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

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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 glucocorticoid 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.

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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 subpopulation 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
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...
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).
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...
Genomic effects

Slow genomic (hours)
- Phosphorylation of ERK1/2, JNK, c-SRC, etc.
- Steroid receptor complex
- Cell nucleus
- Gene expression
- Translation
- Aldosterone induced proteins
- Regulation of electrolyte/fluid balance
- Blood pressure regulation

Non-genomic rapid (minutes)
- Gene transcription
- Effector proteins

Cell nucleus

Translation

Regulation of electrolyte/fluid balance

Blood pressure regulation

Non-genomic effects

Slow nuclear actions

Rapid non-nuclear actions

Mineralocorticoid receptor

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: 0.54 to 0.77, 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
| Author, year          | Subjects                                                                 | Summary findings                                                                                                                                 |
|----------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| Zipser et al., 1981  | 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, 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)
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 | Hypernatremia                                                                                                                                 |
|                 | 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 interindividual 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 |
|                          | Challenges of the definition of a deficiency state identified         | Dissociation of aldosterone and renin shown, implying loss of negative feedback or aldosterone resistance |
|                          | Variable levels of cortisol have been described in critical illness, in different populations and different critical illness diseases | Inadequate comparative data |
|                          | 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 |
|                          |                                                                       | Dissociation of aldosterone and renin shown, implying loss of negative feedback or aldosterone resistance |

CIRCI, critical illness-related corticosteroid insufficiency; CIRMI, critical illness-related 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
Classical pathway of aldosterone secretion

Injury
Inflammation
Stress

RAAS activation

Angiotensin I
Angiotensinogen

Angiotensin II

Dysregulation of HPA axis
-dissociation of renin and aldosterone

↑CRH

Hypothalamus

Anterior pituitary

↑Renin

Angiotensin I

↑ACTH

Angiotensinogen

Angiotensin II

Adrenal cortex

Cortisol
Aldosterone

Loss of negative feedback regulatory mechanisms

Dysregulation of HPA axis
-dissociation of ACTH and cortisol

Altered cortisol metabolism

Tissue corticosteroid resistance

CIRCI

? CIRMI

Tissue corticosteroid resistance

? Tissue mineralocorticoid resistance

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 illness-related 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
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 angiotensin 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-

| Table 5 | Comparison of randomized controlled trials investigating hydrocortisone therapy in septic shock |
|---------|--------------------------------------------------------------------------------------------------|
| Study   | Population                                                                                       | Intervention                                                                                     | Primary outcomes                                                                 |
| Annane et al., 2002, 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 corticotropin test (250 µg) | Patients randomized to hydrocortisone 50 mg IV 6 hourly for 5 days, 12 hourly for 3 days, 24 hourly for 3 hours, 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)] |
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.

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