorticoid receptor. J Endocrinol 2012;213:15-24.
138. Polito A, Hamitouche N, Ribot M, et al. Pharmacokinetics of oral fludrocortisone in septic shock. Br J Clin Pharmacol 2016;82:1509-16.
139. Fludrocortisone Dose Response Relationship in Septic Shock - FluDReSS - Full Text View - ClinicalTrials.gov [Internet]. [cited 2021 Apr 5]. Available online: https://clinicaltrials.gov/ct2/show/NCT04494789
140. Bellomo R, Forni LG, Busse LW, et al. Renin and Survival in Patients Given Angiotensin II for Catecholamine-Resistant Vasodilatory Shock. A Clinical Trial. Am J Respir Crit Care Med 2020;202:1253-61.
141. Young EA, Lopez JF, Murphy-Weinberg V, et al. Mineralocorticoid receptor function in major depression. Arch Gen Psychiatry 2003;60:24-8.

Cite this article as: Nethathe GD, Lipman J, Anderson R, Feldman C. CIRMI—a new term for a concept worthy of further exploration: a narrative review. Ann Transl Med 2022;10(11):646. doi: 10.21037/atm-21-5572

