ANESTHESIOLOGY

Mineralocorticoid Dysfunction during Critical Illness

A Review of the Evidence

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ABSTRACT

The recent demonstration of the significant reduction in mortality in patients with septic shock treated with adjunctive glucocorticoids combined with fludrocortisone and the effectiveness of angiotensin II in treating vasodilatory shock have renewed interest in the role of the mineralocorticoid axis in critical illness. Glucocorticoids have variable interactions at the mineralocorticoid receptor. Similarly, mineralocorticoid receptor–aldosterone interactions differ from mineralocorticoid receptor–glucocorticoid interactions and predicate receptor–ligand interactions that differ with respect to cellular effects. Hyperreninemic hypoaldosteronism or selective hypoaldosteronism, an impaired adrenal response to increasing renin levels, occurs in a subgroup of hemodynamically unstable critically ill patients. The suggestion is that there is a defect at the level of the adrenal zona glomerulosa associated with a high mortality rate that may represent an adaptive response aimed at increasing cortisol levels. Furthermore, cross-talk exists between angiotensin II and aldosterone, which needs to be considered when employing therapeutic strategies.

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Two recent large-scale clinical trials have demonstrated a beneficial effect of adjunctive glucocorticoid treatment in septic shock on shock reversal, weaning from mechanical ventilation, and duration of intensive care stay, with, however, divergent effects on mortality.[1,2] A possible explanation for the discrepancy is that adjunctive fludrocortisone was added to the treatment regimen in the trial that reported a mortality benefit.[3]

Additionally, a phase II clinical trial of angiotensin has demonstrated that angiotensin II is effective in treating vasodilatory shock.[4] These recent demonstrations of significant reductions in mortality in patients with septic shock treated with adjunctive glucocorticoid combined with fludrocortisone, as well as the effectiveness of angiotensin II in treating vasodilatory shock, have renewed interest in the role of the mineralocorticoid axis in critical illness.[1,5–7]

This narrative review aims to summarize current insights into the pathophysiologic mechanisms and clinical implications of the renin–angiotensin–aldosterone system in critical illness. We focus on the issue of fludrocortisone supplementation in critical illness, as well as current understanding of the role of mineralocorticoid replacement in this group of patients. Other aspects of mineralocorticoid dysfunction, such as the presentation of a different approach to the understanding of mineralocorticoid dysfunction with a focus on hyperreninemic hypoaldosteronism, are additional sections that are included in this review.

Physiology of Mineralocorticoid Secretion and Metabolism

Adrenal Steroid Biosynthesis

The acute effect of corticotropin (adrenocorticotropic hormone) released from the pituitary gland is to stimulate early steps in the process of adrenal steroidogenesis by promoting the transport of cholesterol into mitochondria. By binding to a cell-surface receptor on the adrenal cortex, the melanocortin receptor-2, adrenocorticotropic hormone leads to activation of adenylyl cyclase, which, in turn, leads to an increase in cyclic adenosine monophosphate production, stimulation of protein kinase A, and protein phosphorylation.[8–11] More chronically, adrenocorticotropic hormone causes an overall increase in all adrenal steroid production and secretion, primarily through increasing the synthesis of most of the enzymes of the steroidogenic pathway.[12–14]

The mammalian adrenal gland consists of the adrenal cortex and medulla. The adrenal cortex consists of three zones; the zona fasciculata, the zona reticularis, and the zona glomerulosa, which secrete glucocorticoids, androgenic precursors, and mineralocorticoids, respectively.[15]

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All steroid hormones are produced from modifications of cholesterol (fig. 1).[16] Steroidogenesis entails regulation of cellular uptake and conversion of cholesterol to biologically active steroid hormones and occurs in the adrenal glands, placenta, brain, and gonads. Subsequent chemical modifications of cholesterol include a series of hydroxylations that require cytochrome P-450 enzymes.[14,17] There are zonal differences in enzymatic concentrations. Notably, 17-hydroxylase is present in low concentrations in the zona glomerulosa. The zona glomerulosa is the only zone that has the enzyme required to convert deoxycorticosterone to aldosterone.[18] This zonal difference in enzyme concentrations results in compartmentalization of enzymatic reactions. Adrenal cortical cells take up cholesterol from the circulation (as lipoproteins) or synthesize cholesterol *de novo*.[19] In the mitochondria, cholesterol is converted to Δ5-pregnenolone and then subsequently to progesterone.[17,20]

The main glucocorticoid secreted in response to adrenocorticotropic hormone is cortisol. Cortisol plays a role in carbohydrate metabolism and promotes protein catabolism to provide gluconeogenesis substrates. It also plays a role in immune and cardiovascular function.[21] In addition, corticotropin secretion stimulates aldosterone release through responses mediated by melanocortin receptor-2.[22]

Androgens play a role in secondary reproductive development and are secreted as precursors by the zona reticularis. They include dehydroepiandrosterone, dehydroepiandrosterone sulfate, and androstenedione. Androstenedione is subsequently converted peripherally to testosterone.[23,24]

Aldosterone is the primary mineralocorticoid secreted by the adrenal cortex and is essential in the maintenance of sodium, potassium, and extracellular fluid balance. Other sites of aldosterone synthesis include the brain, blood vessels, and the heart.[25,26] The primary regulator of aldosterone synthesis is the renin–angiotensin–aldosterone system. This is mediated through adrenal angiotensin II receptors and results in sodium retention and renal potassium loss. Corticotropin release stimulates production of aldosterone, but compared with cortisol, aldosterone is relatively independent of adrenocorticotropic hormone secretion. Aldosterone synthase catalyzes synthesis by converting deoxycorticosterone to corticosterone and then to aldosterone.[22] Aldosterone synthase expression is restricted to the zona glomerulosa. Unlike cortisol, aldosterone is not specifically bound to plasma proteins, making it less affected by plasma protein concentrations and binding alterations that occur in critical illness.[26]

Regulation of Aldosterone Secretion

In healthy subjects, angiotensin II, together with a rise in serum potassium concentration, are the primary secretagogues that stimulate aldosterone release.[22,26] Levels of aldosterone also fluctuate with changes in adrenocorticotropic hormone and renin levels.[26]

Renin is a proteolytic enzyme that is cleaved from its precursor, prorenin, and stored in the granules of renal macula densa and juxtaglomerular cells.[27] Prorenin production also occurs in a number of extrarenal sites such as the adrenal glands, gonads, and placenta.[27] The release of renin is triggered by a number of mechanisms, most importantly changes in blood pressure, sympathetic nervous system activity, and in response to hyponatremia.[28] A fall in plasma volume or blood pressure causes renin release, which in turn activates angiotensinogen synthesis from the liver to form angiotensin I. Angiotensin I is converted to angiotensin II by angiotensin-converting enzyme, an enzyme located in many tissues.[26] Angiotensin II, a potent vasoconstrictor, stimulates aldosterone release from the adrenal cortex.[29]

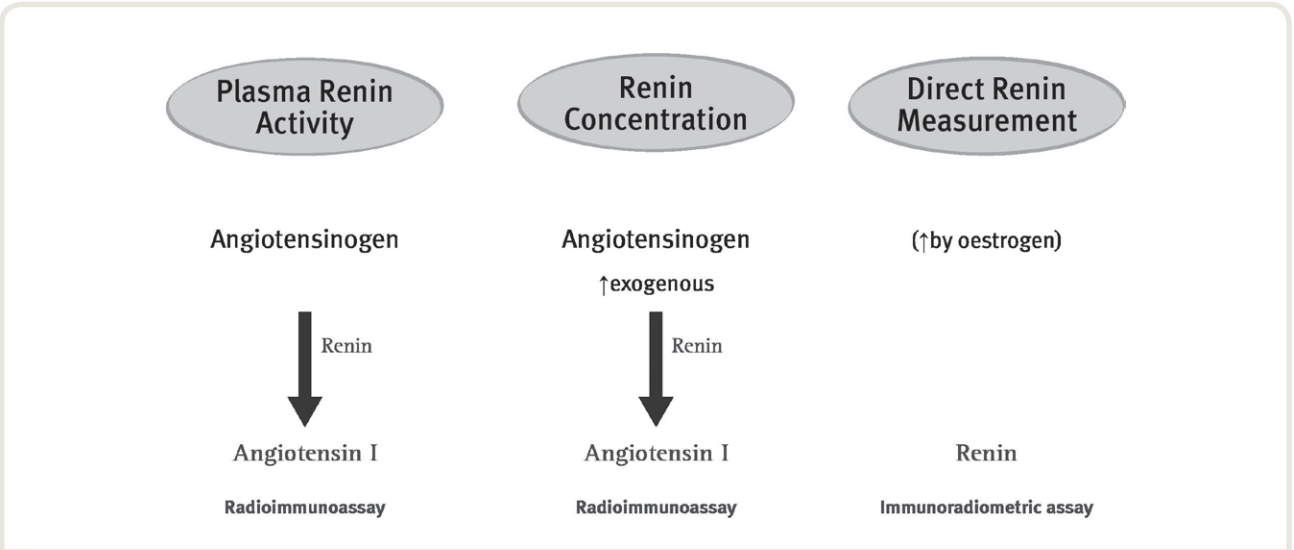

Fig. 1. Adrenal steroid biosynthetic pathway. Figure modified from Payne and Hales,[16] with permission from Oxford University Press and the Endocrine Society.

The resultant increase in blood pressure causes a decline in renin release, inhibiting further aldosterone production (fig. 2).[30] Angiotensin is currently understood to be one of a number of drivers of aldosterone secretion.

Recently, in a murine model, the hormone leptin has been found to be a new direct regulator of aldosterone secretion.[31] Obesity is associated with higher levels of aldosterone, and in both humans and murine models, obesity has been demonstrated to increase plasma renin activity and angiotensin II levels.[32–35] Although the clinical relevance of these findings requires further testing, the added effect of increased aldosterone secretion mediated by leptin may contribute to the increased cardiovascular risk associated with obesity.[29] More importantly, this suggests that leptin-mediated cardiovascular and endothelial dysfunction may be ameliorated pharmacologically by mineralocorticoid receptor antagonists. In the acute critical care setting, we postulate that increased levels of aldosterone in obesity may confer potential benefit through hemodynamic and vascular tone effects as much as increased levels of aldosterone in pregnancy are postulated to be adaptive and to mediate vascular tone.[36–38] Given the rising incidence of obesity

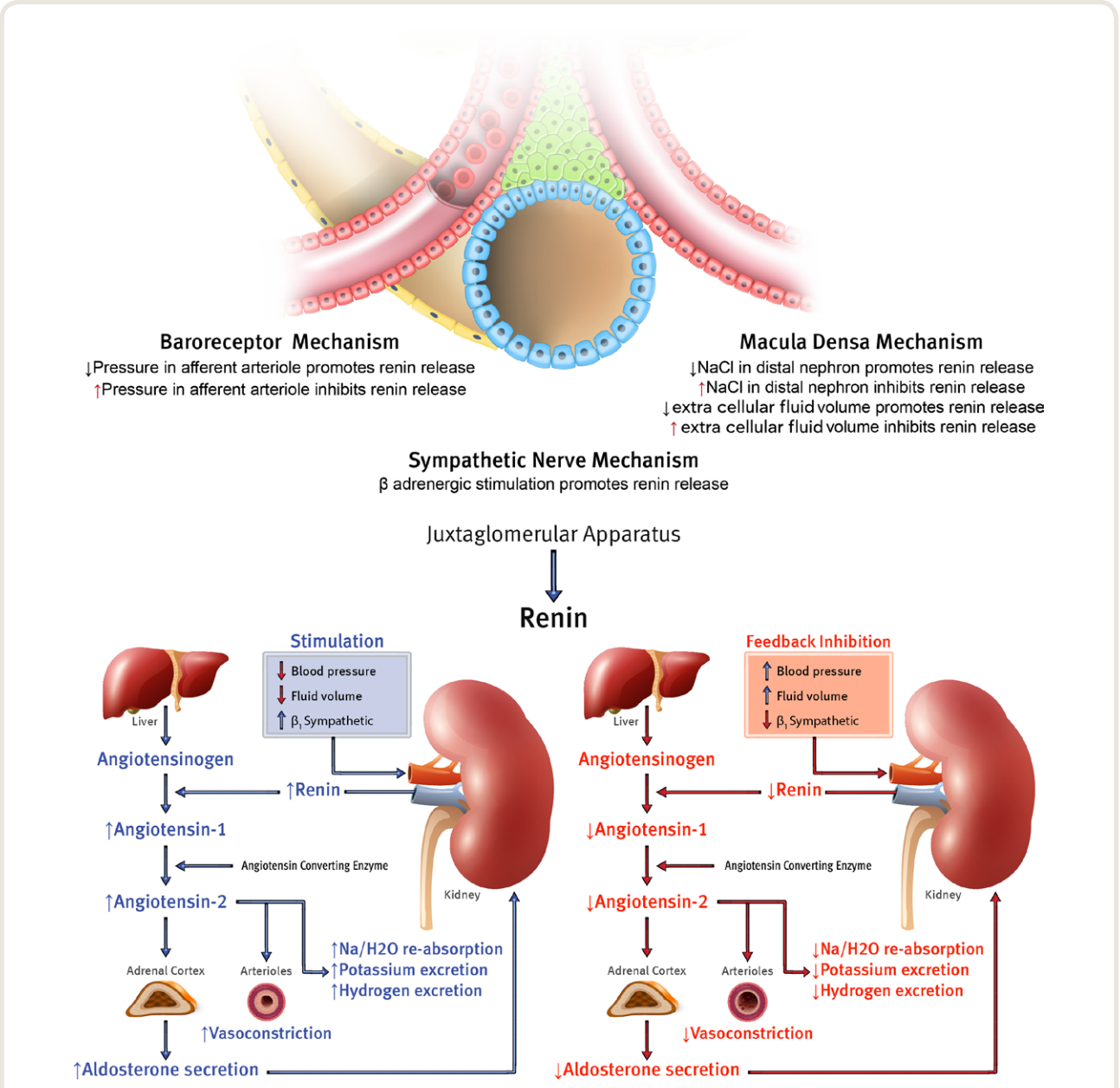

Fig. 2. Mechanisms of renin release and aldosterone secretion. Figure modified from Raffa *et al.*,[30] with permission from Elsevier. Na, sodium; H2O, water.

worldwide and the association of obesity with outcomes in critical illness, further investigations are warranted.[39]

Plasma/serum levels of aldosterone also vary according to population, age, sex, posture, and acute salt loading, as well as among different laboratories because of variations in assay procedures.[40,41] As a result, there is currently no standard reference range that applies to all populations. Serum levels (sitting position) have been found to range between 35 and 827 pmol/l and 15 and 408 pmol/l (before and after sodium-loading test, respectively) in some populations.[40] Reference values between 12 and 140 ng/l (males) and 5.0 and 134.0 ng/l (females) in the adult population have also been described.[42]

Extraadrenal Synthesis of Aldosterone

With the exception of the brain, evidence suggesting local aldosterone synthesis in the cardiovascular and renal systems, as well as in adipose tissue, has been proposed but is conflicting and unconvincing.[32,34] Adipocytes contain angiotensin I and angiotensin II receptors, mineralocorticoid receptors, 11β-hydroxysteroid dehydrogenase type 2, as well as evidence of selected steroidogenic enzyme messenger RNA.[32] 11β-Hydroxysteroid dehydrogenase, type 2, is an intracellular isoenzyme that converts cortisol to cortisone, thus preventing its binding to mineralocorticoid receptors. The significance of the presence of these enzymes has yet to be elucidated.

The summation of evidence from murine and human models suggests that aldosterone production in the brain, however, may be possible. Mineralocorticoid receptors are present in high density in certain regions of the brain, even though the blood–brain barrier significantly reduces exposure of the brain to circulating aldosterone. Furthermore, the presence of messenger RNA encoding corticosteroidogenic enzymes in certain regions of the human brain suggests that specific areas of the brain are able to produce low levels of aldosterone. The ligand for the mineralocorticoid receptor in the brain has not been proven to be necessarily aldosterone (glucocorticoid presence in the brain is at higher concentration).[43]

Evidence supporting the extraadrenal synthesis of aldosterone challenges the conventional understanding of aldosterone action, because aldosterone synthesis is thought to be secreted exclusively by the adrenal gland. Locally synthesized aldosterone has been shown to regulate blood pressure in murine models and to confer high spatial specificity of aldosterone action. Exploration of these pathways in the critical care setting may reveal previously unexplained physiologic and therapeutic avenues.[44–47]

Aldosterone Mode of Action and Cellular Effects

The essential role of mineralocorticoids in regulating sodium and water homeostasis has been demonstrated in adrenalectomized rats. Adrenalectomy results in weight loss, severe dehydration as a result of sodium loss, hyperkalemia, and hyponatremia, which resolve on treatment with mineralocorticoids.[48,49] The action of aldosterone is primarily on the kidney, where it causes sodium and water retention and active excretion of potassium and hydrogen ions. Its action on luminal cortical tubular cells results in an increased number of open sodium channels promoting sodium reabsorption.[50] Removal of sodium from the tubular fluid creates an electrical gradient that favors the secretion of potassium and hydrogen ions into the lumen. Aldosterone effects are purportedly mediated by genomic interaction with the Na,K-ATPase pump, as well as by nongenomic increases in the permeability of cells to sodium and protons.[49]

Glucocorticoids and mineralocorticoids have similar affinity for mineralocorticoid receptors. In conditions such as congestive heart failure, cortisol has been shown to activate the mineralocorticoid receptor.[51] Differences in the interaction of various ligands with the mineralocorticoid receptor have been previously demonstrated, and a number of factors confer mineralocorticoid action of glucocorticoids.[52] Mineralocorticoid receptors bound to aldosterone have been shown to be more resistant to proteolysis than mineralocorticoid receptors bound to either spironolactone or cortisol.[53] Notably, mineralocorticoid receptor activation by glucocorticoids is not applicable to all glucocorticoids. On a molecular level, glucocorticoid conformational mobility conveys specificity to the mineralocorticoid receptor. Steroids are compounds with a molecular skeleton consisting of four rings of carbon atoms designated A, B, C, and D.[54] Steroid ring A is required for glucocorticoid action and is rigid in the "pure" glucocorticoids (*e.g.*, dexamethasone) and flexible in aldosterone. Ring C conformation is required for mineralocorticoid action and is rigid in aldosterone (but is relatively flexible in the pure glucocorticoids). The exception is 11-deoxycorticosterone and its synthetic derivative, δ11,12-deoxycorticosterone, which are specific mineralocorticoids with marked glucocorticoid activity and a flexible C ring.[55,56] A putative mechanism for this difference is the lack of C-11 oxygenation of 11-deoxycorticosterone, which may confer versatility.[55,57] Additionally, the action of 11β-hydroxysteroid dehydrogenase, type 2, an intracellular isoenzyme that converts cortisol to cortisone thus preventing its binding to mineralocorticoid receptors, further renders mineralocorticoid responsive tissues, such as the kidney, sensitive to mineralocorticoids only.[49,58,59]

Multiple new members of the renin–angiotensin–aldosterone system have been shown to exist. The current and continuously evolving understanding is that the renin–angiotensin–aldosterone system consists of at least three additional local or tissue axes that regulate renal function, blood pressure, and the cardiovascular and nervous systems. These axes include a number of multifunctional enzymes, mediators, and their receptors; angiotensin-converting enzyme 2 (an angiotensin-converting enzyme homolog), angiotensin-(1–7) heptapeptide, and its G protein–coupled receptor, Mas. Other tissue or local axes include the precursor prorenin, the enzyme renin, and the (pro)renin receptor, which activates mitogen-activated protein kinases and the extracellular signal–related protein kinase 1/2, and last the angiotensin

IV hexapeptide, angiotensin 4 receptor, and insulin-regulated aminopeptidase axes.[60,61] This is in contrast to the classical endocrine system and its circulating mediators. Thus the understanding that blood pressure is under the sole control of the classical renin–angiotensin–aldosterone system is debatable.[60] Importantly, cross-talk between the renin–angiotensin–aldosterone system and aldosterone production is well established, and thus these two systems should not be seen in isolation.[62] Experimentally, aldosterone has been demonstrated to potentiate the constrictor effect of angiotensin II on vascular smooth muscle and to have a combined role with angiotensin II on vascular remodeling, endothelial dysfunction, and oxidative stress. The apparent involvement of angiotensin II with the additional axes of the renin–angiotensin–aldosterone system clearly merits further intensive investigations.

Causes of Hypoaldosteronism and Clinical Implications in Critical Illness

Causes of reduced levels of aldosterone include inherited and acquired disorders that may lead to a reduction in aldosterone synthesis, reduced renin secretion, or an impairment of the renal response to aldosterone.[63] Hyporeninemia, pharmacologic inhibition of aldosterone, renin, or angiotensin II, and primary adrenal insufficiency are important examples of such factors. Hypoaldosteronism can be classified as hyporeninemic or hyperreninemic.[64]

Hyporeninemic Hypoaldosteronism

Hyporeninemic hypoaldosteronism represents the most common cause of secondary mineralocorticoid insufficiency and is characterized by reduced aldosterone production secondary to reduced renin release or action and reduced angiotensin II production.[65] It is most commonly seen secondary to renal dysfunction or as an effect of pharmacologic agents.[65]

Primary Adrenal Insufficiency. Primary adrenal insufficiency is associated with a lack of both aldosterone and cortisol and is characterized by hyponatremia, hyperkalemia, worsening fatigue, muscle weakness, volume depletion, and hypotension.[66] In secondary adrenal insufficiency, because of a lack of adrenocorticotropic hormone, hypoaldosteronism is not a feature because adrenocorticotropic hormone does not play a significant role in the regulation of aldosterone release in this condition. A lack of aldosterone or reduced aldosterone results in an increase in plasma renin activity except in cases of hyporeninemic hypoaldosteronism.

Hyporeninemic Hypoaldosteronism in Renal Dysfunction: Is Prorenin–Renin Conversion Impaired? More than 50% of patients in the intensive care unit (ICU) develop acute kidney injury during the course of their ICU stay, with an associated mortality over 50%.[67] Patients with mild-to-moderate renal insufficiency (glomerular filtration rate of 45 to 89 ml/min)[68] have been previously shown to exhibit reduced angiotensin II production, which in turn contributes to reduced aldosterone secretion.[65,69–71]

Prorenin–renin conversion classically occurs in the kidney and has more recently been shown to have extrarenal sites of conversion.[72] It is currently accepted that the number of renin-producing cells varies according to demand.[72,73] Previously thought to be an inactive precursor of renin, prorenin is currently understood to be functional; to be elevated in certain conditions, such as pregnancy and diabetes mellitus; and to have extrarenal sites of production (notably adrenal).[72] Increasing evidence also suggests that prorenin plays a role in the regulation of sodium and water balance.[74] In critically ill ICU patients, evidence describing the association of raised renin levels with acute kidney injury has been conflicting, with some suggesting the use of renin as a marker of tissue perfusion and as a risk stratification tool in septic shock.[75] The concept of hyperreninemic hypoaldosteronism as an etiological factor in acute kidney injury associated with septic shock has also been proposed.[75,76] What is also apparent is that mechanisms responsible for renin release in the acute setting (cyclic adenosine monophosphate, calcium signaling pathways) differ from mechanisms responsible for chronic renin stimulation (metaplastic transformation of renin cell precursors).[73,75] The significance of this, and the degree to which renin and prorenin exert identical effects, are currently unknown and present knowledge gaps that warrant further investigation.[72] Available studies to date have included heterogeneous populations with acute and chronic pathophysiologic states, probably associated with variable mechanisms of renin release.

Hyporeninemic Hypoaldosteronism in Traumatic Head Injury and Subarachnoid Hemorrhage: Is Fludrocortisone Beneficial in Cerebral Salt Wasting? Hyponatremia and perturbations of water balance are common in traumatic head pathology or subarachnoid hemorrhage.[77] Cerebral salt wasting and the syndrome of inappropriate antidiuretic hormone secretion are potential causes of hyponatremia in this population. The pathophysiologic mechanisms involved have been studied in both conditions, more so in subarachnoid hemorrhage.[77] Although not a consistent finding in all studies, likely because of the heterogeneous populations included in various studies, high levels of atrial natriuretic peptide and brain natriuretic peptide in patients with cerebral salt wasting are purported to be contributory.[77–79]

Hyporeninemic hypoaldosteronism in cerebral salt wasting and normal or high aldosterone levels in the syndrome of inappropriate antidiuretic hormone secretion have been demonstrated previously.[80] Treatment for cerebral salt wasting in traumatic brain injury and in subarachnoid hemorrhage is not, however, well defined. Although the evidence for the role of fludrocortisone in cerebral salt wasting states is poor, hyponatremia in cerebral salt wasting associated

with trauma or traumatic brain injury has previously been successfully treated with fludrocortisone.[77,80]

In subarachnoid hemorrhage, management of cerebral salt wasting by hypovolemia and fluid restriction may increase the risk of cerebral vasospasm, and fludrocortisone has been advocated as a therapeutic intervention in the management of plasma volume and hyponatremia.[81,82] The two clinical trials conducted to date that have investigated the role of mineralocorticoid supplementation in the management of subarachnoid hemorrhage have found a significant reduction of sodium excretion after treatment with fludrocortisone.[83,84] In a controlled randomized trial involving three centers and consisting of 91 patients, treatment with fludrocortisone at a dose of 400 μg/day (orally or intravenously) administered for a maximum of 12 days was found to reduce excessive natriuresis in the first 6 days of admission compared with controls. Fludrocortisone was administered to 46 of the 91 patients in the study. Mean daily fluid intake was 3,261 ml during the first 6 days and 3,352 ml during the 12-day study period in the treatment group and 3,341 and 3,264 ml, respectively in the control group. Mean daily sodium intake was 219 mmol during the first 6 days and 222 mmol during the 12-day study period in the treatment group and 208 and 202 mmol, respectively, in the control group. The frequency of a negative sodium balance was reduced from 63 to 38% in the first 6 days ($P = 0.041$) and 70 to 29% ($P = 0.0023$) during the 12-day study period.[83] This study confirms the presence of natriuresis in patients with subarachnoid hemorrhage that was significantly reduced with fludrocortisone treatment.

Similar findings were noted by Mori *et al.*[84] in a randomized controlled trial consisting of 30 patients with subarachnoid hemorrhage who were within 1 to 2 days of surgery for aneurysmal clipping. Of these 30 patients, 15 received intravenous hypervolemic therapy (group 1), and 15 received oral or nasogastric fludrocortisone acetate at a total divided dose of 300 μg/day for 8 days in addition to hypervolemic therapy (group 2). Oral salt and hypertonic saline were also administered to manage hyponatremia, whereas water replacement was administered at 8-h intervals to match losses, and 6% hydroxyethyl starch was administered additionally from days 2 to 14 for volume expansion. The mean daily sodium intake was found to be significantly lower for group 2 (487 ± 34.52 mEq/day compared with 634.2 ± 42.86 mEq/day; $P < 0.05$). In addition, group 1 patients demonstrated a significant decline in serum sodium levels from days 4 to 7, which was not evident in group 2 ($P < 0.01$).[84]

The management of subarachnoid hemorrhage, however, has since evolved, with less focus on hypervolemia and a substantial focus on endovascular techniques. Furthermore, fludrocortisone dosing and timing, as well as sodium intake, differed between these two studies. The bioavailability of oral fludrocortisone has been shown to be variable in critical illness, and oral sodium intake may influence sodium balance.[85] In the study by Hasan *et al.*,[83] fludrocortisone given within 72 h of the hemorrhage was administered intravenously or orally at a dose of 0.4 mg in two doses for 12 days, whereas in the study by Mori *et al.*,[84] fludrocortisone was given orally only at a dose of 0.3 mg/day in three divided doses from days 1 to 8. Patients who were able to tolerate an oral diet were placed on a controlled low-sodium diet to reduce variability in sodium intake. This was not controlled for in the study by Mori *et al.*[84]

Although also limited by factors such as sample size, these studies nonetheless highlight the potentially beneficial effects of early treatment with fludrocortisone on sodium and water balance in patients with subarachnoid hemorrhage.[86] In addition, they also raise the question of potential hypoaldosteronism in this group of patients. There was, however, no neurologic outcome benefit in either study. The contribution of serum sodium to complications such as cerebral edema and seizures in individual patients with subarachnoid hemorrhage remains difficult to determine.[86] The role of therapies aimed at reversing hyponatremia remains debatable because the evidence that hyponatremia influences prognosis in patients with subarachnoid hemorrhage is inconclusive.[86] It is, however, considered reasonable practice (as per consensus guidelines) to use fludrocortisone and hypertonic saline to prevent and correct hyponatremia in the management of subarachnoid hemorrhage.[81]

Pharmacologic Causes of Hyporeninemic Aldosteronism. Angiotensin-converting enzyme inhibitors inhibit aldosterone release by reducing the conversion of angiotensin I to angiotensin II. Angiotensin II receptor blockers interfere with angiotensin II action at the receptor level, whereas direct renin inhibitors act by binding competitively to the active site of the enzyme.[87] Renin secretion is, however, increased with angiotensin-converting enzyme inhibitors.[88] Potassium load and potassium-sparing diuretics are another type of medications that are also known to interfere with aldosterone metabolism.[89]

Nonsteroidal antiinflammatory drugs have been shown to impair both renal renin secretion and angiotensin II–induced release of aldosterone. Interestingly, agents such as diclofenac, mefenamic acid, and naproxen have also been shown to inhibit the glucuronidation of aldosterone by human kidney cells and liver microsomes and to increase plasma and renal aldosterone concentrations by as much as 320%, potentially counteracting the effects of mineralocorticoid antagonists[90,91] and posing a considerable cardiovascular risk in patients with conditions such as moderate or severe heart failure.[91] This mechanism of action of nonsteroidal antiinflammatory drugs (NSAIDs) appears to vary between different NSAIDs and may be a potential mechanism for cardiovascular adverse events related to NSAID use.[90,92,93]

Increased sympathetic flow to the kidneys, through β1-adrenergic stimulation, directly activates a blood-pressure mechanism of renin secretion by the juxtaglomerular

cells.[73] Evidently, direct β1-adrenergic receptor stimulation of aldosterone secretion in bovine zona glomerulosa cells has been observed.[94,95] Additionally, cyclosporine has also been shown to cause reduced plasma renin activity and reduced tubular sensitivity to aldosterone, leading to reduced secretion and responsiveness to aldosterone, an effect possibly mediated by reduced mineralocorticoid receptor expression.[96,97]

Cyclosporine has been associated with a hyporeninemic hypoaldosteronism state that leads to hyperkalemia and metabolic acidosis in transplant patients caused by tubular insensitivity to aldosterone mediated by downregulation of mineralocorticoid receptor expression.[97,98] Normal or near normal aldosterone levels have been described in this condition, and treatment with fludrocortisone has been shown to be beneficial.[97,98]

Other pharmacologic effects, which require further exploration, include that of heparin therapy. Heparin has a direct toxic effect on the adrenal zona glomerulosa cells and has been shown to lead to a substantial reduction in plasma aldosterone concentrations, even at low doses.[89] Heparin-induced hyperkalemia is a potentially life-threatening complication that may occur in patients who have concurrent renal dysfunction, type 4 renal tubular acidosis, metabolic acidosis, and diabetes.[89] Serum potassium and sodium should be regularly monitored in these patients on initiation of heparin therapy. Heparin-induced hyperkalemia has been successfully treated using oral fludrocortisone.[89] The underlying mechanism is unclear and may be mediated by reduced numbers and affinity of adrenal angiotensin II receptors.[89,99,100] Collectively, such routinely prescribed agents may significantly alter renal and plasma aldosterone concentrations, potentially counteracting effects of mineralocorticoids and their antagonists in some instances (moderate or severe heart failure) or modifying compensatory mechanisms in conditions such as septic shock.

Aldosterone Resistance and Hyperaldosteronism

The administration of potassium-sparing diuretics is the most common cause of aldosterone resistance. These diuretics act by antagonizing the action of aldosterone on the collecting tubules, by competing for the aldosterone receptor (spironolactone and eplerenone), or by closing the sodium channels in the luminal membrane (amiloride and probably triamterene). Other pharmacologic agents implicated in aldosterone resistance include antibiotics such as trimethoprim, which inhibit the collecting tubule sodium channel, the site of action of aldosterone.[89] More rarely, genetic disorders are the cause.[101]

Hyperaldosteronism is a hallmark of chronic heart failure.[102–105] The value of mineralocorticoid receptor antagonism in moderate-to-severe heart failure has been demonstrated to reduce morbidity and mortality and is supported by well conducted trials, including the Randomized ALdactone Evaluation Study (RALES) and the EPlerenone neuroHormonal Efficacy and the SUrvival Study (EPHESUS) trials.[106] The persistent and evidently detrimental effects of chronic renin-angiotensin-aldosterone system activation seen in chronic heart failure should be distinguished from the acute renin-angiotensin-aldosterone system activation seen in critical illness from trauma and/or sepsis.[107] The initial beneficial effects of renin-angiotensin-aldosterone system activation on sodium and water balance, as seen in acute states such as trauma and sepsis, become deleterious and maladaptive when sustained, as seen in heart failure, because the counterregulatory mediators (natriuretic peptides types A and B) become overwhelmed.[102,108] In addition, long-term renin-angiotensin-aldosterone system activation as seen in congestive heart failure results in cytokine- and growth factor–mediated remodeling of the heart and vasculature.[109,110]

Mineralocorticoid Dysfunction during Critical Illness

Physiologic responses to shock include increased secretion of catecholamines, vasopressin, and activation of the renin–angiotensin–aldosterone system. Decreased adrenal production of aldosterone and stress-induced hypersecretion of adrenocorticotropic hormone are additional features that have been demonstrated in some patients in earlier reports.[111]

More recently, plasma adrenocorticotropic hormone in critical illness has been shown to be mostly low during the early phase of ICU stay, correlating with higher than normal plasma free-cortisol levels.[112] The rise in adrenocorticotropic hormone and cortisol to supranormal levels was a feature seen 1 week after ICU discharge in one study.[112] A concurrent adrenocorticotropic hormone/aldosterone response was not demonstrated in this study. Feedback inhibition mediated by high free-cortisol levels explains the low adrenocorticotropic hormone in association with high free-cortisol levels. Evidently hypothalamus–pituitary–adrenal axis alterations vary, depending on the etiology as well as the phase of critical illness.[113,114] Concurrent changes in aldosterone levels during acute and prolonged critical illness warrant further investigation because they may help clarify the role of mineralocorticoid supplementation in these patients.

Plasma renin activity has been shown to be frequently elevated in critical illness. The associated inappropriately low aldosterone levels have resulted in the changes being described as hyperreninemic hypoaldosteronism.[115,116] Such a state of dissociation between plasma renin and aldosterone levels has been previously associated with hypotension and is interpreted to represent a state of aldosterone deficiency.[115,117]

The first description of selective hypoaldosteronism (hyperreninism with hypoaldosteronism) in hemodynamically unstable critically ill patients was in a subset of 18 critically ill patients.[117] In this single-center study,

which enrolled 28 patients, a spectrum of aldosterone responsiveness was demonstrated in 18 patients with persistent hypotension. Although plasma renin activity was increased in all participants (21.6 ± 7.2 ng · ml^{-1} · h^{-1}), plasma aldosterone levels were inappropriately low in 18 patients (1 to 9 ng/dl). This subgroup had a high mortality rate (78% *vs.* 30% for the high-aldosterone group, $P < 0.001$). A defect at the level of the zona glomerulosa was suggested by the lack of an aldosterone response to an infusion of angiotensin II or adrenocorticotropic hormone in this group.[117] Although the study was small and the methods used to measure both aldosterone and renin have since been improved, it nevertheless highlighted that there exists a population of hemodynamically unstable critically ill patients with hypoaldosteronism despite high plasma renin activity.[117] These findings suggest that as much as there is a subset of critically ill hemodynamically unstable patients with inappropriately low cortisol levels, similar (or corresponding) changes affecting aldosterone may coexist in this population.

In a similar study, which included 83 critically ill patients, plasma renin activity, angiotensin II, potassium, and adrenocorticotropic hormone levels were measured. Plasma renin activity was found to be greater than 2.0 ng · ml^{-1} · h^{-1} in 59 patients, and plasma renin and aldosterone were found to be dissociated in 24 patients.[118] Those with an impaired aldosterone response to renin (plasma aldosterone–to–plasma renin activity ratio less than 2) had mean aldosterone levels of 19 ± 5 ng/dl compared with significantly higher mean aldosterone levels of 48 ± 6 ng/dl ($P < 0.5$) in those with an appropriate renin response to aldosterone.[118] Patients with a plasma aldosterone–to–plasma renin activity ratio less than 2 (defined as inappropriately low) had a significantly higher mortality rate (75%) than those with an plasma aldosterone–to–plasma renin activity ratio of 2 or more (46%; $P < 0.001$).[118]

Similar findings have been described in pediatric septic shock.[119,120] Inappropriately low aldosterone levels were demonstrated in a pediatric critically ill population encompassing 60 children. Of these patients, 31 were admitted with acute meningococcal disease, and 29 had other diagnoses (major surgery, severe respiratory infection). Plasma renin activity was measured in 15 participants with meningococcal disease, 80% of whom (12 of 15) had demonstrable aldosterone/plasma renin activity ratios of less than 2 on admission.[119]

Patients with meningococcal sepsis had mean plasma aldosterone levels of 427.5 ± 88.1 pg/ml (96.7% of values within the normal range for age for healthy children), whereas the levels were 1,489.2 ± 244.2 pg/ml ($P < 0.0001$) for the group with other diagnoses (59.3% of values above the normal range for age for healthy children).[119] The meningococcal sepsis group had a higher predicted risk of mortality compared with the nonmeningococcal sepsis group (32.3% *vs.* 9.4%) and had higher levels of serum cortisol.[119] Interestingly, those with the highest plasma aldosterone levels had the lowest cortisol measurements on admission. All participants survived.

Taken together, these studies suggest that inappropriately low aldosterone levels despite high plasma renin activity occur, much like evidence of inappropriately low cortisol and adrenal androgen secretion[118] may occur in the critically ill, potentially as an adaptive response aimed at increasing cortisol production. Recent studies suggesting the presence of this entity in the critically ill and its association with organ dysfunction have since been published.[76,121] Renin has been suggested as a marker of tissue perfusion and prognosis in the critically ill.[75]

The Role of Mineralocorticoid Supplementation during Critical Illness

Several clinical trials have examined the role of mineralocorticoid supplementation in critical illness. However, an adequately powered study comparing fludrocortisone to a matched control group has not yet been performed. Notably, the role of mineralocorticoid replacement in patients with septic shock is not discussed in recent consensus statements (Society of Critical Care Medicine, European Society of Intensive Care Medicine 2017).[58,122,123]

Annane *et al.*[124] investigated 300 patients with septic shock who had undergone a short corticotropin test, allocated to a 7-day period of treatment with a 50-mg intravenous bolus of hydrocortisone administered every 6 h and a 50-μg daily dose of nasogastrically delivered fludrocortisone or placebo. The patients were characterized as either responders or nonresponders to the corticotropin test. Of these, 229 were classified as nonresponders and 70 as responders (1 patient withdrew consent). Of the responders, 115 were randomized to the placebo group, and 114 were randomized to the corticosteroid group. Of the nonresponders, 34 were randomized to the placebo group, and 36 were randomized to the corticosteroid group. Treatment with low doses of hydrocortisone and fludrocortisone was found to significantly reduce the risk of death in patients with septic shock and relative adrenal insufficiency (so-called nonresponders; 73 deaths (63%) in the placebo group and 60 deaths (53%) in the corticosteroid group; hazard ratio, 0.67; 95% CI, 0.47 to 0.95; $P = 0.02$), suggesting that mineralocorticoid therapy combined with glucocorticoid therapy confers a mortality benefit in patients with septic shock. Apart from the methodologic concerns that have been raised regarding the utility and accuracy of the short synacthen test in critical illness, the bioavailability of a single dose of fludrocortisone administered in this study (50-μg tablet daily) is debatable. A single dose (50 μg) was shown to lead to undetectable plasma levels in one third of patients with septic shock in one study.[85] Mineralocorticoid insufficiency was not specifically reported.

Corticosteroid Treatment and Intensive Insulin Therapy for Septic Shock in Adults (COIITSS) was a randomized, 2 × 2 factorial trial with a primary objective of assessing the

efficacy of intensive insulin therapy in patients with septic shock treated with hydrocortisone and, as a secondary objective, assessing the benefit of fludrocortisone as an oral dose of 50 μg administered for 7 days. The study consisted of 509 patients with septic shock presenting with multiple organ dysfunction (Sequential Organ Failure Assessment score of 8 or more) who received hydrocortisone (50-mg bolus at 6-h intervals for 7 days). Of these, 245 received fludrocortisone in combination with hydrocortisone administered as a daily single oral dose (50 μg).

With regards to the secondary objective, 105 (42.9%) of 245 patients treated with fludrocortisone died, and 121 of 264 (45.8%) in the control group died (relative risk, 0.94; 95% CI, 0.77 to 1.14; $P = 0.50$). Neither aldosterone levels nor plasma renin levels were assessed in this study. However, the study was not adequately powered to detect a clinically relevant treatment effect, and no significant effect was observed.[125]

More recently, 1,241 patients from 34 centers were enrolled over a 7-yr period in the Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial. Overall, 614 patients were randomized to receive a combination of a 60-mg hydrocortisone IV bolus every 6 h and 50 μg of fludrocortisone *via* nasogastric tube for 7 days, whereas 627 patients received placebo.[1] Ninety day all-cause mortality at ICU discharge was lower among those who received hydrocortisone plus fludrocortisone than among those who received placebo (35.4% *vs.* 41.0%; $P = 0.04$). The hydrocortisone-fludrocortisone group also had more vasopressor-free and organ failure–free days. However, in this study, the role of fludrocortisone in improving outcomes was not well delineated for a number of reasons. Fludrocortisone was administered concurrently with high doses of hydrocortisone (240 mg daily). Such a dose of hydrocortisone would have sufficient mineralocorticoid activity. The relative mineralocorticoid potencies of hydrocortisone and fludrocortisone are 1 and 12, respectively, and a dose of 20 mg of hydrocortisone provides a mineralocorticoid effect equivalent to 0.1 mg of fludrocortisone. The mineralocorticoid effect of the dose of hydrocortisone given in the study would therefore have amounted to an equivalent of a total of 1.2 mg (1,200 μg) per day of fludrocortisone.[126] Clinical evidence for activation of the mineralocorticoid receptor at high doses of hydrocortisone also exists.[51,126] Additionally, few data exist on the bioavailability of multiple oral fludrocortisone dosing in patients with septic shock.[85]

The combined evidence from the above-mentioned studies indicates that the additive beneficial role of fludrocortisone to hydrocortisone is clearly challenging to delineate.[127] Notably, the mineralocorticoid receptor is permissive of the binding of various ligands. The action of cortisol on the mineralocorticoid receptor can be both as an agonist and an antagonist, depending on the underlying pathophysiology.[128] Under normal conditions, cortisol binds to the mineralocorticoid receptor but does not lead to its activation (mineralocorticoid antagonistic effect). In conditions of tissue damage and in the presence of reactive oxygen species, cortisol activates the receptor and acts as a mineralocorticoid agonist.[128]

Such variable effects of cortisol at receptor level may support the argument for concurrent fludrocortisone administration in critical illness; however, this contention requires support through investigations that will take into account the assessment of mineralocorticoid (dys)function (defined pathology), the bioavailability of orally administered fludrocortisone (effectively administered treatment), and more proximal endpoints such as shock resolution (well defined response to treatment).

Hyperreninemic Hypoaldosteronism in Trauma: Are Trauma Patients Mineralocorticoid-deficient?

The first demonstration of mineralocorticoid deficiency in a cohort of trauma patients was in a study consisting of 32 trauma patients admitted in hemorrhagic shock.[120] In this study, mineralocorticoid deficiency (plasma aldosterone–to–plasma renin activity ratio less than 2) was found in 48% of trauma patients at ICU admission.[120] Normal aldosterone levels were demonstrated in patients with and without mineralocorticoid deficiency; however, markedly elevated renin levels were demonstrable only in the mineralocorticoid-deficiency cohort ($P < 0.0033$).[120] Patients with mineralocorticoid deficiency were more likely to be hypotensive during the study period, required more blood products and crystalloids, and were at higher risk of acute kidney injury.[120] This was a single-center study limited by methodologic concerns in addition to the small sample size. All patients were administered etomidate, an adrenal mitochondrial 11β-hydroxylase inhibitor, for intubation. The enzyme 11β-hydroxylase is required for the conversion of both 11-deoxycortisol to cortisol and 11-deoxycorticosterone to corticosterone and subsequently to aldosterone and has been shown to contribute significantly to adrenal insufficiency in critical illness.[129]

Apart from sepsis and trauma, hyperreninemic hypoaldosteronism has since been described in murine models of hypoxia, chronic physiologic stress, and acute hemorrhage. These conditions have also been associated with a reduction in plasma aldosterone levels despite rising adrenocorticotropic hormone and renin levels.[130,131] The failure of aldosterone levels to increase after angiotensin II or adrenocorticotropic hormone infusions suggests that damage to the zona glomerulus is a cause of the hyperreninemic hypoaldosteronism syndrome, with recovery of normal plasma renin and aldosterone ratios in survivors, suggesting a reversible cause.[116,117] The clinical significance of pharmacologic reversal of these changes is not yet validated; however, early identification of these patients may help identify potential therapeutic avenues and improve prognostication.

Additional Theoretical Considerations in Critical Illness

The Role of Adrenocorticotropic Hormone

The role of adrenocorticotropic hormone in the regulation of aldosterone production is normally minimal but may become important under specific conditions.[22,132,133] Hypersecretion of adrenocorticotropic hormone has been demonstrated *in vitro* (cultured bovine cells) and may theoretically lead to reduced aldosterone synthesis by diverting precursors in this pathway to the production of cortisol in conditions of physiologic stress.[111] Using bovine zona glomerulosa cells exposed to various concentrations of adrenocorticotropic hormone, Braley *et al.*[111] demonstrated increased 17α-hydroxylase activity in zona glomerulosa cells, suggesting a shift from aldosterone to cortisol production. Histological and immunohistochemical studies suggest that a difference exists between bovine and human adrenal morphology and function, making the extrapolation of such data to humans debatable.[134] High levels of adrenocorticotropic hormone have been described in patients undergoing surgery and are seen in the acute phase of critical illness.[132,133] More recently, in critical illness, adrenocorticotropic hormone–cortisol dissociation has been described. Adrenocorticotropic hormone levels have been shown to be variable in various phases of disease, with the initial rise in acute disease being subsequently followed by low–adrenocorticotropic hormone levels in chronic critical illness.[114] Mechanisms responsible for this may include negative feedback inhibition mediated by increased *free* cortisol availability and suppression of adrenocorticotropic hormone release mediated by circulating bile acids in the acute phase of critical illness.[114]

Effects of Electrolytes and Fluid Shifts

Volume expansion may theoretically contribute to decreased adrenal production of aldosterone in some patients with critical illness. The stimulation of aldosterone release by potassium should also be considered.[22,26] A concurrent lack or relative lack of cortisol in some patients with adrenal insufficiency may stimulate ADH secretion, as a result of loss of negative feedback control, leading to further water retention and hyponatremia.[135–138]

Challenges Relating to the Diagnosis of Mineralocorticoid Insufficiency in Critical Illness

Previous investigators have shown that 40 to 65% of critically ill patients have high plasma renin activity and low plasma aldosterone concentrations.[117,118] The currently well accepted definition of critical illness–associated hyperreninemic hypoaldosteronism is defined by a plasma aldosterone–to–plasma renin activity ratio of less than 2, which corresponds to the 98th percentile of the control population.[115] This current definition is based on values used in non–critically ill patients with mineralocorticoid deficiency. There are currently no internationally accepted standardized methodologies of assessment, and reference material and reporting units for both aldosterone and renin also differ.[66,139,140] The diagnosis of hypoaldosteronism based on renin and aldosterone measurements using reference ranges obtained from non–critically ill populations poses a number of challenges.

Measurement of Plasma Renin Activity

The measurement of plasma renin activity is based on: (a) indirect measurement of the combined effect of angiotensinogen and renin; (b) indirect renin concentration measurement, which involves the *ex vivo* addition of angiotensinogen to the assay; and (c) more recently, direct immunoradiometric measurements (fig. 3).[141–143] Plasma renin activity has previously relied on the quantification of the cumulative generation of angiotensin I and not the direct quantification of renin *per se*.[142,143] Plasma renin activity is, in turn, reliant on the available levels of renin substrate (angiotensinogen) and measures the combined effect of angiotensinogen levels and renin.

Not much is known about levels of angiotensinogen in critical illness. Angiotensinogen, an α2-globulin, released primarily by the liver, has been shown to be reduced in liver dysfunction and congestive heart failure and to be elevated by factors such as adrenal insufficiency, corticosteroid therapy, and estrogen levels.[144,145] Higher circulating levels of angiotensinogen are found in women and in those on estrogen-replacement therapy and contraceptives.[142] This indicates that measurements of plasma renin activity overestimate circulating renin levels in the face of high levels of angiotensinogen in the assay.[145]

Low renin levels found in conditions of low angiotensinogen levels may underestimate the active renin concentration when plasma renin activity is measured.[146] When measured using direct assays, renin levels are shown to be suppressed in women compared with men, in premenopausal women more than postmenopausal women, and in postmenopausal women using estrogen therapy than in postmenopausal women without estrogen replacement.[145] Direct immunometric measurements of renin are currently used, although not widely.[141,142]

The implications of varying methods of plasma renin activity measurement in the critically ill setting are currently unclear; however, this variability in measurement methods highlights potential concerns with the comparative use of data from older studies where plasma renin activity was measured indirectly, as well as the effect that changes in the plasma concentration of angiotensinogen may have on angiotensin II synthesis and as a result, indirect renin concentration measurements.[117,147]

Plasma renin activity has been validated for use in non–critically ill patients for the investigation of primary

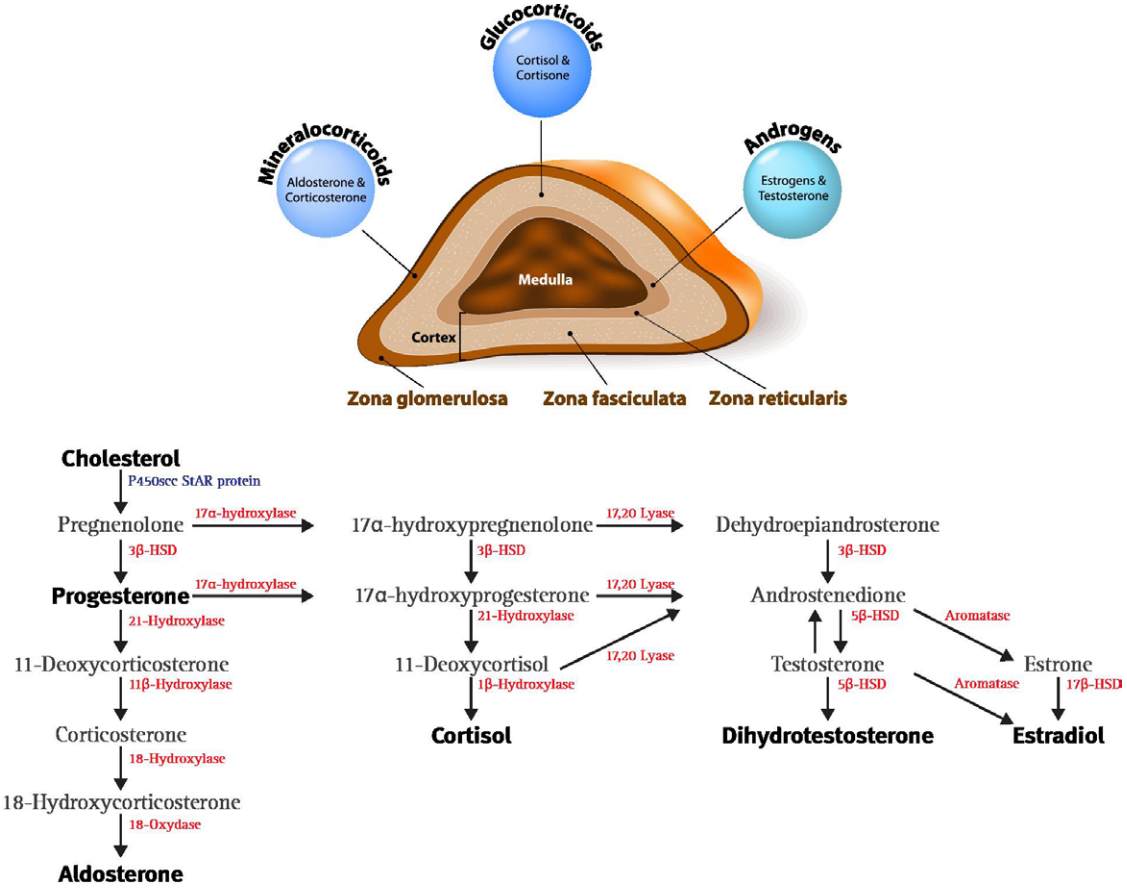

Fig. 3. Methods for renin measurement. Figure modified from Fischer *et al.*,[142] with permission from Oxford University Press and the European Society of Cardiology. HSD, hydroxysteroid dehydrogenase.

and secondary hypoaldosteronism. In the non–critical care setting, plasma renin activity and serum aldosterone measurements should be performed after 3 h in the upright or seated position, which increases renin and aldosterone release in normal individuals.[143] The normal concentration of plasma renin activity has been shown to be 1 pmol/l.[143] Currently, no reference ranges exist for the critically ill population.

Aldosterone Levels Are Difficult to Interpret in Isolation

In the setting of renal impairment, the use of homogenous immunoassays (which do not require a separation step to distinguish bound from unbound labeled antibody or antigen) has been shown to result in marked overestimation of aldosterone levels, possibly because of antibody cross-reactivity with uncleared aldosterone metabolites.[140] Aldosterone levels determined by high-performance liquid chromatography and tandem mass spectrometry are more accurate and should be used.[140,148] However, because of the cost implications and technical demands associated with high-performance liquid chromatography and tandem mass spectrometry systems, radioimmunoassays and automated immunoassays are still used in many laboratories, and radioimmunoassays are the method of choice.[139,149] Most importantly, there is currently no published standardized high-performance liquid chromatography and tandem mass spectrometry reference method or standard reference material available.[140] Such variability in analytic methods presents challenges to diagnosis and screening, as well as leading to uncertainty such as in the interpretation of outcomes from clinical investigations of aldosterone disorders.

Effect of Concurrent Pharmacotherapy

The use of drugs that impair aldosterone release, such as nonsteroidal antiinflammatory drugs, angiotensin inhibitors, calcineurin inhibitors, heparin, or β-adrenergic blockers has been discussed and should be considered as possible causes of hypoaldosteronism in the critically ill. The presence of preexisting disease such as chronic kidney disease, diabetes-associated hyporeninemic hypoaldosteronism, and HIV infection are other potential confounders of measurements occurring in critical illness.[150]

Other factors that may interfere with the assessment include differentiating preexisting hyporeninemic hypoaldosteronism from hyperreninemic hypoaldosteronism associated with critical illness and the prognostic and clinical implications of low renin levels in this population, as well as the effects of volume depletion or hypotension on plasma renin activity measurements. Patients with primary adrenal insufficiency are characterized by both low serum aldosterone and low cortisol concentrations but may have a high plasma renin activity because of concurrent volume depletion and/or hypotension.

Pathophysiology and Clinical Manifestations of Hypoaldosteronism

In patients without critical illness, a loss of mineralocorticoid activity results in dehydration associated with increased renal sodium excretion, metabolic acidosis, and hyperkalemia. Despite the role of aldosterone in sodium retention, hypoaldosteronism is not typically associated with prominent sodium wasting because there are compensatory mechanisms that help retain sodium, such as the effect of angiotensin II and norepinephrine.[69]

Unlike isolated aldosterone deficiency, there are a number of unique factors that affect aldosterone release, as well as sodium and water balance, in the critically ill population. These include the effects of drug therapy, such as pharmacologic inhibition of angiotensin II and impairment of aldosterone release by heparin therapy, calcineurin inhibitors, and nonsteroidal antiinflammatory drugs.

Therapeutic Implications

Fludrocortisone Replacement

Therapy with both glucocorticoids and mineralocorticoids is routinely instituted for primary adrenal insufficiency because these patients have low serum aldosterone and cortisol concentrations.[66] Either hydrocortisone, cortisone acetate, or dexamethasone can be used and should be titrated to clinical response (blood pressure, body weight, signs of glucocorticoid excess). Mineralocorticoid replacement should be instituted in those with a confirmed deficiency state with fludrocortisone (50 to 100 μg in adults).[66]

The benefits of fludrocortisone replacement in patients with septic shock are debatable and not yet well described. The pharmacokinetics of a single oral dose (50 μg) of fludrocortisone in adult patients with septic shock were investigated in a single-center study consisting of 21 adults.[85] Fludrocortisone plasma concentrations were measured by liquid chromatography–mass spectrometry tandem analysis, before and repeatedly until 18 h after the oral dose. Plasma levels were found to be highly variable and undetectable in one third of patients in this study. The pharmacokinetics of daily dosing and of higher doses of fludrocortisone, as well as other factors that may influence fludrocortisone bioavailability in the critically ill, still requires further investigation.

Novel Therapeutic Options

A number of therapeutic agents for the management of catecholamine-resistant shock are currently under investigation.

Angiotensin II Infusion Therapy. Currently, no pharmacologic agents in routine clinical use support the renin–angiotensin–aldosterone system in the treatment of septic shock. The addition of angiotensin II may be beneficial, however.[151] Angiotensin II for the Treatment of High-Output Shock 3 (ATHOS-3) was a phase III, multicenter, double-blind, randomized controlled trial, which aimed to compare the efficacy and safety of angiotensin II *versus* placebo in catecholamine-resistant shock.[151] The trial consisted of 321 patients.[4] The primary endpoint was a mean arterial pressure (MAP) of 75 mmHg or an increase in MAP by 10 mmHg within 3 h of infusion initiation. The average MAP was 66 mmHg. Patients with a low cardiac output were excluded from the study. Of the patients in the angiotensin group, 70% reached the primary endpoint compared with 23% of the placebo group. The angiotensin group had a reduced mortality (46%) compared with the placebo group (54%; $P = 0.12$) but was not powered for this endpoint. There was no difference in the frequency of adverse events between the groups.[4]

Because of the exclusion of patients with a low cardiac output, as well as the fact that the study was not powered to detect a mortality benefit, the mortality benefit and safety profile of angiotensin II infusion therapy in low cardiac output states is thus currently unknown. Angiotensin II as a potent vasoconstrictor will likely be appropriate because cotherapy in conditions in which cardiac contractility is reduced.[152,153] Additionally, as discussed, cross-talk exists between angiotensin II and aldosterone beyond the role of the latter in mineralocorticoid effects, the implications and clinical relevance of which remain uncertain. Angiotensin acts on the zona glomerulosa, stimulating the release of aldosterone, which leads to increased sodium reabsorption and a subsequent increase in extracellular and blood fluid volume.[154] Further cross-talk mechanisms between aldosterone and angiotensin II also appear to be important in the development of endothelial dysfunction, cellular proliferation, and hypertrophy and in diseases such as hypertension.[155]

Currently, the results of a randomized, placebo-controlled trial that aims to evaluate the effect of LJPC-501 (angiotensin II) infusion on mean arterial pressure, as well as the safety and tolerability of LJPC-501 in pediatric patients, are awaited.[156] Additionally, a number of experimental and clinical studies assessing novel agents that modulate the renin–angiotensin–aldosterone system in the management

of diseases such as congestive heart failure, myocardial ischemia, and hypertension are currently underway.[157]

A substantial change in our understanding of the renin–angiotensin–aldosterone system has occurred over the last decade. The classical components of the system have now been expanded to include new enzymes and receptors, bringing into perspective the possibility of new avenues for investigation.[61]

Conclusions

Hyperreninemic hypoaldosteronism associated with a high mortality rate has been previously described in critically ill patients with shock. Variable plasma levels of aldosterone are seen in critical illness, as well as an impaired adrenal aldosterone response to increased levels of renin. However, the assessment of hypoaldosteronism, as well as the role of mineralocorticoid replacement in the critically ill, remains a challenge, while the effect of angiotensin II in shock states remains untested.

Summary of Key Points

There is renewed interest in the role of renin–angiotensin–aldosterone in critical illness. The available evidence is limited compared with what is known about the glucocorticoid axis. Whether mineralocorticoid deficiency exists as a relevant pathophysiologic entity in critical illness and the role of fludrocortisone treatment remain unknown. Further studies investigating these issues are warranted.

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Competing Interests

The authors declare no competing interests.

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References

1. Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot JP, Siami S, Cariou A, Forceville X, Schwebel C, Martin C, Timsit JF, Misset B, Ali Benali M, Colin G, Souweine B, Asehnoune K, Mercier E, Chimot L, Charpentier C, François B, Boulain T, Petitpas F, Constantin JM, Dhonneur G, Baudin F, Combes A, Bohé J, Loriferne JF, Amathieu R, Cook F, Slama M, Leroy O, Capellier G, Dargent A, Hissem T, Maxime V, Bellissant E; CRICS-TRIGGERSEP Network: Hydrocortisone plus fludrocortisone for adults with septic shock. N Engl J Med 2018; 378:809–18
2. Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, Billot L, Correa M, Glass P, Harward M, Joyce C, Li Q, McArthur C, Perner A, Rhodes A, Thompson K, Webb S, Myburgh J; ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group: Adjunctive glucocorticoid therapy in patients with septic shock. N Engl J Med 2018; 378:797–808
3. Cohen J, Venkatesh B: Adjunctive corticosteroid treatment in septic shock. ANESTHESIOLOGY 2019; 131:410–9
4. Khanna A, English SW, Wang XS, Ham K, Tumlin J, Szerlip H, Busse LW, Altaweel L, Albertson TE, Mackey C, McCurdy MT, Boldt DW, Chock S, Young PJ, Krell K, Wunderink RG, Ostermann M, Murugan R, Gong MN, Panwar R, Hästbacka J, Favory R, Venkatesh B, Thompson BT, Bellomo R, Jensen J, Kroll S, Chawla LS, Tidmarsh GF, Deane AM; ATHOS-3 Investigators: Angiotensin II for the treatment of vasodilatory shock. N Engl J Med 2017; 377:419–30
5. Venkatesh B, Finfer S, Myburgh J; ADRENAL Investigators: Glucocorticoids with or without fludrocortisone in septic shock. N Engl J Med 2018; 379:895
6. Newsome AS, Bissell BD, Burry LD, Defayette AA, Gagnon DJ, Gilbert BW, Kramer CJ, Miller CJ, Semanco M, Smith MN, Hammond DA: Major publications in critical care pharmacotherapy literature in 2018. J Crit Care 2019; 52:200–7
7. Pourmand A, Whiteside T, Yamane D, Rashed A, Mazer-Amirshahi M: The controversial role of corticosteroids in septic shock. Am J Emerg Med 2019; 37:1353–61
8. Manna PR, Stetson CL, Slominski AT, Pruitt K: Role of the steroidogenic acute regulatory protein in health and disease. Endocrine 2016; 51:7–21
9. Manna PR, Dyson MT, Stocco DM: Regulation of the steroidogenic acute regulatory protein gene expression: Present and future perspectives. Mol Hum Reprod 2009; 15:321–33
10. Stocco DM, Clark BJ: Regulation of the acute production of steroids in steroidogenic cells. Endocr Rev 1996; 17:221–44
11. Lim CT, Khoo B: Normal physiology of ACTH and GH release in the hypothalamus and anterior pituitary in man. In Endotext. Edited by Feingold KR, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A, Hershman JM, Kaltsas G, Koch C, Kopp P, Korbonits M, McLachlan R, Morley JE, New M, Perreault L, Purnell J, Rebar R, Singer F, Trence DL, Vinik A,

Wilson DP. South Dartmouth, MA, MDText.com, Inc., 2000. Available at: http://www.ncbi.nlm.nih.gov/books/NBK279116/. Accessed April 23, 2020.
12. Dickerman Z, Grant DR, Faiman C, Winter JS: Intraadrenal steroid concentrations in man: Zonal differences and developmental changes. J Clin Endocrinol Metab 1984; 59:1031–6
13. Gallo-Payet N, Martinez A, Lacroix A: ACTH action in the adrenal cortex: From molecular biology to pathophysiology. Front Endocrinol (Lausanne) 2017; 8:101
14. Miller WL: Molecular biology of steroid hormone synthesis. Endocr Rev 1988; 9:295–318
15. Turcu A, Smith JM, Auchus R, Rainey WE: Adrenal Androgens and Androgen Precursors: Definition, Synthesis, Regulation and Physiologic Actions, Comprehensive Physiology. Edited by Terjung R. Hoboken, John Wiley & Sons, Inc., 2014, pp 1369–81
16. Payne AH, Hales DB: Overview of steroidogenic enzymes in the pathway from cholesterol to active steroid hormones. Endocr Rev 2004; 25:947–70
17. Chung BC, Matteson KJ, Voutilainen R, Mohandas TK, Miller WL: 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
18. White PC: Disorders of aldosterone biosynthesis and action. N Engl J Med 1994; 331:250–8
19. Miller WL, Auchus RJ: The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders. Endocr Rev 2011; 32:81–151
20. Simpson ER, Waterman MR: Regulation of the synthesis of steroidogenic enzymes in adrenal cortical cells by ACTH. Annu Rev Physiol 1988; 50:427–40
21. Heming N, Sivanandamoorthy S, Meng P, Bounab R, Annane D: Immune effects of corticosteroids in sepsis. Front Immunol 2018; 9:1736
22. 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
23. Endoh A, Kristiansen SB, Casson PR, Buster JE, Hornsby PJ: 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 3β-hydroxysteroid dehydrogenase. J Clin Endocrinol Metab 1996; 81:3558–65
24. Rainey WE, Nakamura Y: Regulation of the adrenal androgen biosynthesis. J Steroid Biochem Mol Biol 2008; 108:281–6
25. Hatakeyama H, Miyamori I, Fujita T, Takeda Y, Takeda R, Yamamoto H: Vascular aldosterone: Biosynthesis and a link to angiotensin II-induced hypertrophy of vascular smooth muscle cells. J Biol Chem 1994; 269:24316–20
26. Williams GH: Aldosterone biosynthesis, regulation, and classical mechanism of action. Heart Fail Rev 2005; 10:7–13
27. Li W, Peng H, Seth DM, Feng Y: The prorenin and (pro) renin receptor: New players in the brain renin–angiotensin system? Int J Hypertens 2012; 2012:290635
28. Persson PB: Renin: Origin, secretion and synthesis. J Physiol 2003; 552:667–71
29. Faulkner JL, Kennard S, Huby AC, Antonova G, Lu Q, Jaffe IZ, Patel VS, Fulton DJR, Belin de Chantemèle EJ: Progesterone predisposes females to obesity-associated leptin-mediated endothelial dysfunction via upregulating endothelial MR (mineralocorticoid receptor) expression. Hypertension 2019; 74:678–86
30. Raffa RB, Rawls SM, Beyzarov EP: Netter's Illustrated Pharmacology E-Book, Updated edition. Philadelphia, Saunders, 2013
31. Davel AP, Jaffe IZ, Tostes RC, Jaisser F, Belin de Chantemèle EJ: New roles of aldosterone and mineralocorticoid receptors in cardiovascular disease: Translational and sex-specific effects. Am J Physiol Heart Circ Physiol 2018; 315:H989–99
32. MacKenzie SM, Connell JM, Davies E: Non-adrenal synthesis of aldosterone: A reality check. Mol Cell Endocrinol 2012; 350:163–7
33. Faulkner JL, Bruder-Nascimento T, Belin de Chantemèle EJ: The regulation of aldosterone secretion by leptin: Implications in obesity-related cardiovascular disease. Curr Opin Nephrol Hypertens 2018; 27:63–9
34. Cassis LA, Police SB, Yiannikouris F, Thatcher SE: Local adipose tissue renin–angiotensin system. Curr Hypertens Rep 2008; 10:93–8
35. Dobrian AD, Davies MJ, Prewitt RL, Lauterio TJ: Development of hypertension in a rat model of diet-induced obesity. Hypertension 2000; 35:1009–15
36. Nolten WE, Ehrlich EN: Sodium and mineralocorticoids in normal pregnancy. Kidney Int 1980; 18:162–72
37. Scaife PJ, Mohaupt MG: Salt, aldosterone and extrarenal Na^+-sensitive responses in pregnancy. Placenta 2017; 56:53–8
38. Tapia HR, Johnson CE, Strong CG: Renin–angiotensin system in normal and in hypertensive disease of pregnancy. Lancet 1972; 2:847–50
39. Arabi YM, Dara SI, Tamim HM, Rishu AH, Bouchama A, Khedr MK, Feinstein D, Parrillo JE, Wood KE, Keenan SP, Zanotti S, Martinka G, Kumar A, Kumar A; Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group: Clinical characteristics, sepsis interventions and outcomes in the obese patients with septic shock: An international multicenter cohort study. Crit Care 2013; 17:R72
40. Kerstens MN, Kobold AC, Volmer M, Koerts J, Sluiter WJ, Dullaart RP: Reference values for aldosterone–renin ratios in normotensive individuals and effect of

changes in dietary sodium consumption. Clin Chem 2011; 57:1607–11
41. Tiu SC, Choi CH, Shek CC, Ng YW, Chan FK, Ng CM, Kong AP: 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
42. Hannemann A, Friedrich N, Lüdemann J, Völzke H, Rettig R, Peters J, Reincke M, Döring A, Nauck M, Wallaschofski H: 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
43. Wyrwoll CS, Holmes MC, Seckl JR: 11β-Hydroxysteroid dehydrogenases and the brain: From zero to hero, a decade of progress. Front Neuroendocrinol 2011; 32:265–86
44. Scheuer DA: Stimulation of aldosterone synthesis by angiotensin II in the brain: Support for positive feedback in hypertension? Hypertension 2013; 62:459–60
45. Gomez-Sanchez EP, Gomez-Sanchez CE: Is aldosterone synthesized in the CNS regulated and functional? Trends Endocrinol Metab 2003; 14:444–6
46. Gomez-Sanchez EP, Gomez-Sanchez CM, Plonczynski M, Gomez-Sanchez CE: Aldosterone synthesis in the brain contributes to Dahl salt-sensitive rat hypertension. Exp Physiol 2010; 95:120–30
47. Wang HW, Huang BS, Chen A, Ahmad M, White RA, Leenen FH: Role of brain aldosterone and mineralocorticoid receptors in aldosterone-salt hypertension in rats. Neuroscience 2016; 314:90–105
48. Berger S, Bleich M, Schmid W, Cole TJ, Peters J, Watanabe H, Kriz W, Warth R, Greger R, Schütz G: Mineralocorticoid receptor knockout mice: Pathophysiology of Na^+ metabolism. PNAS 1998; 95:9424–9
49. Ngarmukos C, Grekin RJ: Nontraditional aspects of aldosterone physiology. Am J Physiol Endocrinol Metab 2001; 281:E1122–7
50. Gotoh K, Shibata H: Aldosterone: History and introduction. In Textbook of Nephro-endocrinology, 2nd Edition. Edited by Singh AK, Williams GH. Cambridge, MA, Academic Press, 2018, pp 465–76
51. Epstein M, Calhoun DA: Aldosterone blockers (mineralocorticoid receptor antagonism) and potassium-sparing diuretics. J Clin Hypertens (Greenwich) 2011; 13:644–8
52. Trapp T, Holsboer F: Ligand-induced conformational changes in the mineralocorticoid receptor analyzed by protease mapping. Biochem Biophys Res Commun 1995; 215:286–91
53. Fuller PJ, Yao Y, Yang J, Young MJ: Mechanisms of ligand specificity of the mineralocorticoid receptor. J Endocrinol 2012; 213:15–24
54. Kirk DN, Marples BA: The structure and nomenclature of steroids. In Steroid Analysis. Edited by Makin HLJ, Gower DB, Kirk DN. Dordrecht, Springer, 1995, pp 1–24
55. Brookes JC, Galigniana MD, Harker AH, Stoneham AM, Vinson GP: System among the corticosteroids: Specificity and molecular dynamics. J R Soc Interface 2012; 9:43–53
56. Vinson GP: The mislabelling of deoxycorticosterone: Making sense of corticosteroid structure and function. J Endocrinol 2011; 211:3–16
57. Galigniana MD, Piwien Pilipuk G, Kanelakis KC, Burton G, Lantos CP: Molecular mechanism of activation and nuclear translocation of the mineralocorticoid receptor upon binding of pregnanesteroids. Mol Cell Endocrinol 2004; 217:167–79
58. Annane D: Is there a mineralocorticoid deficiency in critically ill patients? How can it be diagnosed? Should it be treated? Evidence-based Practice of Critical Care. Philadelphia, Elsevier, 2010, pp 521–4
59. Funder JW: Aldosterone action. Annu Rev Physiol 1993; 55:115–30
60. Zhuo JL, Ferrao FM, Zheng Y, Li XC: New frontiers in the intrarenal renin–angiotensin system: A critical review of classical and new paradigms. Front Endocrinol (Lausanne) 2013; 4:166
61. Santos RA: Angiotensin-(1-7). Hypertension 2014; 63:1138–47
62. Briet M, Schiffrin EL: Vascular actions of aldosterone. J Vasc Res 2013; 50:89–99
63. Rodríguez Soriano J: Renal tubular acidosis: The clinical entity. J Am Soc Nephrol 2002; 13:2160–70
64. Diederich S, Mai K, Bähr V, Helffrich S, Pfeiffer A, Perschel FH: The simultaneous measurement of plasma–aldosterone- and –renin–concentration allows rapid classification of all disorders of the renin–aldosterone system. Exp Clin Endocrinol Diabetes 2007; 115:433–8
65. Sousa AG, Cabral JV, El-Feghaly WB, de Sousa LS, Nunes AB: Hyporeninemic hypoaldosteronism and diabetes mellitus: Pathophysiology assumptions, clinical aspects and implications for management. World J Diabetes 2016; 7:101–11
66. Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA, Torpy DJ: Diagnosis and treatment of primary adrenal insufficiency: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2016; 101:364–89
67. Mohsenin V: Practical approach to detection and management of acute kidney injury in critically ill patient. J Intensive Care 2017; 5:57

68. Stevens PE, Levin A; Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members: Evaluation and management of chronic kidney disease: Synopsis of the kidney disease: Improving Global Outcomes 2012 clinical practice guideline. Ann Intern Med 2013; 158:825–30
69. DeFronzo RA: Hyperkalemia and hyporeninemic hypoaldosteronism. Kidney Int 1980; 17:118–34
70. Haas CS, Pohlenz I, Lindner U, Muck PM, Arand J, Suefke S, Lehnert H: Renal tubular acidosis type IV in hyperkalaemic patients: A fairy tale or reality? Clin Endocrinol (Oxf) 2013; 78:706–11
71. Karet FE: Mechanisms in hyperkalemic renal tubular acidosis. J Am Soc Nephrol 2009; 20:251–4
72. Jan Danser AH, Batenburg WW, Esch JHM van: Prorenin and the (pro)renin receptor-an update. Nephrology Dialysis Transplantation 2007; 22:1288–92
73. Kurtz A: Control of renin synthesis and secretion. Am J Hypertens 2012; 25:839–47
74. Yang T, Xu C: Physiology and pathophysiology of the intrarenal renin–angiotensin system: An update. J Am Soc Nephrol 2017; 28:1040–9
75. Gleeson PJ, Crippa IA, Mongkolpun W, Cavicchi FZ, Van Meerhaeghe T, Brimioulle S, Taccone FS, Vincent JL, Creteur J: Renin as a marker of tissue-perfusion and prognosis in critically ill patients. Crit Care Med 2019; 47:152–8
76. Cheyron D du, Lesage A, Daubin C, Ramakers M, Charbonneau P: Hyperreninemic hypoaldosteronism: A possible etiological factor of septic shock-induced acute renal failure. Intensive Care Med 2003; 29:1703–9
77. Leonard J, Garrett RE, Salottolo K, Slone DS, Mains CW, Carrick MM, Bar-Or D: Cerebral salt wasting after traumatic brain injury: A review of the literature. Scand J Trauma Resusc Emerg Med 2015; 23:98
78. Berendes E, Walter M, Cullen P, Prien T, Van Aken H, Horsthemke J, Schulte M, von Wild K, Scherer R: Secretion of brain natriuretic peptide in patients with aneurysmal subarachnoid haemorrhage. Lancet 1997; 349:245–9
79. Bismarck P von, Ankermann T, Eggert P, Claviez A, Fritsch MJ, Krause MF: Diagnosis and management of cerebral salt wasting (CSW) in children: The role of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). Child's Nervous System 2006; 22:1275–81
80. Lee P, Jones GR, Center JR: Successful treatment of adult cerebral salt wasting with fludrocortisone. Arch Intern Med 2008; 168:325–6
81. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, Hoh BL, Kirkness CJ, Naidech AM, Ogilvy CS, Patel AB, Thompson BG, Vespa P; American Heart Association Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Council on Cardiovascular Surgery and Anesthesia; Council on Clinical Cardiology: Guidelines for the management of aneurysmal subarachnoid hemorrhage: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2012; 43:1711–37
82. Woo MH, Kale-Pradhan PB: Fludrocortisone in the treatment of subarachnoid hemorrhage-induced hyponatremia. Ann Pharmacother 1997; 31:637–9
83. Hasan D, Lindsay KW, Wijdicks EF, Murray GD, Brouwers PJ, Bakker WH, van Gijn J, Vermeulen M: Effect of fludrocortisone acetate in patients with subarachnoid hemorrhage. Stroke 1989; 20:1156–61
84. Mori T, Katayama Y, Kawamata T, Hirayama T: Improved efficiency of hypervolemic therapy with inhibition of natriuresis by fludrocortisone in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg 1999; 91:947–52
85. Polito A, Hamitouche N, Ribot M, Polito A, Laviolle B, Bellissant E, Annane D, Alvarez JC: Pharmacokinetics of oral fludrocortisone in septic shock. Br J Clin Pharmacol 2016; 82:1509–16
86. Rabinstein AA, Bruder N: Management of hyponatremia and volume contraction. Neurocrit Care 2011; 15:354–60
87. Wood JM, Maibaum J, Rahuel J, Grütter MG, Cohen NC, Rasetti V, Rüger H, Göschke R, Stutz S, Fuhrer W, Schilling W, Rigollier P, Yamaguchi Y, Cumin F, Baum HP, Schnell CR, Herold P, Mah R, Jensen C, O'Brien E, Stanton A, Bedigian MP: Structure-based design of aliskiren, a novel orally effective renin inhibitor. Biochem Biophys Res Commun 2003; 308:698–705
88. Brown NJ, Vaughan DE: Angiotensin-converting enzyme inhibitors. Circulation 1998; 97:1411–20
89. Bhaskar B, Fraser JF, Mullaney D: Lest we forget: Heparin-induced hyperkalemia. J Cardiothorac Vasc Anesth 2012; 26:106–9
90. Knights KM, Winner LK, Elliot DJ, Bowalgaha K, Miners JO: Aldosterone glucuronidation by human liver and kidney microsomes and recombinant UDP-glucuronosyltransferases: Inhibition by NSAIDs. Br J Clin Pharmacol 2009; 68:402–12
91. Knights KM, Mangoni AA, Miners JO: Non-selective nonsteroidal anti-inflammatory drugs and cardiovascular events: Is aldosterone the silent partner in crime? Br J Clin Pharmacol 2006; 61:738–40
92. Crilly MA, Mangoni AA: Non-steroidal anti-inflammatory drug (NSAID) related inhibition of aldosterone glucuronidation and arterial dysfunction in patients with rheumatoid arthritis: A cross-sectional clinical study. BMJ Open 2011; 1:e000076
93. Crilly MA, Mangoni AA, Knights KM: Aldosterone glucuronidation inhibition as a potential mechanism for arterial dysfunction associated with chronic celecoxib and diclofenac use in patients with rheumatoid arthritis. Clin Exp Rheumatol 2013; 31:691–8

94. De Léan A, Racz K, McNicoll N, Desrosiers ML: Direct β-adrenergic stimulation of aldosterone secretion in cultured bovine adrenal subcapsular cells. Endocrinology 1984; 115:485–92
95. Pratt JH, Turner DA, McAteer JA, Henry DP: β-Adrenergic stimulation of aldosterone production by rat adrenal capsular explants. Endocrinology 1985; 117:1189–94
96. Bantle JP, Nath KA, Sutherland DE, Najarian JS, Ferris TF: Effects of cyclosporine on the renin–angiotensin–aldosterone system and potassium excretion in renal transplant recipients. Arch Intern Med 1985; 145:505–8
97. Heering PJ, Kurschat C, Vo DT, Klein-Vehne N, Fehsel K, Ivens K: Aldosterone resistance in kidney transplantation is in part induced by a down-regulation of mineralocorticoid receptor expression. Clin Transplant 2004; 18:186–92
98. Farouk SS, Rein JL: The many faces of calcineurin inhibitor toxicity: What the FK? Adv Chronic Kidney Dis 2020; 27:56–66
99. Oster JR, Singer I, Fishman LM: Heparin-induced aldosterone suppression and hyperkalemia. Am J Med 1995; 98:575–86
100. Ben Salem C, Badreddine A, Fathallah N, Slim R, Hmouda H: Drug-induced hyperkalemia. Drug Saf 2014; 37:677–92
101. Arai K, Chrousos GP: Aldosterone deficiency and resistance. In Endotext. Edited by Feingold KR, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A, Hershman JM, Kaltsas G, Koch C, Kopp P, Korbonits M, McLachlan R, Morley JE, New M, Perreault L, Purnell J, Rebar R, Singer F, Trence DL, Vinik A, Wilson DP. South Dartmouth, MA, MDText.com, Inc., 2000. Available at: http://www.ncbi.nlm.nih.gov/books/NBK279079/. Accessed April 25, 2019.
102. Weber KT: Aldosterone in congestive heart failure. N Engl J Med 2001; 345:1689–97
103. Díez J: Effects of aldosterone on the heart. Hypertension 2008; 52:462–4
104. Sayer G, Bhat G: The renin–angiotensin–aldosterone system and heart failure. Cardiol Clin 2014; 32:21–32
105. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L; CONSENSUS Trial Study Group: Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. Circulation 1990; 82:1730–6
106. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J; Randomized Aldactone Evaluation Study Investigators: The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999; 341:709–17
107. Orsborne C, Chaggar PS, Shaw SM, Williams SG: 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
108. Díez J: Chronic heart failure as a state of reduced effectiveness of the natriuretic peptide system: Implications for therapy. Eur J Heart Fail 2017; 19:167–76
109. Weber KT: Aldosterone and spironolactone in heart failure. N Engl J Med 1999; 341:753–5
110. Ames MK, Atkins CE, Pitt B: The renin–angiotensin–aldosterone system and its suppression. J Vet Intern Med 2019; 33:363–82
111. Braley LM, Adler GK, Mortensen RM, Conlin PR, Chen R, Hallahan J, Menachery AI, Williams GH: 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
112. Peeters B, Meersseman P, Vander Perre S, Wouters PJ, Vanmarcke D, Debaveye Y, Billen J, Vermeersch P, Langouche L, Van den Berghe G: Adrenocortical function during prolonged critical illness and beyond: A prospective observational study. Intensive Care Med 2018; 44:1720–9
113. Peeters B, Meersseman P, Vander Perre S, Wouters PJ, Debaveye Y, Langouche L, Van den Berghe G: 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
114. Téblick A, Peeters B, Langouche L, Van den Berghe G: Adrenal function and dysfunction in critically ill patients. Nat Rev Endocrinol 2019; 15:417–27
115. Davenport MW, Zipser RD: Association of hypotension with hyperreninemic hypoaldosteronism in the critically ill patient. Arch Intern Med 1983; 143:735–7
116. Stern N, Beck FW, Sowers JR, Tuck M, Hsueh WA, Zipser RD: Plasma corticosteroids in hyperreninemic hypoaldosteronism: Evidence for diffuse impairment of the zona glomerulosa. J Clin Endocrinol Metab 1983; 57:217–20
117. Zipser RD, Davenport MW, Martin KL, Tuck ML, Warner NE, Swinney RR, Davis CL, Horton R: Hyperreninemic hypoaldosteronism in the critically ill: A new entity. J Clin Endocrinol Metab 1981; 53:867–73
118. Findling JW, Waters VO, Raff H: The dissociation of renin and aldosterone during critical illness. J Clin Endocrinol Metab 1987; 64:592–5
119. Lichtarowicz-Krynska EJ, Cole TJ, Camacho-Hubner C, Britto J, Levin M, Klein N, Aynsley-Green A: Circulating aldosterone levels are unexpectedly low in children with acute meningococcal disease. J Clin Endocrinol Metab 2004; 89:1410–4
120. Tolstoy NS, Aized M, McMonagle MP, Holena DN, Pascual JL, Sonnad SS, Sims CA: Mineralocorticoid

deficiency in hemorrhagic shock. J Surg Res 2013; 180:232–7
121. Cheyron D du, Bouchet B, Cauquelin B, Guillotin D, Ramakers M, Daubin C, Ballet J-J, Charbonneau P: Hyperreninemic hypoaldosteronism syndrome, plasma concentrations of interleukin-6 and outcome in critically ill patients with liver cirrhosis. Intensive Care Med 2008; 34:116–24
122. Annane D, Pastores SM, Arlt W, Balk RA, Beishuizen A, Briegel J, Carcillo J, Christ-Crain M, Cooper MS, Marik PE, Meduri GU, Olsen KM, Rochwerg B, Rodgers SC, Russell JA, Van den Berghe G: 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
123. Marik PE, Pastores SM, Annane D, Meduri GU, Sprung CL, Arlt W, Keh D, Briegel J, Beishuizen A, Dimopoulou I, Tsagarakis S, Singer M, Chrousos GP, Zaloga G, Bokhari F, Vogeser M; American College of Critical Care Medicine: 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
124. Annane D, Sébille V, Charpentier C, Bollaert PE, François B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troché G, Chaumet-Riffaud P, Chaumet-Riffaut P, Bellissant E: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002; 288:862–71
125. Annane D, Cariou A, Maxime V, Azoulay E, D'Honneur G, Timsit JF, Cohen Y, Wolf M, Fartoukh M, Adrie C, Santré C, Bollaert PE, Mathonet A, Amathieu R, Tabah A, Clec'h C, Mayaux J, Lejeune J, Chevret S; COIITSS Study Investigators: Corticosteroid treatment and intensive insulin therapy for septic shock in adults: A randomized controlled trial. JAMA 2010; 303:341–8
126. Ramsahoye BH, Davies SV, el-Gaylani N, Sandeman D, Scanlon MF: The mineralocorticoid effects of high dose hydrocortisone. BMJ 1995; 310:656–7
127. Laviolle B, Nesseler N, Massart C, Bellissant E: 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
128. Funder JW: Aldosterone and mineralocorticoid receptors: Physiology and pathophysiology. Int J Mol Sci 2017; 18
129. Cotton BA, Guillamondegui OD, Fleming SB, Carpenter RO, Patel SH, Morris JA Jr, Arbogast PG: Increased risk of adrenal insufficiency following etomidate exposure in critically injured patients. Arch Surg 2008; 143:62–7
130. Aguilera G, Kiss A, Sunar-Akbasak B: Hyperreninemic hypoaldosteronism after chronic stress in the rat. J Clin Invest 1995; 96:1512–9
131. 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
132. Marana E, Annetta MG, Marana R, Maussier ML, Galeone M, Mensi S, D'Angelo F, Proietti R: Neuroendocrine stress response in laparoscopic surgery for benign ovarian cyst. Can J Anaesth 2004; 51:943–4
133. Marana E, Colicci S, Meo F, Marana R, Proietti R: Neuroendocrine stress response in gynecological laparoscopy: TIVA with propofol *versus* sevoflurane anesthesia. J Clin Anesth 2010; 22:250–5
134. Jelinek F, Konecny R: Adrenal glands of slaughtered bulls, heifers and cows: A histological study. Anat Histol Embryol 2011; 40:28–34
135. Rushworth RL, Torpy DJ, Falhammar H: Adrenal crisis. N Engl J Med 2019; 381:852–61
136. Keller-Wood ME, Dallman MF: Corticosteroid inhibition of ACTH secretion. Endocr Rev 1984; 5:1–24
137. Raff H: Glucocorticoid inhibition of neurohypophysial vasopressin secretion. Am J Physiol 1987; 252:R635–44
138. Schrier RW: Body water homeostasis: Clinical disorders of urinary dilution and concentration. J Am Soc Nephrol 2006; 17:1820–32
139. O'Shea PM, Griffin TP, Browne GA, Gallagher N, Brady JJ, Dennedy MC, Bell M, Wall D, Fitzgibbon M: Screening for primary aldosteronism using the newly developed IDS-iSYS® automated assay system. Pract Lab Med 2017; 7:6–14
140. Rehan M, Raizman JE, Cavalier E, Don-Wauchope AC, Holmes DT: Laboratory challenges in primary aldosteronism screening and diagnosis. Clin Biochem 2015; 48:377–87
141. Barnes SC: Measurement of Plasma Renin Activity, Hormone Assays in Biological Fluids. Edited by Wheeler MJ. Totowa, NJ, Humana Press, 2013, pp 235–44
142. Fischer M, Baessler A, Schunkert H: Renin angiotensin system and gender differences in the cardiovascular system. Cardiovasc Res 2002; 53:672–7
143. Sealey JE: Plasma renin activity and plasma prorenin assays. Clin Chem 1991; 37:1811–9
144. O'Connell T, Horita TJ, Kasravi B: Understanding and interpreting the serum protein electrophoresis. AFP 2005; 71:105–12
145. Schunkert H, Danser AH, Hense HW, Derkx FH, Kürzinger S, Riegger GA: Effects of estrogen

replacement therapy on the renin–angiotensin system in postmenopausal women. Circulation 1997; 95:39–45

146. Arnal JF, Cudek P, Plouin PF, Guyenne TT, Michel JB, Corvol P: Low angiotensinogen levels are related to the severity and liver dysfunction of congestive heart failure: Implications for renin measurements. Am J Med 1991; 90:17–22
147. Dickson ME, Sigmund CD: Genetic basis of hypertension: Revisiting angiotensinogen. Hypertension 2006; 48:14–20
148. Raizman JE, Diamandis EP, Holmes D, Stowasser M, Auchus R, Cavalier E: A renin-ssance in primary aldosteronism testing: Obstacles and opportunities for screening, diagnosis, and management. Clin Chem 2015; 61:1022–7
149. Cawood ML: Measurement of aldosterone in blood. In Hormone Assays in Biological Fluids. Edited by Wheeler MJ, Hutchinson JSM. Totowa, NJ, Humana Press, 2006, pp 177–85. Available at: https://doi.org/10.1385/1-59259-986-9:177. Accessed April 23, 2020.
150. Kalin MF, Poretsky L, Seres DS, Zumoff B: Hyporeninemic hypoaldosteronism associated with acquired immune deficiency syndrome. Am J Med 1987; 82:1035–8
151. Chawla LS, Russell JA, Bagshaw SM, Shaw AD, Goldstein SL, Fink MP, Tidmarsh GF: Angiotensin II for the Treatment of High-Output Shock 3 (ATHOS-3): Protocol for a phase III, double-blind, randomised controlled trial. Crit Care Resusc 2017; 19:43–9
152. Corrêa TD, Takala J, Jakob SM: Angiotensin II in septic shock. Crit Care 2015; 19
153. Dellinger RP, Trzeciak S: Angiotensin II for the treatment of vasodilatory shock: Promise and caution. N Engl J Med 2017; 377:486–7
154. Fountain JH, Lappin SL: Physiology, Renin Angiotensin System, StatPearls. Treasure Island (FL), StatPearls Publishing, 2020. Available at: http://www.ncbi.nlm.nih.gov/books/NBK470410/. Accessed March 19, 2020.
155. Min LJ, Mogi M, Iwanami J, Li JM, Sakata A, Fujita T, Tsukuda K, Iwai M, Horiuchi M: Cross-talk between aldosterone and angiotensin II in vascular smooth muscle cell senescence. Cardiovasc Res 2007; 76:506–16
156. National Library of Medicine (US): A study of LJPC-501 in paediatric patients with hypotension associated with distributive or vasodilatory shock. Identifier: NCT03623529 2000. Available at: https://clinicaltrials.gov/ct2/show/NCT03623529. Accessed March 5, 2019.
157. Gromotowicz-Poplawska A, Szoka P, Kolodziejczyk P, Kramkowski K, Wojewodzka-Zelezniakowicz M, Chabielska E: New agents modulating the renin–angiotensin–aldosterone system: Will there be a new therapeutic option? Exp Biol Med (Maywood) 2016; 241:1888–99