Adrenal Insufficiency in Cirrhosis

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Abstract

Hypothalamus-pituitary-adrenal axis assessment in patients with cirrhosis is challenging. The phenotype of fatigue, hypotension, electrolyte disarray, and abdominal pain characterizing primary adrenal insufficiency (AI) overlaps significantly with decompensated liver disease. Reliance on total cortisol assays in hypoproteinemic states is problematic, yet abnormal stimulated levels in cirrhosis are associated with poor clinical outcomes. Alternative measures including free plasma or salivary cortisol levels have theoretical merit but are limited by unclear prognostic significance and undefined cirrhosis-specific reference ranges. Further complicating matters is that AI in cirrhosis represents a spectrum of impairment. Although absolute cortisol deficiency can occur, this represents a minority of cases. Instead, there is an emerging concept that cirrhosis, with or without critical illness, may induce a "relative" cortisol deficiency during times of stress. In addition, the limitations posed by decreased synthesis of binding globulins in cirrhosis necessitate re-evaluation of traditional AI diagnostic thresholds.

Key Words: adrenal insufficiency, cirrhosis, liver disease, hypoproteinemia, hepatoadrenal

Abbreviations: 11β-HSD, 11 beta-hydroxysteroid dehydrogenase; AI, adrenal insufficiency; CBG, corticosteroid-binding globulin; CIRCI, critical illness-related corticosteroid insufficiency; CSR_{max}, maximal cortisol secretion rate; DHEAS, dehydroepiandrosterone sulfate; FPC, free plasma cortisol; HDL, high-density lipoprotein; HPA, hypothalamus-pituitary-adrenal; LCAT, lecithin-cholesterol acyltransferase; LC-MS, liquid chromatography-tandem mass spectrometry; LD-SST, low-dose cosyntropin (Synacthen) stimulation test; PAI, primary adrenal insufficiency; RAI, relative adrenal insufficiency; SC, salivary cortisol; SD-SST, standard-dose cosyntropin (Synacthen) stimulation test; TC, total cortisol

Hypoproteinemic states represent a challenge when assessing hypothalamus-pituitary-adrenal (HPA) axis functionality [1]. This scenario is common in cirrhosis and further complicated by significant overlap between clinical manifestations of adrenal insufficiency (AI) and decompensated liver disease. Additionally, AI exists along a spectrum in patients with cirrhosis and thus it is incumbent on the evaluating physician to determine whether adrenal function is sufficient, relatively insufficient (RAI), or absolutely insufficient (absolute AI).

Relative adrenal insufficiency was originally described in the critically ill population and is currently termed critical illness-related corticosteroid insufficiency (CIRCI). Marik et al. first reported the condition in patients with cirrhosis in 2005, naming it the "hepato-adrenal syndrome" [2]. At baseline, patients have adequate adrenal reserve to meet homeostatic demands but are unable to either produce excess cortisol or respond at the tissue receptor level to increased cortisol production. However, there is significant heterogeneity in the existing literature with regard to the diagnosis and characterization of AI (i.e., is it relative or absolute?). Many authors acknowledge the challenge posed by measuring serum total cortisol (TC) in cirrhosis yet there is insufficient evidence for current guidelines to provide recommendations regarding optimal diagnostic strategies and clinical thresholds [3].

The prevalence of AI in cirrhosis is variable (15%-72%) and dependent on patient and methodologic factors [2, 4-12].

Negative prognostic implications are associated with RAI by TC criteria in both critical and noncritical illness [2, 6-9, 11, 13-15]; however, whether free plasma or salivary cortisol levels portend similar outcomes is unknown. A fragmented approach to the diagnosis and characterization of AI in cirrhosis has slowed its widespread recognition and contributed to current clinical confusion.

Another challenge unique to cirrhosis is that the development of AI may be both multifactorial and multilevel in nature [6, 16-19]. Trying to segregate a specific case into a purely primary or secondary (or tertiary) process may not be possible given clinical heterogeneity. Finally, patients with cirrhosis are at increased risk to develop critical illness, which is an established AI risk factor in the general population [20]. Discriminating whether AI in this scenario is related to the underlying liver disease or current illness state may not be possible. However, given that AI develops in stable outpatients [4, 5, 21-24], longitudinal study is necessary to understand whether AI is a dynamic or static organ dysfunction in cirrhosis.

In this review, we summarize the literature on AI in cirrhosis across all severity of illness given significant heterogeneity in patient characteristics and HPA assessment technique. Importantly, we highlight the diagnostic and management controversies that present a unique partnership opportunity for endocrinologists and hepatologists to provide state-of-the-art care.

Abnormal HPA Axis Functionality and Cortisol Metabolism in Liver Disease

Adrenal insufficiency is an underrecognized endocrine dysfunction spanning the spectrum of liver disease. Although its pathophysiology is complex and will be discussed in greater detail in a later section, abnormal pituitary (and/or hypothalamic) ACTH secretion may play role. Montagense et al. reported differences in free cortisol secretion rhythm, such that the morning peak was delayed in patients with cirrhosis, particularly those with decompensated disease [25]. Though limited by sample size and no concurrent measurement of ACTH, these findings provide evidence for pituitary dysfunction being a sequela of cirrhosis. Emerging evidence suggests that liver transplantation absolves these abnormalities, supporting the pivotal role of the liver in maintaining normal endocrine function [26].

Cortisol secretion is non-linear in healthy individuals, oscillating in circadian and ultradian (60- to 90-minute cycles) fashion with an early morning peak and nocturnal nadir [27]. Disruption of normal circadian rhythm is common in decompensated cirrhosis yet whether it exerts a significant effect on cortisol secretion is unsettled [25]. One small study suggested no change in patients with cirrhosis compared with controls, although most patients had compensated disease [28]. Conversely, another small study noted that patients with cirrhosis had a delayed peak free plasma cortisol (FPC); this effect was more pronounced in those with decompensated disease [29].

Metabolism of cortisol is also abnormal in cirrhosis. The 11 beta-hydroxysteroid dehydrogenase (11β-HSD) enzyme (types 1 and 2, both contained within hepatic and renal cells) shuttles cortisol between its biologically active and inert form (cortisone). Animal and human studies demonstrate that liver disease is associated with reduced 11β-HSD enzyme levels and thus an increase in circulating glucocorticoids [30, 31]. Additionally, cortisol elimination is impaired in cirrhosis and parallels liver disease severity [32].

Altered Binding Globulin Production in Cirrhosis

Endocrine dysfunction in cirrhosis is also a byproduct of impaired hepatic synthetic function. The liver produces all hormonal binding globulins, thus there is a global decrease (SHBG excepted) in cirrhosis. This is particularly relevant when evaluating the adrenal axis because 90% of cortisol is bound to either corticosteroid-binding globulin (CBG; 70%) or albumin (20%). Decreased levels of both are well established in cirrhosis [33, 34], yet whether differential loss exists is unknown. Interestingly, CBG and albumin levels are only weakly correlated [1].

The molecular and thus functional characteristics of albumin are altered in cirrhosis. Effective albumin concentration describes the observation that a higher proportion of albumin in patients with cirrhosis may be dysfunctional and is associated with severity of liver disease as well as clinical outcomes, including mortality [35]. Nonetheless, whether the hypoalbuminemia and associated intrinsic molecular dysfunction unique to cirrhosis impair cortisol-binding remains an avenue for future research.

Pathophysiology of AI in Cirrhosis

Causal pathways of AI in cirrhosis are incompletely understood but appear multifactorial [6, 36]. Traditional etiologies of absolute AI can occur, but this represents a minority of cases as the sequelae of liver disease disrupts normal adrenal function. Adrenal steroidogenesis is dependent on hepatic cholesterol trafficking via high-density lipoprotein (HDL). The latter is principally composed of apolipoproteins, including apo-A1. It is well-established that apo-A1 and HDL levels correlate with hepatic synthetic function [37-39]. Similarly, impairment of lecithin-cholesterol acyltransferase (LCAT) enzymatic activity appears to parallel liver disease severity [40, 41]. Given that LCAT binds to apo-A1 to facilitate the esterification of free cholesterol and form a mature HDL particle, there is significant interdependence among all three factors (Fig. 1). Dyslipidemia in liver disease, manifest by reduction in HDL levels, has been associated with AI [6-8]. Although postulated as a potential contributory mechanism, evidence for direct causality is lacking. In the noncirrhotic state, low HDL does not alter HPA response to ACTH stimulation testing [42]. However, whether there is differential effect of this substrate deficiency in patients with cirrhosis, particularly in response to stress, is unknown. Furthermore, low CBG levels in cirrhosis could confound the relationship between HDL and AI, yet the literature is inconsistent about its plausibility [5, 6, 9, 43].

Besides dyslipidemia, several other mechanisms (Fig. 2) are conceptually valid for implication in the development of AI in cirrhosis but require further study:

1) Deficient intrinsic adrenal enzymatic activity leading to either excess precursor steroids (in relation to cortisol) or pathway shunting,
2) Altered vascular tone in the setting of splanchnic vasodilation and low effective circulating volume leading to chronic adrenal hypoperfusion, and
3) Suppressive effects of pro-inflammatory cytokines on HPA axis hormonal secretion [11, 36].

Cirrhosis is a pro-inflammatory state and differential profiles of cytokine expression correlate with disease severity [17]. Levels of TNF-alpha and IL-6 were compared in one study of noncritically ill patients with cirrhosis both with and without RAI. Patients with RAI had numerically superior but nonsignificantly higher pro-inflammatory cytokine levels in this exploratory analysis [9]. This finding requires further investigation, including broadening to measurement of other cytokines. Nonetheless, there exists the potential for significant confounding, as acute illness (particularly critical illness) increases levels of pro-inflammatory cytokines.

In addition to their direct suppressive effects on all 3 levels of the HPA axis, pro-inflammatory cytokines reduce peripheral tissue glucocorticoid sensitivity [44]. The concept of multilevel impairment is further supported by Fede et al. The previously mentioned authors showed that AI in cirrhosis could be reversed with prolonged, supra-physiologic ACTH stimulation, suggesting an amalgam of both partial primary and secondary insufficiency [45].
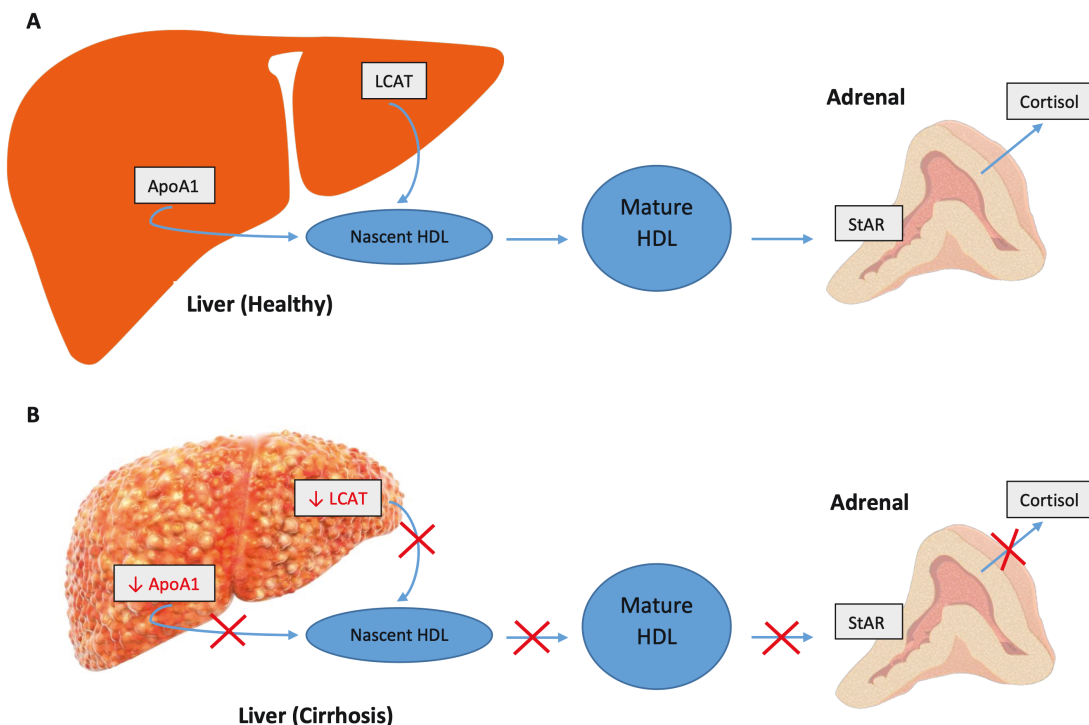
Figure 1. Lipid metabolism and the adrenal gland. The liver is the principal site of apolipoprotein synthesis. One of the key apolipoproteins, ApoA1, comprises a large fraction of high-density lipoprotein (HDL) particles. The hepatically derived lecithin-cholesterol acyltransferase enzyme (LCAT) binds to ApoA1 on HDL and esterifies free cholesterol. Once this process is complete, the HDL particle is mature and can be trafficked to peripheral tissues. Within the adrenal gland, cholesterol is offloaded, and uptake occurs through the mitochondrial steroidogenic acute regulatory protein (StAR), which is the rate-limiting step in the production of steroid hormones (A). In cirrhosis, this process is disrupted by decreased hepatic synthesis of both ApoA1 and LCAT, leading to impaired formation of adequate mature HDL molecules to provide adequate substrate for normal adrenal steroidogenesis. However, whether this leads to a clinically significant decrease in cortisol production is unknown (B).
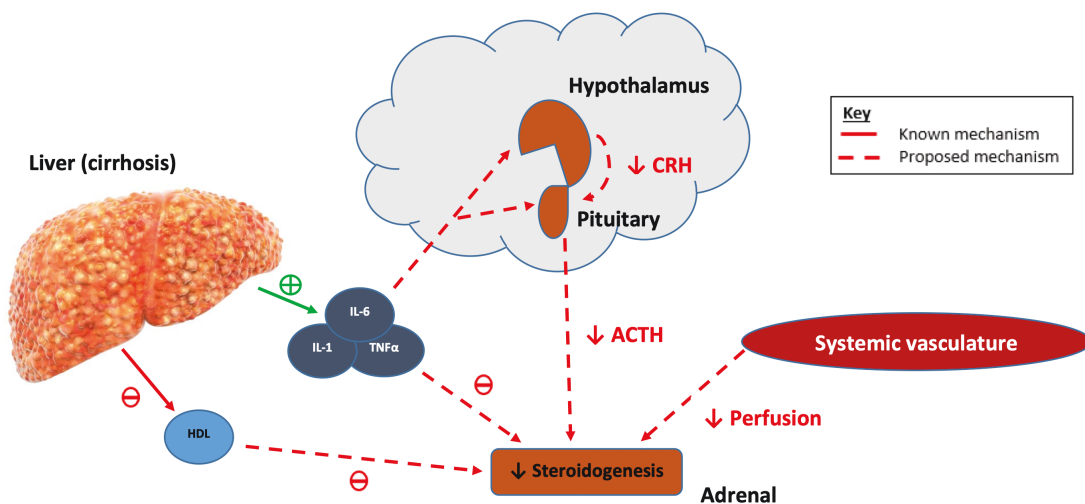

Figure 2. Pathogenesis of adrenal insufficiency in cirrhosis. The development of adrenal insufficiency in cirrhosis may be multifactorial. Contributions from dyslipidemia are described in detail in Figure 1.

Measurement of Total Cortisol and ACTH Stimulation Testing in Liver Disease

Measurement of TC levels in cirrhosis is controversial. Given impaired binding globulin synthesis, standard diagnostic testing modalities may be inaccurate. Current Endocrine Society guidelines exclusively support use of TC when evaluating a patient for primary AI [3]. In the setting of cirrhosis, however, the generalizability of these recommendations falters. First, lower baseline and stimulated TC levels may overestimate the presence of AI [36]. Second, the pathophysiology of AI in cirrhosis may be multilevel and/or situational.

Measurement of cortisol levels is assay dependent. The gold standard, liquid chromatography-tandem mass spectrometry (LC-MS), is most specific and yields lower TC levels than immunoassays [46]. Although LC-MS use is ideal, it is more expensive and less widely available in routine clinical practice (vs a research setting). Clinicians therefore need to heed these

limitations and interpret cortisol levels cautiously to avoid misdiagnosis. Consequently, recalibration of the TC threshold to define sufficient adrenal response is necessary.

Currently, an early-morning TC level of <138 nmol/L is suggestive of AI and confirmed with a peak TC level < 500 nmol/L after ACTH stimulation [3]. However, these values are based on historical immunoassays using polyclonal antibodies to cortisol, which are less specific given cross-reactivity with other serum steroids. Newer methods to measure TC levels, including more specific monoclonal antibodies or the gold standard LC-MS, net TC levels approximately 22% to 39% lower than historical levels [47]. Given this significant variation, a new baseline TC threshold of <55 nmol/L or a peak TC between 386 and 414 nmol/L to define AI has been proposed in the general population when using newer generation immunoassays or LC-MS [47]; formal adoption remains pending.

Further complicating matters is the lack of validated cirrhosis-specific and/or hypoproteinemic TC reference ranges. Additionally, these values would require adjustment for disease severity. A recent study by Lovato et al. demonstrated that albumin, CBG, TC, and maximal cortisol secretion rate (CSR_{max}; the CSR obtained under maximal ACTH stimulation) were all inversely related to Child-Pugh classification. Importantly, both albumin and CBG levels were correlated with stimulated TC levels, whereas CSR_{max} was not [32]. These findings highlight that, although adrenal dysfunction is common in cirrhosis, measurement with a protein-dependent assay such as TC is imprecise.

Despite its flaws, TC remains the preferred modality to assess adrenal functionality in clinical practice. Notable strengths include its wide availability, rapidity of results to inform bedside decision-making, and physician familiarity. In addition, TC levels carry prognostic significance in patients with decompensated cirrhosis. Relative adrenal insufficiency, as defined by a delta cortisol (peak minus baseline) of <250 nmol/L, independently predicts mortality, highlighting the importance of both diagnosis and appropriate management [6-9].

Two dosages of Cosyntropin have been used to assess for AI in both the general population and hypoproteinemic states. Current guidelines recommend use of standard-dose (SD-SST; 250 µg) Cosyntropin in both scenarios rather than the low-dose (1 µg) alternative [3]. Proponents of the latter in patients with cirrhosis argue that the lower Cosyntropin dose improves diagnostic sensitivity, particularly in noncritically ill states where the standard dose may be excessively supraphysiologic [22, 48]. Low-dose Cosyntropin stimulation testing (LD-SST) has compared favorably with SD-SST in meta-analysis, but significant limitations include a lack of validation of LD-SST in acutely ill patients or abnormal sleep-wake cycles, as may occur in patients with cirrhosis and hepatic encephalopathy [49]. Additionally, preparation of 1 µg of Cosyntropin requires careful technical skill to ensure proper dilution and injection, inviting potential error in both administration and result interpretation [50]. Given these significant limitations, SD-SST remains the standard of care.

Adrenal Function in Critical Illness and Liver Disease

Critical illness represents another scenario rife with controversy when assessing adrenal functionality. In the general population, there is a lack of consensus regarding optimal assessment. Some authors argue for use of either a random TC level < 276 nmol/L or a delta TC < 250 nmol/L as being diagnostic [51, 52]. Although critically ill hypoproteinemic patients are expected to have random TC levels > 262 nmol/L, the validity of using baseline and Cosyntropin-stimulated TC levels in this population is questioned [53]. Hamrahian et al. found that nearly 40% of critically ill patients with albumin ≤ 2.5 g/dL had peak TC levels < 510 nmol/L despite normal and stimulated FPC levels [54]. The same study also noted that in the hypoproteinemic subpopulation, basal FPC accounted for 19% to 62% of measured TC [54]. Thus, a threshold random FPC level of ≥ 50 nmol/L has been proposed as a binding-protein independent marker of adequate adrenal function [53].

Although FPC levels offer attractive diagnostic advantages in patients with cirrhosis and hypoproteinemia, its widespread adoption is limited by current lack of validation of the 50 nmol/L threshold and slow turnaround time. At present, we prefer use of delta TC. The rate of change, rather than achievement of a specific peak TC level, is at least partially independent of underlying hepatic synthetic function and may more readily identify patients with RAI [6]. However, whether basal levels of TC and/or the degree of hypoalbuminemia affect its diagnostic accuracy are unclear in both the critically ill and noncritically ill populations.

Low CBG levels may also play an important role in patients with cirrhosis and critical illness. Inflammatory states such as sepsis induce conformational change in CBG such that its affinity for cortisol decreases, allowing for molecular uncoupling and enhancing cortisol delivery to tissues [55, 56]. However, CBG levels decline proportional to illness severity and are a poor prognostic marker [56]. In the noncirrhotic population, a recent study found CBG levels < 200 nmol/L were independently predictive of short-term mortality in patients with septic shock [57]. Although not explicitly studied, reasonable inference suggests that in patients with cirrhosis (with low basal CBG levels) and critical illness, tissue delivery of cortisol may be inadequate to meet increased local demands. Moreover, the ACTH-cortisol dissociation phenomenon in critical illness demonstrates that despite maximal levels of endogenous cortisol, ACTH levels are frequently lower than anticipated and may reflect suppression of pulsatile ACTH and cortisol secretion [58]. Although prior studies of AI in critically ill patients with cirrhosis did not measure ACTH levels [2, 11, 12, 15], noncritically ill patients with RAI have similar or lower ACTH levels compared with patients with preserved adrenal function [5, 7].

Impairment of steroidogenesis in critical illness is not limited to glucocorticoid deficiency. Accumulating evidence suggests that adrenal androgenesis is also negatively impacted. Several studies demonstrate decreased dehydroepiandrosterone sulfate (DHEAS) levels and an increased cortisol to DHEAS ratio associates with increased mortality [59-61]. This important prognostic finding was also demonstrated in a more recent cohort of patients with cirrhosis [62]. Whether this represents adrenal steroidogenesis pathway shunting or differential effects of disease is unclear, but its presence supports the concept of a functional adrenal exhaustion. Interestingly, low DHEAS levels have also been reported in noncritically ill patients with nonalcoholic steatohepatitis and advanced fibrosis, although whether these carry similar prognostic implications are unknown [63]. Although promising, more research is needed to

understand whether DHEAS is an independent risk factor for mortality in both critical and noncritical illness.

Alternative Methodologies to Assess Adrenal Function in Cirrhosis

Limitations of TC measurement in cirrhosis have led to consideration of binding globulin-independent markers of adrenal function (Table 1). The CSR_{max} previously mentioned is a calculated parameter that has been reported in several populations, including cirrhosis, but requires mathematical modeling and is best used for research rather than at bedside [32, 64-66]. Because FPC is biologically active and unbound to CBG or albumin, some advocate for its use in cirrhosis. Proponents of FPC argue that AI is overdiagnosed in cirrhosis when standard TC thresholds are used to interpret ACTH stimulation testing [5, 22, 67]. It is important to note, however, that the concept of AI in liver disease represents a spectrum of adrenal impairment. Current literature is not dogmatic in its characterization, as the terms AI and RAI are often used interchangeably. An abnormal stimulated TC response in a patient with cirrhosis therefore could represent one of three possibilities:

1) True (absolute) AI: a nonsituational reduction in adrenal steroid secretion,
2) Relative AI: an inadequate adrenal response to stressful stimuli [6], or
3) False positive: an artifact of decreased hepatic binding globulin synthesis.

Scenarios 1 and 3 may be distinguished by FPC measurement, as multiple studies have shown appropriate responses to ACTH stimulation testing [5, 22, 67]. Its utility in RAI (scenario 2) remains ill-defined, however. Interestingly, basal levels of TC and FPC are similar in patients with and without RAI and correlate well [1, 5, 6, 68]. However, the clinical significance of FPC is unknown; outcomes-based literature where FPC is measured primarily define RAI with respect to TC response [6, 8, 9].

Several other drawbacks to FPC prevent its adoption as the gold standard for adrenal function assessment in cirrhosis. Similar to TC, a unique FPC threshold for patients with cirrhosis is not established; most authors use a stimulated peak FPC level < 33 nmol/L stimulation [5, 22, 67]. Direct measurement of FPC is also problematic in clinical practice. Patient samples are frequently sent to an external reference laboratory given the analytic requirement for LC-MS. Thus, the increased expense and reporting delay of up to 1 to 2 weeks precludes use in urgent clinical situations where glucocorticoid replacement therapy is being considered. Estimated FPC levels can be obtained, most commonly using the Coolens formula, although this is more imprecise and primarily used in research [69].

In response to the issues with both TC and FPC measurement in patients with cirrhosis, salivary cortisol (SC) is a proposed alternative. When using basal SC < 5.0 nmol/L, peak SC < 35 nmol/L, or delta SC < 8.3 nmol/L thresholds, all of which are derived from the noncirrhotic population, the prevalence of AI is less robust [70]. Although acquisition of SC is straightforward, its prognostic significance is unknown. Salivary sample collection typically requires a period of oral rest, which can introduce minor logistical challenges in certain patients. Additionally, SC and TC level correlation may be dependent on the degree of hypoalbuminemia present [70, 71]. Further validation is required to make a definitive conclusion. In summary, SC has potential to be a valuable tool to assess adrenal function in patients with cirrhosis, but additional research is needed before it can be recommended as a first-line test.

Whom and How to Test for AI in Cirrhosis

Prevalence of AI in cirrhosis parallels disease severity [8, 68, 72]. Adrenal dysfunction may also be situational according to present illness state. Clinicians should therefore use a diagnostic approach that is able to distinguish between absolute and relative AI because this has therapeutic implications.

We recommend a low threshold for provisional diagnosis of RAI in patients with cirrhosis and hemodynamic instability, particularly in the setting of critical illness. Because RAI is well documented in decompensated liver disease with and without critical illness, we hypothesize that its presence may be a byproduct of both underlying conditions. However, a lack of longitudinal study regarding the timeline (or actuality) of adrenal function recovery limits further inference.

Table 1. Relative comparison of cortisol forms to assess adrenal insufficiency in cirrhosis

Diagnostic methodology	Pros	Cons	Suggested clinical use
Total cortisol	• Ubiquitous • Acquisition and interpretative ease • Rapid results • Prognostic significance	• Binding globulin dependent • Assay-dependent levels (liquid chromatography-mass spectrometry gold standard) • Lack of cirrhosis-specific reference ranges • Various diagnostic thresholds used in literature	Routine, interpret with caution
Free plasma cortisol	• Binding globulin independent • Measures biologically active cortisol • Basal levels correlate well with total cortisol	• Slow turnaround time • Lack of widespread availability • Unknown prognostic significance	Adjunctive, if available[a]
Salivary cortisol	• Acquisition ease	• Slow turnaround time • Lack of widespread availability • Unknown prognostic significance	Not currently recommended[b]

[a]Able to distinguish absolute vs relative adrenal insufficiency.
[b]Currently used primarily in research setting; additional evidence required before ready for routine use.

Assessment of the HPA axis in critical illness is difficult, as previously described. In short, we advocate for SD-SST administration and use of the delta TC < 250 nmol/L threshold to define RAI (CIRCI) at this time. Our rationale for this conditional recommendation is 2-fold. The supraphysiologic dose of ACTH and assessment of a rate of change rather than peak levels may mitigate some of effect of impaired hepatic synthetic function. Importantly, this diagnostic approach also has better clinical validation as prior studies in patients with sepsis or variceal bleeding and RAI had worse clinical outcomes including increased vasopressor dependency and short-term mortality [12, 73]. Other diagnostic thresholds and/or use of FPC or SC are significantly limited by lack of validity in this population and unclear prognostic significance.

Diagnosis of RAI in noncritically ill patients is equally unsettled. The literature is heterogeneous with respect to diagnostic methodology and thresholds used. Additionally, no formal criteria exist to outline parameters necessitating evaluation. Factors predictive for AI in cirrhosis include higher Model for End Stage Liver Disease and Child-Pugh scores, ascites, and lower albumin levels; interestingly, specific markers of synthetic function such as bilirubin or international normalized ratio are not associated [74]. Low HDL levels are also more prominent in patients with cirrhosis and AI, although the sensitivity or specificity of specific HDL thresholds have yet to be determined [6]. We suggest that patients with decompensated cirrhosis and any of the following be evaluated for AI:

1) Severe hyponatremia (sodium < 125 mEq/L), particularly if no alternative explanation is apparent,
2) Persistent hypotension, particularly in the outpatient setting, and/or
3) Unexplained abdominal pain.

In this population, it is important to assess for both primary and secondary components to the AI. An early-morning TC level can be considered for screening purposes, although its use is likely greater in cases where absolute AI is being consider rather than for detection of RAI. First, the high specificity of basal TC levels < 138 nmol/L (< 55 nmol/L with newer assays) for AI is derived from the general population and there is a paucity of literature validating its use in patients with cirrhosis. Second, whether basal TC levels differ between patients with and without RAI is unsettled given conflicting reports [6, 7, 48, 75].

Instead, we suggest performing a SD-SST with measurement of both basal and peak stimulated TC and FPC (Fig. 3). Optimal timing of administration in patients with liver disease is unknown. Recent literature suggests that in the general population, stimulation test results are agnostic to time of day [76]. However, extrapolation to the cirrhosis population is of uncertain validity. Thus, we suggest early morning testing when cortisol levels are predicted to be highest. Given the potential influence of degree of illness and circadian rhythm disruption to affect results, clinicians may also wish to consider repeating the SD-SST on a subsequent day to confirm (or refute) initial findings.

As previously described, RAI is heterogeneously defined. Interpretation of TC levels should be assay dependent and account for the degree of hepatic synthetic impairment. Use of delta rather than peak cortisol allows for a more dynamic assessment of adrenal responsiveness and is less influenced by

basal binding protein deficiency. Abnormal TC levels can rapidly provide a provisional diagnosis of RAI, although there will be a significant number of false positives [5]. Once FPC levels are available, these can assist in confirming or refuting RAI. There is not enough evidence at present to determine the utility of SC or the insulin tolerance test; in addition, the latter may be unsafe in patients with decompensated cirrhosis. Concurrent measurement of baseline plasma ACTH may be helpful to distinguish between primary or secondary contributions to AI, although cautious interpretation is paramount given concurrent illness (even if noncritical). Measurement of DHEAS levels can also be considered to assess for a central (secondary or tertiary) AI component. A high cortisol to DHEAS ratio is suggestive of central AI because adrenal androgenesis within the zona reticularis is under strong ACTH trophic effect and impaired androgen secretion may precede glucocorticoid deficiency [77]. However, this finding was noted in a noncirrhotic population administered the LD-SST and its external validity is unclear.

In the general population, plasma aldosterone levels and renin activity may further distinguish between primary and central AI. Conversely, in cirrhosis, the validity of these measurements is unproven as the renin-angiotensin-aldosterone system is typically upregulated. Furthermore, concurrent renal dysfunction and/or aldosterone antagonists use is common, both of which confound interpretation. Presently, we do not routinely recommend obtaining aldosterone levels or plasma aldosterone levels and renin activity outside of a research context unless hyperkalemia and hemodynamic instability exist in the absence of aldosterone antagonist therapy.

Management and Prognosis of AI in Patients With Cirrhosis

Proper classification as to the form of AI (absolute vs relative), in addition to patient context, is vital when devising a management strategy. In patients with evidence of absolute primary AI (PAI), prompt glucocorticoid replacement should be initiated as per current guidelines with a total of 15 to 25 mg of hydrocortisone in 2 or 3 divided doses [3]. However, whether mineralocorticoid replacement (typical doses of 0.05-0.1 mg/d) is needed in the setting of PAI and cirrhosis is unclear. Cirrhotic physiology can mimic mineralocorticoid deficiency and concurrent loop diuretic and/or aldosterone antagonist use confound the picture. Androgen replacement is controversial in women with PAI and has not been adequately studied in cirrhosis.

If secondary AI exists, evaluation and treatment of any concurrent pituitary hormone deficiencies should be undertaken in addition to glucocorticoid administration. Mineralocorticoid or androgen therapy is typically unnecessary given ACTH does not principally regulate aldosterone secretion. The far more common clinical scenario regarding management of AI in cirrhosis is when the degree of adrenal impairment is "relative."

In patients with critical illness, glucocorticoid replacement has been well studied in the general population. Current critical care and Surviving Sepsis Campaign guidelines recommend use of corticosteroids in patients with septic shock unresponsive to volume resuscitation and initial vasopressor therapy given improvements in shock resolution, vasopressor-free days, and short-term mortality [52, 78]. Hydrocortisone
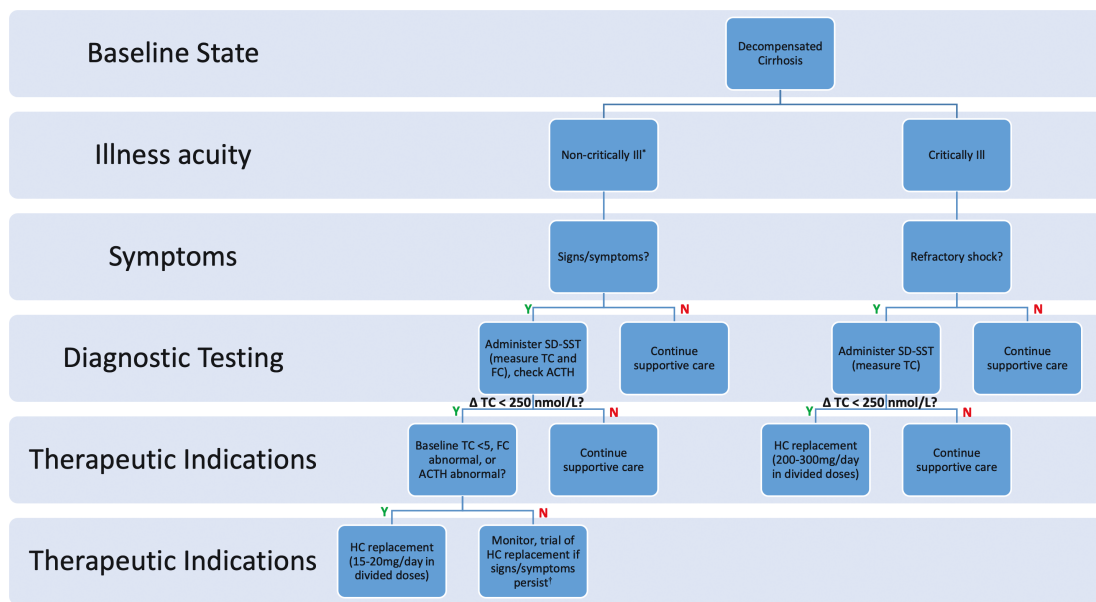
Figure 3. Novel algorithm for diagnosis and management of adrenal insufficiency in cirrhosis. *Includes outpatients and patients hospitalized in a nonintensive care unit setting. †Low threshold to consider trial of HC replacement in setting of unexplained or severe fatigue, hypotension, hyponatremia, and/or abdominal pain after exclusion of other reversible causal factors. Abbreviations: FPC, free plasma cortisol; HC, hydrocortisone; SD-SST, standard-dose ACTH stimulation test; TC, total cortisol.

use in cirrhosis at standard stress dosage of 200 to 300 mg/d in 3 to 4 divided doses has shown more mixed results. As seen in Table 2, 4 retrospective observational studies have shown a consistent decrease in vasopressor requirements and in-hospital mortality, although there has been some signal regarding an increase in resistant bacterial infection [2, 11, 13, 15]. A single randomized controlled trial showed reduction in vasopressor dose and shock reversal, but the study was terminated early given increases in shock relapse, gastrointestinal bleeding, and absence of reduction of 28-day mortality [14]. Methodologic differences, including study design, likely account for these contrasting findings and should serve as caution for clinicians.

Another possible explanation for the lack of uniform benefit to high-dose hydrocortisone is that limited CBG availability may lead to excess renal filtration and urinary excretion of cortisol. In patients without significant renal impairment, elevated urinary cortisol levels are common in states of hypercortisolism [79]. However, older literature suggests that patients with liver disease may have reduced urinary cortisol excretion [80]. Unfortunately, a lack of concurrent measurement of glomerular filtrate rate clouds the ability to discern whether this effect is related to renal impairment or an intrinsic effect of the liver disease. This relationship is hard to quantify because many patients with cirrhosis and critical illness suffer from kidney injury.

Conversely, glucocorticoid therapy could induce iatrogenic Cushing syndrome given the previously mentioned reduction in both binding globulin levels and 11β-HSD enzymatic activity seen in patients with liver and/or renal disease (including the hepatorenal syndrome). This has not been well studied but excess glucocorticoids are known to alter immune function, leading to upregulation of pro-inflammatory cytokines and increased susceptibility to infection [81]. Thus, although glucocorticoid therapy can be considered in critically ill patients with cirrhosis, further study is needed to specifically elucidate optimal subpopulations and duration of therapy [18, 82].

Treatment of RAI in noncritical illness, the most common clinical scenario, is controversial. Although RAI is associated with increased Model for End Stage Liver Disease score–independent mortality [6-9], there are no trials assessing the efficacy and safety of steroid replacement outside of an intensive care unit setting. Given the lack of evidence to support routine use, and the potential risk of infection in patients already with functional immunodeficiency, a strong motive for empiric therapy is necessary. In asymptomatic patients, we do not recommend upfront hydrocortisone, but empiric replacement may be considered in the future should critical illness develop. In patients with potentially attributable symptoms, such as persistent hypotension or unexplained abdominal pain, a trial of glucocorticoids may be reasonable to see if symptoms improve. Close monitoring for signs of cortisol excess or infection is imperative. We caution against use of glucocorticoid supplementation in patients who only have electrolyte disarray unless all other possible contributors have been eliminated. Fatigue as an attributable symptom must be present in conjunction with other features suggestive of AI given its commonality in chronic liver disease [83].

The longitudinal nature of RAI is not established. Current pathogenic understanding suggests an unrelenting nature if present in the absence of critical illness. Recently, the development of RAI has been considered to represent an organ failure akin to the more widely recognized renal dysfunction of cirrhosis (the hepatorenal syndrome) [7]. Steroid replacement therapy, if tolerated and demonstrative of clinical improvement, should therefore be continued indefinitely or until transplantation. The transition of HPA physiology from a cirrhotic to noncirrhotic state has been well-characterized with regard to other hormones [26]. Many transplanted patients can be successfully weaned from induction steroid therapy within 1 to 3 months posttransplant, suggesting that cirrhosis-related RAI resolves as a consequence of homeostatic normalization in the absence of portal hypertension and systemic inflammation. Whether patients with known RAI and treated with

Table 2. Evidence for hydrocortisone therapy in patients with liver disease and critical illness

Author	Year	N	Population	Study design	ACTH stimulation test	RAI definition	RAI prevalence	HC dosage	Outcome
Harry et al.	2003	40	Mixed – acute liver failure or decompensated cirrhosis + vasopressor dependence	Retrospective case-control • Group 1 (20): HC • Group 2 (20): no HC	SD-SST	1) Baseline TC < 250 nmol/L OR 2) ΔTC < 250 nmol/L OR 3) Peak TC < 500 nmol/L	Baseline: 28% Δ: 69% Peak: 44%	300 mg/d	↓ vasopressor dose at 48 h ↑ ICU LOS, infections with MDR organisms ↔ in-hospital survival, GI bleeding
Marik et al.	2005	340	Mixed – acute and chronic liver failure, liver transplant recipients on steroid-free protocol, GI bleeding	Retrospective cohort	LD-SST	4) Random TC < 552 nmol/L (highly stressed)[a] OR 5) Random TC < 414 nmol/L (non-highly stressed) OR 6) Peak TC < 552 nmol/L	72%	100 mg every 8 h	↓ vasopressor dose at 24 h, in-hospital mortality
Fernandez et al.	2006	75	Cirrhosis + septic shock	Hybrid prospective/retrospective cohort • Group 1 (25): Adrenal function measured, HC if RAI (prospective) • Group 2 (50): Adrenal function unmeasured (retrospective)	Group 1: SD-SST	1) Baseline TC < 414 nmol/L OR 2) Δ TC < 250 nmol/L	Group 1: 68%	50 mg every 6 h (if RAI)	↓ renal failure ↑ shock resolution, ICU survival, hospital survival ↔ infection rate, GI bleeding
Arabi et al.	2010	75	Cirrhosis + septic shock	RCT • 39 HC • 36 placebo	SD-SST	Δ TC < 250 nmol/L	76%	50 mg every 6 h or placebo	↓ vasopressor doses, shock reversal ↑ shock relapse, GI bleeding ↔ 28-d mortality
Vu et al.	2020	64	Cirrhosis + vasopressor-dependence[b]	Retrospective cohort • 40 HC • 24 none	SD-SST	1) Random TC < 552 nmol/L OR 2) Baseline TC < 414 nmol/L OR 3) ΔTC < 250 nmol/L and baseline TC 386-938 nmol/L		150-300 mg/d in divided doses[c]	↓ vasopressor days ↓ in-hospital mortality ↔ infection rate, LOS

Abbreviations: GI, gastrointestinal; HC, hydrocortisone; ICU, intensive care unit; LD-SST, low-dose short Synacthen test; LOS, length of stay; MDR, multidrug resistant; RAI, relative adrenal insufficiency; RCT, randomized controlled trial; SD-SST, standard-dose short Synacthen test; TC, total cortisol.
[a]Highly stressed defined as hypoxemic respiratory failure with hypotension or requirement of vasopressors.
[b]Excluded hemorrhagic or cardiogenic shock.
[c]Exact dosage at discretion of intensivist.

glucocorticoids before transplantation should be prescribed a longer taper given potential HPA suppression is unknown.

In summary, treatment of AI in cirrhosis requires an individualized approach given the lack of consensus for optimal management. Given the chronicity of disease and need for expert interpretation of diagnostic tests, we recommend patients with cirrhosis and either potential or confirmed AI be managed jointly by a hepatologist and endocrinologist.

Conclusions

Assessment of AI in cirrhosis is difficult and requires careful attention to many patient-related variables. Traditional endocrinology approaches to the diagnosis and management of AI do not account for the physiology in the cirrhotic state. Importantly, the majority of AI in cirrhosis is "relative" but represents an independent predictor of short- to medium-term mortality. More research is needed to fully understand the mechanisms underlying AI in cirrhosis. Given the lack of clear benefit of glucocorticoid replacement in many common clinical scenarios, low TC levels in the absence of consistent signs and symptoms of AI do not warrant empiric treatment. Additionally, clinicians should consider the risks of exogenous glucocorticoids, including exacerbating baseline immunodeficiency and/or induction of an iatrogenic Cushing syndrome.

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Disclosures

None.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References

1. Dichtel LE, Schorr M, Loures de Assis C, *et al*. Plasma free cortisol in states of normal and altered binding globulins: implications for adrenal insufficiency diagnosis. *J Clin Endocrinol Metab*. 2019;104(10):4827-4836. doi:10.1210/jc.2019-00022.
2. Marik PE, Gayowski T, Starzl TE, Group; HCRaAPS. The hepatoadrenal syndrome: a common yet unrecognized clinical condition. *Crit Care Med*. 2005;33(6):1254-1259. doi:10.1097/01.ccm.0000164541.12106.57
3. Bornstein SR, Allolio B, Arlt W, *et al*. Diagnosis and Treatment of Primary Adrenal Insufficiency: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2016;101(2):364-389. doi:10.1210/jc.2015-1710.
4. Moini M, Yazdani Sarvestani M, Shams M, Nomovi M. Evaluation of adrenal function in nonhospitalized patients with cirrhosis. *Can J Gastroenterol Hepatol* 2017;2017:2354253. doi:10.1155/2017/2354253.
5. Tan T, Chang L, Woodward A, *et al*. Characterising adrenal function using directly measured plasma free cortisol in stable severe liver disease. *J Hepatol*. 2010;53(5):841-848. doi:10.1016/j.jhep.2010.05.020.
6. Wentworth BJ, Haug RM, Northup PG, Caldwell SH, Henry ZH. Abnormal cholesterol metabolism underlies relative adrenal insufficiency in decompensated cirrhosis. *Liver Int*. 2021;41(8):1913-1921. doi:10.1111/liv.14970.
7. Piano S, Favaretto E, Tonon M, *et al*. Including relative adrenal insufficiency in definition and classification of acute-on-chronic liver failure. *Clin Gastroenterol Hepatol*. 2020;18(5):1188-1196.e3. doi:10.1016/j.cgh.2019.09.035.
8. Jang JY, Kim TY, Sohn JH, *et al*. Relative adrenal insufficiency in chronic liver disease: its prevalence and effects on long-term mortality. *Aliment Pharmacol Ther*. 2014;40(7):819-826. doi:10.1111/apt.12891.
9. Acevedo J, Fernández J, Prado V, *et al*. Relative adrenal insufficiency in decompensated cirrhosis: relationship to short-term risk of severe sepsis, hepatorenal syndrome, and death. *Hepatology* 2013;58(5):1757-1765. doi:10.1002/hep.26535.
10. Triantos CK, Marzigie M, Fede G, *et al*. Critical illness-related corticosteroid insufficiency in patients with cirrhosis and variceal bleeding. *Clin Gastroenterol Hepatol*. 2011;9(7):595-601. doi:10.1016/j.cgh.2011.03.033.
11. Fernández J, Escorsell A, Zabalza M, *et al*. Adrenal insufficiency in patients with cirrhosis and septic shock: effect of treatment with hydrocortisone on survival. *Hepatology* 2006;44(5):1288-1295. doi:10.1002/hep.21352.
12. Tsai MH, Peng YS, Chen YC, *et al*. Adrenal insufficiency in patients with cirrhosis, severe sepsis and septic shock. *Hepatology* 2006;43(4):673-681. doi:10.1002/hep.21101.
13. Vu T, Vallabh M, Laine G. Adrenal insufficiency and response to stress dose hydrocortisone in patients with cirrhosis and vasopressor dependency using cirrhosis-specific cortisol thresholds. *Ann Pharmacother*. 2020;54(8):742-749. doi:10.1177/1060028019900266.
14. Arabi YM, Aljumah A, Dabbagh O, *et al*. Low-dose hydrocortisone in patients with cirrhosis and septic shock: a randomized controlled trial. *CMAJ* 2010;182(18):1971-1977. doi:10.1503/cmaj.090707.
15. Harry R, Auzinger G, Wendon J. The effects of supraphysiological doses of corticosteroids in hypotensive liver failure. *Liver Int*. 2003;23(2):71-77. doi:10.1034/j.1600-0676.2003.00813.x.
16. Khan S. Understanding the cholesterol and cytokine network in patients with adrenal insufficiency and cirrhosis. *J R Coll Physicians Edinb*. 2020;50(1):92-95. doi:10.4997/JRCPE.2020.126.
17. Dirchwolf M, Podhorzer A, Marino M, *et al*. Immune dysfunction in cirrhosis: distinct cytokines phenotypes according to cirrhosis severity. *Cytokine*. 2016;77(January 2016):14-25. doi:10.1016/j.cyto.2015.10.006.
18. Moreau R, Weiss E. Should patients with cirrhosis and variceal hemorrhage receive glucocorticoid therapy? *Hepatology* 2015;61(5):1758-1760. doi:10.1002/hep.27762.
19. McNeilly AD, Macfarlane DP, O'Flaherty E, *et al*. Bile acids modulate glucocorticoid metabolism and the hypothalamic-pituitary-adrenal axis in obstructive jaundice. *J Hepatol*. 2010;52(5):705-711. doi:10.1016/j.jhep.2009.10.037.
20. Annane D, Pastores SM, Arlt W, *et al*. Critical illness-related corticosteroid insufficiency (CIRCI): a narrative review from a Multispecialty Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). *Intensive Care Med*. 2017;43(12):1781-1792. doi:10.1007/s00134-017-4914-x.
21. Paz-Delgadillo J, Monreal-Robles R, Villarreal-Pérez JZ, Maldonado-Garza HJ, Bosques-Padilla FJ, Lavalle-González FJ. Algorithm for screening of adrenal function in stable patients with cirrhosis. *Ann Hepatol*. 2017;16(5):788-796. doi:10.5604/01.3001.0010.2797.
22. Theocharidou E, Giouleme O, Anastasiadis S, *et al*. Free cortisol is a more accurate marker for adrenal function and does not correlate with renal function in cirrhosis. *Dig Dis Sci*. 2019;64(6):1686-1694. doi:10.1007/s10620-019-5460-x.
23. Kalambokis GN, Tsiakas I, Christaki M, *et al*. Assessment of adrenal response in patients with stable cirrhosis and ascites using different short Synacthen tests and definitions. *Eur J Gastroenterol Hepatol*. 2021;33(1S Suppl 1):e540-e547. doi:10.1097/MEG.0000000000002153

24. Araz F, Soydaş B, Özer B, Serin E. The importance of salivary cortisol in the diagnosis of adrenal insufficiency in cirrhosis. *Turk J Gastroenterol*. 2016;27(3):268-272. doi:10.5152/tjg.2016.15544.

25. Montagnese S, Middleton B, Mani AR, Skene DJ, Morgan MY. On the origin and the consequences of circadian abnormalities in patients with cirrhosis. *Am J Gastroenterol*. 2010;105(8):1773-1781. doi:10.1038/ajg.2010.86.

26. Gariani K, Toso C, Philippe J, Orci LA. Effects of liver transplantation on endocrine function: a systematic review. *Liver Int*. 2016;36(10):1401-1411. doi:10.1111/liv.13158.

27. Oster H, Challet E, Ott V, *et al*. The functional and clinical significance of the 24-hour rhythm of circulating glucocorticoids. *Endocr Rev*. 2017;38(1):3-45. doi:10.1210/er.2015-1080.

28. Velissaris D, Karanikolas M, Kalogeropoulos A, *et al*. Pituitary hormone circadian rhythm alterations in cirrhosis patients with subclinical hepatic encephalopathy. *World J Gastroenterol*. 2008;14(26):4190-4195. doi:10.3748/wjg.14.4190.

29. Montagnese S, Middleton B, Mani AR, Skene DJ, Morgan MY. Changes in the 24-h plasma cortisol rhythm in patients with cirrhosis. *J Hepatol*. 2011;54(3):588-90; author reply 590; author reply 90-1. 10.1016/j.jhep.2010.08.015

30. Stewart PM, Burra P, Shackleton CH, Sheppard MC, Elias E. 11 beta-Hydroxysteroid dehydrogenase deficiency and glucocorticoid status in patients with alcoholic and non-alcoholic chronic liver disease. *J Clin Endocrinol Metab*. 1993;76(3):748-751. doi:10.1210/jcem.76.3.8445034.

31. Escher G, Nawrocki A, Staub T, *et al*. Down-regulation of hepatic and renal 11 beta-hydroxysteroid dehydrogenase in rats with liver cirrhosis. *Gastroenterology* 1998;114(1):175-184. doi:10.1016/s0016-5085(98)70645-6.

32. Lovato CM, Thévenot T, Borot S, *et al*. Decreased maximal cortisol secretion rate in patients with cirrhosis: relation to disease severity. *JHEP Rep* 2021;3(3):100277. doi:10.1016/j.jhepr.2021.100277.

33. Wiest R, Moleda L, Zietz B, Hellerbrand C, Schölmerich J, Straub R. Uncoupling of sympathetic nervous system and hypothalamic-pituitary-adrenal axis in cirrhosis. *J Gastroenterol Hepatol*. 2008;23(12):1901-1908. doi:10.1111/j.1440-1746.2008.05456.x.

34. McDonald JA, Handelsman DJ, Dilworth P, Conway AJ, McCaughan GW. Hypothalamic-pituitary adrenal function in end-stage non-alcoholic liver disease. *J Gastroenterol Hepatol*. 1993;8(3):247-253. doi:10.1111/j.1440-1746.1993.tb01195.x.

35. Garcia-Martinez R, Caraceni P, Bernardi M, Gines P, Arroyo V, Jalan R. Albumin: pathophysiologic basis of its role in the treatment of cirrhosis and its complications. *Hepatology* 2013;58(5):1836-1846. doi:10.1002/hep.26338.

36. Fede G, Spadaro L, Tomaselli T, *et al*. Adrenocortical dysfunction in liver disease: a systematic review. *Hepatology* 2012;55(4):1282-1291. doi:10.1002/hep.25573.

37. Miller JP. Dyslipoproteinaemia of liver disease. *Baillieres Clin Endocrinol Metab* 1990;4(4):807-832. doi:10.1016/s0950-351x(05)80080-1.

38. Florén CH, Franzén J, Albers JJ. Apolipoprotein A-I in liver disease. *Scand J Gastroenterol*. 1987;22(4):454-458. doi:10.3109/00365528708991490.

39. Chang L, Clifton P, Barter P, Mackinnon M. High density lipoprotein subpopulations in chronic liver disease. *Hepatology* 1986;6(1):46-49. doi:10.1002/hep.1840060109.

40. Kaiser T, Kinny-Köster B, Bartels M, *et al*. Cholesterol esterification in plasma as a biomarker for liver function and prediction of mortality. *BMC Gastroenterol*. 2017;17(1):57. doi:10.1186/s12876-017-0614-9.

41. Tahara D, Nakanishi T, Akazawa S, *et al*. Lecithin-cholesterol acyltransferase and lipid transfer protein activities in liver disease. *Metabolism* 1993;42(1):19-23. doi:10.1016/0026-0495(93)90166-l.

42. Bochem AE, Holleboom AG, Romijn JA, *et al*. Adrenal function in females with low plasma HDL-C due to mutations in ABCA1 and LCAT. *PLoS One*. 2014;9(5):e90967. doi:10.1371/journal.pone.0090967.

43. Singh RR, Walia R, Sachdeva N, Bhalla A, Singh A, Singh V. Relative adrenal insufficiency in cirrhotic patients with ascites (hepatoadrenal syndrome). *Dig Liver Dis*. 2018;50(11):1232-1237. doi:10.1016/j.dld.2018.05.011.

44. Bornstein SR. Predisposing factors for adrenal insufficiency. *N Engl J Med*. 2009;360(22):2328-2339. doi:10.1056/NEJMra0804635.

45. Fede G, Spadaro L, Privitera G, *et al*. Hypothalamus-pituitary dysfunction is common in patients with stable cirrhosis and abnormal low dose Synacthen test. *Dig Liver Dis*. 2015;47(12):1047-1051. doi:10.1016/j.dld.2015.08.006.

46. El-Farhan N, Pickett A, Ducroq D, *et al*. Method-specific serum cortisol responses to the adrenocorticotrophin test: comparison of gas chromatography-mass spectrometry and five automated immunoassays. *Clin Endocrinol (Oxf)* 2013;78(5):673-680. doi:10.1111/cen.12039.

47. Javorsky BR, Raff H, Carroll TB, *et al*. New cutoffs for the biochemical diagnosis of adrenal insufficiency after ACTH stimulation using specific cortisol assays. *J Endocr Soc*. 2021;5(4):bvab022. doi:10.1210/jendso/bvab022.

48. Fede G, Spadaro L, Tomaselli T, *et al*. Assessment of adrenocortical reserve in stable patients with cirrhosis. *J Hepatol*. 2011;54(2):243-250. doi:10.1016/j.jhep.2010.06.034.

49. Kazlauskaite R, Evans AT, Villabona CV, *et al*. Corticotropin tests for hypothalamic-pituitary-adrenal insufficiency: a metaanalysis. *J Clin Endocrinol Metab*. 2008;93(11):4245-4253. doi:10.1210/jc.2008-0710.

50. Wade M, Baid S, Calis K, Raff H, Sinaii N, Nieman L. Technical details influence the diagnostic accuracy of the 1 microg ACTH stimulation test. *Eur J Endocrinol*. 2010;162(1):109-113. doi:10.1530/EJE-09-0746.

51. Marik PE, Pastores SM, Annane D, *et al*. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med*. 2008;36(6):1937-1949. doi:10.1097/CCM.0b013e31817603ba.

52. Annane D, Pastores SM, Rochwerg B, *et al*. Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Crit Care Med*. 2017;45(12):2078-2088. doi:10.1097/CCM.0000000000002737.

53. Arafah BM. Hypothalamic pituitary adrenal function during critical illness: limitations of current assessment methods. *J Clin Endocrinol Metab*. 2006;91(10):3725-3745. doi:10.1210/jc.2006-0674.

54. Hamrahian AH, Oseni TS, Arafah BM. Measurements of serum free cortisol in critically ill patients. *N Engl J Med*. 2004;350(16):1629-1638. doi:10.1056/NEJMoa020266.

55. Meyer EJ, Torpy DJ, Chernykh A, *et al*. Pyrexia and acidosis act independently of neutrophil elastase reactive center loop cleavage to effect cortisol release from corticosteroid-binding globulin. *Protein Sci*. 2020;29(12):2495-2509. doi:10.1002/pro.3982.

56. Nenke MA, Rankin W, Chapman MJ, *et al*. Depletion of high-affinity corticosteroid-binding globulin corresponds to illness severity in sepsis and septic shock; clinical implications. *Clin Endocrinol (Oxf)* 2015;82(6):801-807. doi:10.1111/cen.12680.

57. Meyer EJ, Nenke MA, Davies ML, *et al*. Corticosteroid-binding globulin deficiency independently predicts mortality in septic shock. *J Clin Endocrinol Metab*. 2022;107(6):1636-1646. doi:10.1210/clinem/dgac035

58. Boonen E, Meersseman P, Vervenne H, *et al*. Reduced nocturnal ACTH-driven cortisol secretion during critical illness. *Am J Physiol Endocrinol Metab*. 2014;306(8):E883-E892. doi:10.1152/ajpendo.00009.2014.

59. Beishuizen A, Thijs LG, Vermes I. Decreased levels of dehydroepiandrosterone sulphate in severe critical illness: a sign of exhausted adrenal reserve? *Crit Care*. 2002;6(5):434-438. doi:10.1186/cc1530.

60. Arlt W, Hammer F, Sanning P, *et al*. Dissociation of serum dehydroepiandrosterone and dehydroepiandrosterone sulfate in

septic shock. *J Clin Endocrinol Metab.* 2006;91(7):2548-2554. doi:10.1210/jc.2005-2258.

61. Marx C, Petros S, Bornstein SR, *et al*. Adrenocortical hormones in survivors and nonsurvivors of severe sepsis: diverse time course of dehydroepiandrosterone, dehydroepiandrosterone-sulfate, and cortisol. *Crit Care Med.* 2003;31(5):1382-1388. doi:10.1097/01.CCM.0000063282.83188.3D.

62. Tsai MH, Huang HC, Peng YS, *et al*. Dehydroepiandrosterone sulfate and dehydroepiandrosterone sulfate/cortisol ratio in cirrhotic patients with septic shock: another sign of hepatoadrenal syndrome? *Crit Care.* 2017;21(1):214. doi:10.1186/s13054-017-1768-0.

63. Charlton M, Angulo P, Chalasani N, *et al*. Low circulating levels of dehydroepiandrosterone in histologically advanced nonalcoholic fatty liver disease. *Hepatology* 2008;47(2):484-492. doi:10.1002/hep.22063.

64. Dorin RI, Qiao ZG, Bouchonville M, Qualls CR, Schrader RM, Urban FK. Characterization of cortisol secretion rate in secondary adrenal insufficiency. *J Endocr Soc.* 2017;1(7):945-956. doi:10.1210/js.2017-00198.

65. Dorin RI, Qualls CR, Torpy DJ, Schrader RM, Urban FK. Reversible increase in maximal cortisol secretion rate in septic shock. *Crit Care Med.* 2015;43(3):549-556. doi:10.1097/CCM.0000000000000721.

66. Dorin RI, Qiao Z, Qualls CR, Urban FK. Estimation of maximal cortisol secretion rate in healthy humans. *J Clin Endocrinol Metab.* 2012;97(4):1285-1293. doi:10.1210/jc.2011-2227.

67. Fede G, Spadaro L, Tomaselli T, Privitera G, Scicali R, Vasianopoulou P, *et al*. Comparison of total cortisol, free cortisol, and surrogate markers of free cortisol in diagnosis of adrenal insufficiency in patients with stable cirrhosis. *Clin Gastroenterol Hepatol.* 2014;12(3):504-12.e8; quiz e23.e8; quiz e23-4. doi:10.1016/j.cgh.2013.08.028

68. Thevenot T, Borot S, Remy-Martin A, *et al*. Assessment of adrenal function in cirrhotic patients using concentration of serum-free and salivary cortisol. *Liver Int.* 2011;31(3):425-433. doi:10.1111/j.1478-3231.2010.02431.x.

69. Coolens JL, Van Baelen H, Heyns W. Clinical use of unbound plasma cortisol as calculated from total cortisol and corticosteroid-binding globulin. *J Steroid Biochem.* 1987;26(2):197-202. doi:10.1016/0022-4731(87)90071-9.

70. Galbois A, Rudler M, Massard J, *et al*. Assessment of adrenal function in cirrhotic patients: salivary cortisol should be preferred. *J Hepatol.* 2010;52(6):839-845. doi:10.1016/j.jhep.2010.01.026.

71. Albert L, Profitós J, Sánchez-Delgado J, *et al*. Salivary cortisol determination in ACTH Stimulation test to diagnose adrenal insufficiency in patients with liver cirrhosis. *Int J Endocrinol* 2019;2019:7251010. doi:10.1155/2019/7251010.

72. Thevenot T, Dorin R, Monnet E, *et al*. High serum levels of free cortisol indicate severity of cirrhosis in hemodynamically stable patients. *J Gastroenterol Hepatol.* 2012;27(10):1596-1601. doi:10.1111/j.1440-1746.2012.07188.x.

73. Graupera I, Pavel O, Hernandez-Gea V, *et al*. Relative adrenal insufficiency in severe acute variceal and non-variceal bleeding: influence on outcomes. *Liver Int.* 2015;35(8):1964-1973. doi:10.1111/liv.12788.

74. Kim G, Huh JH, Lee KJ, Kim MY, Shim KY, Baik SK. Relative adrenal insufficiency in patients with cirrhosis: a systematic review and meta-analysis. *Dig Dis Sci.* 2017;62(4):1067-1079. doi:10.1007/s10620-017-4471-8.

75. Chiriac S, Stanciu C, Negru R, Trifan A. Assessment of adrenocortical dysfunction in patients with stable liver cirrhosis. *Acta Endocrinol (Buchar)* 2016;12(3):262-267. doi:10.4183/aeb.2016.262.

76. Munro V, Elnenaei M, Doucette S, Clarke DB, Imran SA. The effect of time of day testing and utility of 30 and 60 minute cortisol values in the 250 mcg ACTH stimulation test. *Clin Biochem.* 2018;54:37-41. doi:10.1016/j.clinbiochem.2018.02.010.

77. Sayyed Kassem L, El Sibai K, Chaiban J, Abdelmannan D, Arafah BM. Measurements of serum DHEA and DHEA sulphate levels improve the accuracy of the low-dose cosyntropin test in the diagnosis of central adrenal insufficiency. *J Clin Endocrinol Metab.* 2012;97(10):3655-3662. doi:10.1210/jc.2012-1806.

78. Evans L, Rhodes A, Alhazzani W, *et al*. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2021. *Crit Care Med.* 2021;49(11):e1063-e1143. doi:10.1097/CCM.0000000000005337.

79. El-Farhan N, Rees DA, Evans C. Measuring cortisol in serum, urine and saliva - are our assays good enough? *Ann Clin Biochem.* 2017;54(3):308-322. doi:10.1177/0004563216687335.

80. McCann VJ, Fulton TT. Cortisol metabolism in chronic liver disease. *J Clin Endocrinol Metab.* 1975;40(6):1038-1044. doi:10.1210/jcem-40-6-1038.

81. Hasenmajer V, Sbardella E, Sciarra F, Minnetti M, Isidori AM, Venneri MA. The immune system in Cushing's syndrome. *Trends Endocrinol Metab.* 2020;31(9):655-669. doi:10.1016/j.tem.2020.04.004.

82. Koch A, Tacke F. Variceal bleeding in liver cirrhosis at the ICU: sufficient data to treat adrenal insufficiency? *Crit Care Med.* 2014;42(12):2639-2640. doi:10.1097/CCM.0000000000000598.

83. Swain MG, Jones DEJ. Fatigue in chronic liver disease: new insights and therapeutic approaches. *Liver Int.* 2019;39(1):6-19. doi:10.1111/liv.13919.