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TOPIC HIGHLIGHT

Anca Trifan, Professor, *Series Editor*

Update on adrenal insufficiency in patients with liver cirrhosis

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Abstract

Liver cirrhosis is a major cause of mortality worldwide, often with severe sepsis as the terminal event. Over the last two decades, several studies have reported that in septic patients the adrenal glands respond inappropriately to stimulation, and that the treatment with corticosteroids decreases mortality in such patients. Both cirrhosis and septic shock share many hemodynamic abnormalities such as hyperdynamic circulatory failure, decreased peripheral vascular resistance, increased cardiac output, hypo-responsiveness to vasopressors, increased levels of proinflammatory cytokines [interleukine(IL)-1, IL-6, tumor necrosis factor-alpha] and it has, consequently, been reported that adrenal insufficiency (AI) is common in critically ill cirrhotic patients. AI may also be present in patients with stable cirrhosis without sepsis and in those undergoing liver transplantation. The term hepato-adrenal syndrome defines AI in patients with advanced liver disease with sepsis and/or other complications, and it suggests that it could be a feature of liver disease *per se*, with a different pathogenesis from that of septic shock. Relative AI is the term given to inadequate cortisol response to stress. More recently, another term is used, namely "critical illness related corticosteroid insufficiency" to define "an inadequate cellular corticosteroid activity for the severity of the patient's illness". The mechanisms of AI in liver cirrhosis are not completely understood, although decreased levels of high-density lipoprotein cholesterol and high levels of proinflammatory cytokines and circulatory endotoxin have been suggested. The prevalence of AI in cirrhotic patients varies widely according to the stage of the liver disease (compensated or decompensated, with or without sepsis), the diagnostic criteria defining AI and the methodology used. The effects of corticosteroid therapy on cirrhotic patients with septic shock and AI are controversial. This review aims to summarize the existing published information regarding AI in patients with liver cirrhosis.

Key words: Liver cirrhosis; Adrenal insufficiency; Septic shock; Corticosteroid therapy

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INTRODUCTION

Adrenocortical dysfunction in patients with liver cirrhosis has been described for over half a century[1], but was ignored until a decade ago when several studies reported that some septic patients had an inappropriately low response of adrenal glands to stimulation, and treatment with corticosteroids decreased mortality[2,3]. Relative adrenal insufficiency (RAI) is the term given to inadequate production of cortisol with respect to the severity of

illness[4,5]. More recently, another term, namely critical illness related corticosteroid insufficiency (CIRCI) defined as "inadequate cellular corticosteroid activity for the severity of the patient's illness"[6], has been used. Despite a large number of published studies during recent years, the concepts of RAI and CIRCI are still under debate.

Liver cirrhosis is a major cause of mortality worldwide[7], often with septic shock as the terminal event[8]. It is a well-established fact that cirrhotic patients have increased susceptibility to bacterial infections[9]. Both cirrhosis and septic shock share many hemodynamic abnormalities such as hyperdynamic circulatory failure, decreased peripheral vascular resistance, decreased mean arterial pressure, increased cardiac output, hyporesponsiveness to vasopressors, increased levels of proinflammatory cytokines [interleukine (IL)-1, IL-6, tumor necrosis factor-α (TNF-α)][5,10,11] and, consequently, several studies reported that adrenal insufficiency (AI) is common in critically ill cirrhotic patients[8,12-14]. Furthermore, AI may occur in compensated and decompensated cirrhosis without sepsis[14-20] or in early and late post-liver transplantation (LT)[12,21-23]. Nowadays, liver cirrhosis is considered to be among the major groups of high-risk diseases with a predisposition to AI[24]. The term hepatoadrenal syndrome is used to define AI in patients with advanced liver disease with sepsis and/or other complications[12,15], suggesting that adrenocortical insufficiency may be a feature of liver disease *per se*, with a different pathogenesis from that occurring in septic shock.

Mechanisms of AI in cirrhotic patients are not entirely known, but they may include impaired synthesis in total cholesterol, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol, as well as increased levels of proinflammatory cytokines and circulating endotoxin (e.g., lipopolysaccharide)[25-27]. The effects of corticosteroid therapy on cirrhotic patients with septic shock and AI are controversial, some studies reporting favorable results[12-14,28], while a recent randomized control study[29] has shown no benefit.

This review aims to summarize the existing published data regarding all aspects of AI prevalence, diagnosis and treatment in patients with liver cirrhosis.

PHYSIOLOGY OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS: A SHORT REVIEW

Cortisol is the main glucocorticoid secreted by the adrenal cortex under the control of adrenocorticotropic hormone (ACTH) which is released from the pituitary gland. The stimulus for ACTH release is corticotropin-releasing hormone (CRH) secreted by the paraventricular nuclei of the hypothalamus. Among factors influencing cortisol synthesis and production (diurnal rhythm of ACTH secretion, negative feedback by cortisol), stress plays the most important role. During stress and severe illness, activation of the hypothalamic-pituitary-adrenal (HPA) axis by the action of cytokines and other factors results in increased secretion of CRH, which will stimulate the production of ACTH and, consequently, increased release of cortisol into the circulatory system[30]. Cortisol is an essential component of the global adaptation to stress, contributing to the maintenance of cellular and organ homeostasis. Adequate levels of cortisol are absolutely necessary to increase cardiac output and vascular tonus, and to decrease proinflammatory cytokines (IL-1, IL-6, TNF-α) released[31,32] in order to overcome critical illness.

Over 90% of circulating cortisol is bound to corticosteroid-binding-globulin (CBG) (also called transcortin) and albumin, with less than 10% in the free biologically active form[33]. CBG is the predominant binding site (85%), with albumin binding smaller amounts of circulating cortisol. During severe sepsis, CBG levels fall, determining a higher percentage of free cortisol[34]. Hypoalbuminemia, frequently present in cirrhotic patients, has also been suggested to increase the free cortisol fraction[35,36]. Approximately 80% of circulating cortisol is synthesized both at rest and during stress from plasma cholesterol (particularly in the form of HDL cholesterol) and this could be relevant in patients with liver cirrhosis where cholesterol is low and may limit the synthesis of cortisol[26]. In the liver, cortisol is converted to its inactive metabolite cortisone by the enzyme 11β - hidroxysteroid dehydrogenase. After diffusion across the cell membrane, cortisol binds to glucocorticoid receptor and translocates into the nucleus of the cell[37] where its effects are exerted (increased vascular tonus and cardiac output, protein catabolism, lipolysis, hyperglycemia, and decreased cytokine production)[38]. These effects of cortisol are beneficial in critical illness, and several studies have shown that corticosteroid therapy is beneficial in patients with severe sepsis or septic shock[12-14,39,40]. As adrenal glands do not store cortisol, this must urgently be synthesized from its precursor, cholesterol, under any conditions of stress. In cirrhotic patients there is a low substrate (HDL cholesterol) for the synthesis of cortisol, favoring AI in conditions of stress[26].

PATHOGENESIS

Mechanisms leading to AI in liver cirrhosis remain largely unknown, although some hypotheses such as endotoxemia, decreased levels of apolipoprotein A-1, HDL cholesterol and LDL cholesterol, increased levels of proinflammatory mediators, structural damage to the adrenal gland due to infarction or hemorrhage, bacterial translocation of enteric organisms, "exhaustion" of the adrenal cortex, and glucocorticoid resistance have been suggested[12,41-49]. Many (if not all) of these pathophysiologic mechanisms are also involved in the genesis of AI in critically ill patients with sepsis[50-56].

As we have mentioned, cholesterol is the main source of steroidogenic substrate in the adrenal gland[26,57]. Several studies reported a significant decrease in the level

of serum HDL in cirrhotic patients which was related to the severity of the disease[12,26,47]. Furthermore, increased levels of circulating endotoxin (lipopolysaccharide) and TNF-α inhibit cortisol synthesis, limiting the delivery of HDL cholesterol to the adrenal gland[58-60]. In addition to this, TNF-α, IL-1 and IL-6 decrease hepatocyte synthesis of apolipoprotein A-1[58], the major component of HDL cholesterol. The lack of substrate for steroidogenesis will eventually lead to the so-called "adrenal exhaustion syndrome"[42] which contributes to AI in cirrhotic patients.

Besides low levels of serum total cholesterol, HDL-cholesterol and LDL-cholesterol, other factors may play a definite role in the pathogenesis of AI in patients with liver cirrhosis. Thus, coagulopathy (frequent in liver cirrhosis) may cause adrenal hemorrhage and infarction leading to structural damage of the adrenal gland[5], resulting in AI. Systemic inflammation is common in cirrhotic patients[61]. Bacterial translocation of enteric organisms has been demonstrated in patients with advanced liver cirrhosis[41,62].

A high prevalence of AI reported in patients with stable cirrhosis[15-19,63], similar to that reported in cirrhosis complicated by sepsis/septic shock, suggests that AI may be a feature of liver disease *per se*, with a different pathogenesis from that occurring in septic shock. These findings are consistent with the observations of Marik *et al*[12] who put forward the term hepato-adrenal syndrome in order to define AI in patients with advanced liver disease.

DIAGNOSIS

Diagnosis of AI made on clinical grounds in critically ill cirrhotic patients is impossible because of the lack of typical addisonian features[5,13]. Hypotension refractory to vasopressors and fluid resuscitation is the most important clinical sign in such patients[52]. Therefore, the diagnosis of AI in patients with liver cirrhosis is based on the following laboratory tests.

Standard dose

Measurement of serum total cortisol, either at baseline or following stimulation by the standard dose-short synacthen test (SD-SST) or low dose-short synacthen test (LD-SST). Baseline serum total cortisol levels under 414 nmol/L[8,13,20,64-66], < 250 nmol/L[45] or < 138 nmol/L[67] have been used to define AI in different studies. The following thresholds were used to diagnose subnormal response to SD-SST or LD-SST: (1) a peak cortisol level (defined as the highest cortisol concentration after synacthen stimulation) < 690 nmol/L[16], < 552 nmol/L[12], < 500 nmol/L[14,15,18,45], < 442 nmol/L[17]; and (2) a delta cortisol (defined as the difference between peak and basal cortisol) less than 250 nmol/L[8,13,15-20,45,64-67].

As one can easily see, there are differences in the thresholds of serum total cortisol used to define AI in published studies, which may explain significant discrepancies in the prevalence of AI in cirrhotic patients. Moreover, the diagnosis of AI based on serum total cortisol in patients with cirrhosis may be inaccurate due to changes in serum concentrations of CBG and albumin (both synthesized in the liver) which are usually low[68-70]. It has been already shown that low levels of CBG and albumin lead to overestimation of the diagnosis of AI[45,67]. As we have mentioned before, over 90% of serum circulating cortisol is bound to CBG and albumin, with less than 10% in the free form. Standard laboratory assays of serum total cortisol measure the bound plus free fractions. This means that a decrease in the binding protein levels, as it often happens in cirrhosis, will reduce serum total cortisol, affecting the interpretation of SD-SST/LD-SST[35,44], and this may lead to the overestimation of AI in cirrhotic patients[45]. However, most of the studies evaluating adrenal function in critically ill patients with liver cirrhosis still rely on the measurement of serum total cortisol, both at baseline and after stimulation.

Serum free cortisol assays are considered the most reliable method to assess adrenal function in critically ill patients[71]. There are several methods used to measure serum free cortisol (gel filtration, ultrafiltration, equilibrium dialysis)[72], all of them expensive and inconvenient for routine clinical practice[73]. In patients with liver cirrhosis, the serum free cortisol level is not altered by a reduced concentration of CBG and albumin[74] and it therefore appears to be a more appropriate marker for assessing adrenal function in such patients[44,74]. Some studies reported significant differences in diagnosis of AI using serum total cortisol and free cortisol criteria in cirrhotic patients with septic shock[75] or in those with stable cirrhosis[15], while others found that assessing serum free cortisol had limited additive diagnostic value over serum total cortisol[76]. Serum free cortisol levels under 50 nmol/L at baseline or less than 86 nmol/L after synacthen stimulation are suggestive for the diagnosis of AI (in critically ill patients)[35], although the reference range for baseline values in healthy subjects varies from 8-25 nmol/L[71] to 12-70 nmol/L[44,77].

Due to the limitations of available assays to estimate serum free cortisol, surrogate markers may be used, such as Coolens equation "$U^2 \times K (1 + N) + U [1 + N + K (G - T)] - T = 0$", where T is total cortisol, G is CBG, U is unbound cortisol, K is the affinity of CBG for cortisol at 37 ℃ and N is the ratio of albumin-bound to unbound cortisol[68], free cortisol index (FCI) (serum total cortisol concentration divided by CBG level)[78], and salivary cortisol[71,79]. However, Coolens equation and FCI do not take into account the concentration of low serum albumin and CBG frequently present in cirrhotic patients and, therefore, both surrogates may not be suitable to estimate serum free cortisol in such patients[69-71]. By contrast, salivary cortisol, regardless of serum binding protein levels, correlates well with free cortisol levels[71,79]. Basal value of salivary cortisol < 1.8 ng/mL or a concentration after stimulation (SD-SST) < 12.7 ng/mL, an increment < 3 ng/mL[45] or a peak serum free cortisol < 33 nmol/L[15] are suggestive of AI. However, there are

significant variations in normal salivary cortisol values reported by different studies[74]. Other limits of salivary cortisol are represented by oral candidiasis, low salivary flow, and contaminated salivary samples from gingival bleeding, common in cirrhotic patients[44].

SD-SST

SD-SST measures total serum cortisol at baseline and 60 min after an intravenous injection of 250 μg of synthetic ACTH. Currently, there are two corticotropic analogues that can be used, namely tetracosactrin (synacthen, Novartis Pharma AG, Basel, Switzerland) and cosyntropin (Cortrosyn, Amphastar Pharmaceuticals, Rancho Cucamonga, CA, United States). Using a supraphysiological dose of 250 μg of corticotropin (which results in approximately 100 times higher than normal maximal stress ACTH levels)[17], SD-SST is not a "physiological test"[17,80]. In the context of critical illness, AI was defined by the International Task Force[6] as a delta cortisol of < 250 nmol/L (< 9 μg/dL) after SD-SST or a random serum total cortisol of < 276 nmol/L (< 10 μg/dL). There is no consensus on the diagnostic criteria of AI in cirrhotic patients, although a delta cortisol under 250 nmol/L has been used by most studies to define AI in such patients[81].

LD-SST

LD-SST uses 1 μg of synacthen given intravenously, and serum cortisol measured after 20 and 30 min (the latter time-point is mostly used). The normal response is a serum cortisol level > 500 nmol/L (> 18 μg/dL)[49]. In a meta-analysis[82] comprising the diagnostic value of SD-SST and LD-SST for diagnosing AI, LD-SST was found to be superior, contrary to another meta-analysis[83] which reported similar operative characteristics for both tests. LD-SST seems to be a more physiological and sensitive test than SD-SST for the diagnosis of AI, and appropriate for use in non-critically ill cirrhotic patients[49].

Insulin-induced hypoglycemia test

Insulin-induced hypoglycemia test (IIHT) has been considered to be the gold standard to evaluate the HPA axis. The test uses injection of 0.15 IU/kg regular insulin to achieve blood glucose less than 40 mg/dL or until symptoms of hypoglycemia develop. Blood samples are taken before and at 15, 30, 45, 60, 90 min post-stimulation. Peak cortisol cut points between 500 and 550 nmol/L (18-20 μg/dL) are used for the diagnosis of adrenal sufficiency. This test is contraindicated in patients with cardio- or cerebrovascular diseases and convulsive disorders. In addition, the IIHT is unpleasant for the patients and therefore it has been replaced by alternative tests (LS-SST, SD-SST) for evaluating the HPA axis[84].

Corticotrophin-releasing hormone test

Corticotrophin-releasing hormone test (CRHT) evaluates the entirety of the HPA axis. Blood samples for the measurement of ACTH and cortisol are taken at baseline and at 15, 30, 45 and 60 min after an intravenous injection of 1 μg/Kg of CRH. Although CRHT is free of serious side effects, it is both difficult and costly and therefore it has been used in few studies in liver disease.

To conclude, in the absence of a gold standard test, SD-SST remains the most used test to assess the adrenal function in critically ill cirrhotic patients, while LD-SST seems to be more appropriate in those with stable cirrhosis. At present, serum free cortisol and salivary cortisol are the most accurate methods for the diagnosis of AI in cirrhotic patients, but cannot be used in routine clinical practice. The use of salivary cortisol needs to be validated. As diagnosis of AI in cirrhotics is of major clinical importance, there is an urgent need for a consensus as to which is the most appropriate diagnostic test of AI in such category of patients.

PREVALENCE AND EXISTING EVIDENCE

Initial reports on AI in liver cirrhosis were followed by multiple studies (Tables 1 and 2) and, recently, by excellent systematic reviews[43,44,46,49,81]. There are significant discrepancies between studies on the prevalence of AI in patients with liver cirrhosis, mainly because of the different tests used for diagnosis of adrenal dysfunction and the criteria applied to define AI. Thus, the prevalence of AI varies between critically ill cirrhotic patients (10%-87%; Table 1), those with stable cirrhosis (7%-83%; Table 2), and patients with liver transplant (61%-92%; Table 1). Overall, several published studies have reported a high prevalence of AI both in critically and non-critically ill cirrhotic patients[17,29,63,64,69,85] as well as in those who had received liver transplant[12].

Critically ill patients with liver cirrhosis

Almost all studies that included critically ill patients with liver cirrhosis[8,13,20,29,64-66,74,85] used SD-SST for the diagnosis of AI and only two performed LD-SST[12,16]. With SD-SST, the reported prevalence of AI in critically ill cirrhotics varied between 10%[74] and 87%[85], while with LD-SST, the prevalence range was between 33%[12] and 60%[16].

Harry *et al*[14] reported a prevalence of AI (defined as peak cortisol levels less than 500 nmol/L) of 69% in critically ill cirrhotic patients requiring vasopressor support. In a prospective study including 25 cirrhotic patients with severe sepsis, Fernández *et al*[13] reported a very high incidence of AI (68%) using SD-SST and defining AI either as baseline serum total cortisol level less than 414 nmol/L or a delta cortisol lower than 250 nmol/L in those with a baseline concentration below 966 nmol/L. The AI prevalence rate was correlated with the severity of liver disease (76% Child-Pugh C *vs* 25% Child-Pugh B).

SD-SST was also used to evaluate adrenal function in a prospective study which included 101 critically ill patients with cirrhosis and severe sepsis[8]. Authors found that 51% of their patients met the criteria for AI (defined as baseline serum total cortisol values under 414 nmol/L

Table 1 Prevalence of adrenal insufficiency in critically ill patients with liver cirrhosis

Ref.	No. of patients (type of cirrhosis)	Diagnosis and definition of AI	Prevalence of AI
Harry *et al*[14]	20 (ALF/CLD)	SD-SST: Peak cortisol < 500 nmol/L[1]	69%
Marik *et al*[12]	340	LD-SST: Peak cortisol < 552 nmol/L or	72%
	(ALF: 24)	random cortisol level < 414 nmol/L in non-stressed patients or	33%
	(CLD: 146)	random cortisol level < 552 nmol/L in stressed patients	66%
	(recent LT: 119)		92%
	(remote LT: 51)		61%
Tsai *et al*[8]	101 (cirrhosis+ severe sepsis)	SD-SST: Baseline cortisol < 414 nmol/L or delta cortisol < 250 nmol/L if baseline cortisol between 414 and 938 nmol/L	51%
Fernandez *et al*[13]	25 (cirrhosis + septic shock)	SD-SST: Baseline cortisol < 414 nmol/L or delta cortisol < 250 nmol/L if baseline cortisol between 414 and 966 nmol/L	68%
Thierry *et al*[64]	14 (cirrhosis + septic shock)	SD-SST: Baseline cortisol < 414 nmol/L; delta cortisol < 250 nmol/L	77%
du Cheyron *et al*[65]	50 (critically ill cirrhosis)	SD-SST: Baseline cortisol < 414 nmol/L; delta cortisol < 250 nmol/L if baseline cortisol between 414 and 938 nmol/L	82%
Vasu *et al*[86]	24 (critically ill cirrhotics)	SD-SST: Definition of AI was not reported	62%
Arabi *et al*[29]	75 (cirrhosis + septic shock)	SD-SST: Delta cortisol < 250 nmol/L	76%
Mohamed *et al*[85]	15 (cirrhosis+septic shock)	SD-SST: Definition of AI was not reported	87%
Thevenot *et al*[74]	30 (cirrhosis + sepsis)	SD-SST: Peak serum total cortisol < 510 nmol/L	10%
Acevedo *et al*[89]	166 (decompensated cirrhosis)	SD-SST: Delta cortisol < 250 nmol/L	26%
Graupera *et al*[20]	37 (severe acute bleeding)	SD-SST: Baseline cortisol < 414 nmol/L and/or delta cortisol < 250 nmol/L	38%
Triantos *et al*[16]	20 (cirrhosis with variceal bleeding)	SD-SST: Baseline cortisol < 276 nmol/L or delta cortisol < 250 nmol/L	30%
		LD-SST: Peak serum cortisol < 690 nmol/L or a delta cortisol < 250 nmol/L	60%
El Damarawy *et al*[66]	45 (cirrhosis with septic shock or HRS, cirrhosis without septic shock or HRS)	SD-SST: Baseline cortisol < 414 nmol/L or delta cortisol < 250 nmol/L in patients with baseline cortisol < 966 nmol/L	73%

[1]To convert serum total cortisol concentrations from nanomoles per liter to micrograms per deciliter divide by 27.59[79]. ALF: Acute liver failure; CLD: Chronic liver disease; HRS: Hepatorenal syndrome; LT: Liver transplant; AI: Adrenal insufficiency; SD-SST: Standard dose short synacthen test; LD-SST: Low dose short synacthen test.

or delta cortisol lower than 250 nmol/L with a baseline value between 414 and 938 nmol/L) which was related to disease severity [Child-Pugh and model for end-stage liver disease (MELD) scores] and increased mortality. Recently, Arabi *et al*[29], using the same test (SD-SST) and definition for AI (delta cortisol < 250 nmol/L) in a similar group of critically ill patients (cirrhosis with septic shock) reported an even higher AI prevalence rate (76%).

The SD-SST test was also used in several other studies to assess adrenal function in critically ill cirrhotic patients[64-66,74,85,86].

Adrenal function has also been evaluated by SD-SST in cirrhotic patients with variceal bleeding[16,20]. Graupera *et al*[20] reported AI prevalence (defined as baseline serum cortisol < 414 nmol/L or delta cortisol < 250 nmol/L) in 38% of bleeding patients. AI was associated with increased risk of failure to control bleeding and lower survival rate at 6 wk. In a prospective observational study on 20 cirrhotic patients with variceal bleeding and 60 with stable cirrhosis, Triantos *et al*[16] reported an AI prevalence rate (defined as basal cortisol < 276 nmol/L or delta cortisol < 250 nmol/L following SD-SST) of 30% (similar to that in stable cirrhosis); with the use of LD-SST, AI prevalence (defined as a peak cortisol < 690 nmol/L or a delta cortisol < 250 nmol/L) was significantly higher in bleeders (60%) than in stable cirrhotics (48%).

LD-SST was also previously used by Marik *et al*[12] to evaluate adrenal function in 340 critically ill patients with liver disease (24 with fulminant hepatic failure, 146 critically ill cirrhotics, 51 with remote LT, and 119 having recently undergone LT). AI was defined as having a random cortisol level of < 552 nmol/L in highly stressed patients (hypotension, hepatic failure, respiratory failure) and a random cortisol level of < 414 nmol/L or a 30 min post LD-SST level of < 552 nmol/L in all other patients. Out of 340 patients studied, 245 (72%) met the criteria for AI (33% fulminant hepatic failure, 66% critically ill cirrhotics, 61% remote LT, 92% recent LT).

Non-critically ill cirrhotics

AI is also common in patients with stable liver cirrhosis (Table 2). However, as in critically ill cirrhotic patients, AI prevalence rate in those with stable liver cirrhosis varies significantly, depending on the diagnostic test used.

In a prospective study, Tan *et al*[15] evaluated adrenal function in 43 clinically stable cirrhotic patients. All patients underwent SD-SST, and AI was defined by delta cortisol < 250 nmol/L or a peak total cortisol < 500 nmol/L, or a peak serum free cortisol < 33 nmol/L. The prevalence of AI was 47% using delta cortisol < 250 nmol/L, 39% using peak total cortisol < 500 nmol/L, and 12% with serum free cortisol < 33 nmol/L. This study clearly shows that the reported prevalence of AI depends largely on the diagnostic test used and criteria for defining AI.

Galbois *et al*[45] have evaluated adrenal function in 88 patients hospitalized for complications of cirrhosis without bleeding and shock. Salivary and serum total cortisol were assessed 60 min before and after stimulation with SD-SST in all patients. Serum free cortisol was estimated

Table 2 Prevalence of adrenal insufficiency in patients with liver cirrhosis, not critically ill

Ref.	No. of patients (type of cirrhosis)	Diagnosis and definition of AI	Prevalence of AI
McDonald *et al*[69]	38 (stable cirrhosis)	IIHT: Reduction in maximal increments of plasma cortisol	64%
		SD-SST: Reduction in maximal increments of plasma cortisol	39%
Zietz *et al*[112]	52 (stable cirrhosis)	CRHT: Peak cortisol < 550 nmol/L or an increase < 250 nmol/L[1]	58%
		rise of plasma ACTH < twice the baseline	42%
Sigalas *et al*[87]	47 (stable cirrhosis)	SD-SST: Baseline cortisol < 250 nmol/L and delta cortisol < 250 nmol/L	36%
Alessandria *et al*[88]	25 (cirrhosis and ascites)	SD-SST: Delta cortisol < 250 nmol/L	36%
Jang *et al*[63]	18 (stable cirrhosis)	SD-SST: Baseline cortisol < 414 nmol/L delta cortisol < 250 nmol/L	83%
Acevedo *et al*[19]	198 (10 compensated and	SD-SST: Baseline cortisol < 414 nmol/L	64%
	188 decompensated cirrhosis)	delta cortisol < 250 nmol/L	27%
Galbois *et al*[45]	88 (stable cirrhosis)	SD-SST: (1) Serum total cortisol: Baseline cortisol < 250 nmol/L or peak cortisol < 500 nmol/L or delta cortisol < 250 nmol/L	33%
		(2) Salivary cortisol: Basal salivary cortisol < 1.8 ng/mL or post-stimulation values < 12.7 ng/mL or increase values < 3 ng/mL	9%
Tan *et al*[15]	43 (stable cirrhosis)	SD-SST: Peak total cortisol < 500 nmol/L;	39%
		delta cortisol < 250 nmol/L;	47%
		peak plasma free cortisol < 33 nmol/L;	12%
		any set of criteria	58%
Thevenot *et al*[67]	95 (stable cirrhosis)	LD-SST: Baseline cortisol < 138 nmol/L;	7%
		< 440 nmol/L after stimulation;	19%
		⩽ 500 nmol/L after stimulation;	27%
		delta cortisol < 250 nmol/L	49%
Fede *et al*[17]	101 (stable cirrhosis)	LD-SST: Peak serum cortisol < 500 nmol/L;	38%
		peak serum cortisol < 442 nmol/L;	29%
		delta cortisol < 250 nmol/L	60%
Triantos *et al*[16]	60 (stable cirrhosis)	SD-SST: Peak serum cortisol < 500 nmol/L	30%
		LD-SST: Peak serum cortisol < 500 nmol/L	48%
Mohamed *et al*[85]	15 (stable cirrhosis)	SD-SST: Definition of AI was not reported	53%
Risso *et al*[18]	85 (cirrhosis with ascites, without sepsis or shock)	SD-SST: Delta cortisol < 250 nmol/L and/or peak cortisol < 500 nmol/L	39%
Vincent *et al*[73]	26 (liver impairment)	SD-SST: Serum total cortisol < 550 nmol/L;	46%
		free cortisol index < 12	13%

[1]To convert serum total cortisol concentrations from nanomoles per liter to micrograms per deciliter divide by 27.59[79]. AI: Adrenal insufficiency; SD-SST: Standard dose short synacthen test; LD–SST: Low dose short synacthen test; CRHT: Corticotropin-releasing hormone test; IIHT: Insulin-induced hypoglycemia test; ACTH: Adrenocorticotropic hormone.

from serum total cortisol and CBG levels using Coolens' formula[68]. The following definitions of AI were used by the authors: (1) according to serum total cortisol assays: baseline < 250 nmol/L, or a peak total cortisol < 500 nmol/L, or delta cortisol < 250 nmol/L; (2) according to salivary cortisol assays: baseline < 1.8 ng/mL, or an increase < 3 ng/mL or a concentration < 12.7 ng/mL after stimulation. The results indicated a significant difference in AI prevalence depending on the test used: 33% when serum total cortisol was considered *vs* 9.1% using salivary cortisol.

Another study performed by Thevenot *et al*[74] has demonstrated that assessment of adrenal function with measurements of serum total cortisol overestimated AI prevalence in cirrhotic patients. In this study, baseline and post-synacthen serum total cortisol, serum free cortisol and salivary cortisol concentrations were measured in 125 cirrhotic patients (95 non-septic, 30 septic). AI was defined as serum total cortisol < 510.4 nmol/L after SD-SST. AI was found in nine patients (7.2%) (6 non-septic; 3 septic) and restricted to cirrhotics with Child-Pugh C. Serum total cortisol concentrations, CBG and albumin levels significantly decreased in non-septic patients as liver function deteriorated (from Child-Pugh A to C). Cirrhotic patients with or without AI had similar basal serum free cortisol and salivary cortisol levels. As the serum total cortisol level overestimated the prevalence of AI in cirrhotic patients, and serum free cortisol is not suitable for routine laboratory use, authors concluded that measurement of salivary cortisol is a useful approach in such patients. The same group of investigators[67] analyzed only the 95 hemodynamically stable cirrhotic patients from the previously mentioned study, who underwent a LD-SST. The serum total cortisol and serum free cortisol concentrations were measured 30 min before and after LD-SST. AI was defined as: (1) basal serum total cortisol < 138 nmol/L and < 440 nmol/L after stimulation; (2) serum total cortisol < 500 nmol/L after stimulation; and (3) cortisol increment < 250 nmol/L. AI prevalence rates varied significantly according to the threshold used: 7.4 % with basal serum total cortisol, 19% using serum cortisol < 440 nmol/L, 27.4 % with serum cortisol < 500 nmol/L, and 49.4% with delta cortisol. Serum free cortisol levels before and after LD-SST stimulation were higher in the more severe cirrhotic patients regardless of CBG and albumin concentrations, and directly associated with the risk of non-transplant-related mortality in hemodynamically stable patients with cirrhosis.

In opposition to the above mentioned studies, recently, in a prospective study, Molenaar *et al*[76], using SD-SST, assessed the value of free *vs* total cortisol levels while evaluating AI in 49 septic and 63 non-septic patients with treatment-insensitive hypotension and found that total cortisol correlated with free cortisol during critical illness. Moreover, in sepsis, hypoalbuminemia did not affect total and free cortisol, contrary to the findings of other published studies[45,67].

Others, using SD-SST or LD-SST to diagnose adrenal dysfunction in patients with stable liver cirrhosis reported high AI prevalence rates[16-19,63,69,73,85,87,88]. Fede *et al*[17] reported an AI prevalence of 38% in 101 patients with stable cirrhosis (absence of infections or hemodynamic instability). AI, defined as a peak serum total cortisol level < 500 nmol/L after LD-SST, was correlated with the severity of liver disease graded according to Child-Pugh or MELD scores.

Using SD-SST in 85 cirrhotics with ascites but without sepsis, Risso *et al*[18] reported AI (delta cortisol < 250 nmol/L and/or peak cortisol < 500 nmol/L) in 39% of patients.

Vincent *et al*[73] evaluated adrenal function by SD-SST in 26 patients with liver impairment. Authors defined AI as serum total cortisol < 550 nmol/L or FCI < 12. Three patients (13%) met both criteria, 12 patients (46%) had a serum total cortisol < 550 nmol/L but an FCI > 12. When serum total cortisol was used, 46% of patients had AI, while when using FCI only 13% fulfilled the criteria for AI. Authors suggested that FCI is better suited for the evaluation of AI in patients with liver impairment.

Acevedo *et al*[19], using SD-SST, evaluated the prevalence of AI in 198 patients with liver cirrhosis [10 with compensated, 188 with decompensated cirrhosis and complications (hepatic encephalopathy, spontaneous bacterial peritonitis, ascites, gastrointestinal bleeding, hepatorenal syndrome)]. AI defined as basal serum total cortisol < 414 nmol/L was found in 64% of patients, and only in 27% when delta cortisol < 250 nmol/L was used, with no differences between compensated and decompensated cirrhosis. The same group of researchers evaluated the prevalence and prognostic value of AI in 166 patients with advanced cirrhosis (no severe sepsis or septic shock)[89]. AI, defined as delta cortisol < 250 nmol/L after SD-SST, was found in 26% of patients. Those with AI had a higher degree of circulatory dysfunction, greater prevalence of systemic inflammatory response syndrome, increased probability to develop severe infections, and higher hospital mortality rates than patients without AI.

AI after LT

AI has been reported both early as well as late after LT[12,21-23,90].

With LD-SST, Marik *et al*[12] found that 92% of 119 patients undergoing recent LT and maintained on steroid-free immunosuppressive regimens had AI. The steroid-free immunosuppressive regimen may expose patients undergoing LT to an increased risk for AI, while the use of steroids intra and postoperatively in LT may reduce such a risk or mask an AI[46]. Furthermore, LD-SST is not recommended for the diagnosis of AI in high-stress conditions like LT[6] as it may lead to an overestimated AI prevalence in such patients.

Toniutto *et al*[21], using SD-SST, reported an AI prevalence rate of 26% in 87 patients having received LT for end-stage liver disease and maintained on prolonged immunosuppressive treatment.

Patel *et al*[90] reported significantly reduced requirements for fluid, vasopressors, invasive ventilation, and renal replacement therapy, and intensive care unit stay for patients undergoing LT who received 1000 mg methylprednisolone prior to the liver graft reperfusion.

TREATMENT

Cortisol has several beneficial effects such as an increase of the vascular tonus and cardiac output, enhancement of catecholamine responsiveness, inhibition of the production of nitric oxide, modulation of cytokine production in septic shock[32,91-97], but the effects of corticosteroid therapy in sepsis, severe sepsis and septic shock remain, however, controversial. Thus, a significant reduction in mortality rate with hydrocortisone therapy in patients with septic shock has been reported in several studies and meta-analyses[6,28,39,98-101], while others have shown no effect on the 28-d mortality rate[14,29,102]. Both doses and duration of corticosteroid therapy vary significantly in published studies[6,28,39,40,102,103]. Thus, some used a daily dose of hydrocortisone (or equivalent) of 200-300 mg ("low-dose", also called "physiologic-dose" or "stress-dose")[3,28,39,98,100-105] while others used a "supra-physiologic" dose (> 300 mg)[98,106-108].

None of the early studies using high doses of corticosteroids for short courses reported any benefit[98,106-108], while more recent studies using a "physiologic-dose" for longer durations have shown a significant reduction in vasopressor agents requirement and in intensive care unit length of stay, greater shock resolution, and decreased mortality[6,28,39,98,100,104,105,109-111]. A randomized, double-blind placebo controlled trial, CORTICUS (Corticosteroid Therapy of Septic Shock)[102] including 499 patients with septic shock randomized to hydrocortisone (50 mg intravenously every 6 h for 5 d, followed by 50 mg intravenously every 12 h for 3 d, and then by 50 mg daily for 3 d) or placebo, concluded that there was no benefit in terms of mortality, although steroid administration was associated with a greater shock reversal, but also with a higher incidence of episodes of new infections. On the other hand, Annane *et al*[28] in a randomized, double-blind controlled trial have found that the administration of hydrocortisone (50 mg intravenously every 6 h) and oral fludrocortisone (50 μg once daily) in patients with refractory septic shock and AI (delta cortisol < 250 nmol/L) resulted in a 30% decrease in 28-d mortality. It should be mentioned that consensus statements from an international task force[6] recommended corticosteroid therapy

Table 3 Published studies on corticosteroid therapy in patients with liver cirrhosis

Ref.	No. of patients (type of cirrhosis)	Study design	Steroid dose	Outcomes
Harry *et al*[14]	20 (ALF or ACLF)	Retrospective	Hydrocortisone 300 mg/d	Reduction in vasopressor doses, but higher incidence of infection and no survival benefit
Marik *et al*[12]	140 (ALF or CLD)	Not RCT	Hydrocortisone 300 mg/d	Reduction in the dose of norepinephrine at 24 h, and lower mortality rate increased survival
Fernandez *et al*[13]	17 (cirrhosis and septic shock)	Prospective but not RCT	Hydrocortisone 200 mg/d	Significant increase in shock resolution and high hospital survival rate
Arabi *et al*[29]	39 (cirrhosis and septic shock)	RCT	Hydrocortisone 200 mg/d	Reduction in vasopressor doses and higher rates of shock reversal, but no benefit in 28 d mortality, increase in gastrointestinal bleeding and shock relapse

ALF: Acute liver failure; ACLF: Acute-on-chronic liver failure; CLD: Chronic liver disease; RCT: Randomized controlled trial.

(intravenous hydrocortisone 200-300 mg/d in four divided doses for a week before tapering slowly) in patients with vasopressor-dependant septic shock.

Like in patients with severe sepsis/septic shock with other causes than liver cirrhosis, as mentioned above, the effects of steroid therapy in cirrhotic patients with AI remain controversial, some studies reporting beneficial results[12-14] while a recent randomized control study[29] has shown no benefit (Table 3).

Harry *et al*[14] evaluated the effects of stress doses of hydrocortisone in a retrospective comparative study including 40 patients. Twenty patients received hydrocortisone (300 mg/d) for 4-5 d. In patients with acute-on-chronic liver failure requiring norepinephrine support, the results showed a reduction in vasopressor doses, but no survival benefit; moreover, corticosteroid therapy was associated with a significant increase in infections.

Another study, carried out by Marik *et al*[12] evaluated the effect of 300 mg/d hydrocortisone given intravenously in vasopressor-dependant patients with acute or chronic liver disease. In patients with AI, treatment with hydrocortisone was associated with a significant reduction of the norepinephrine dosage at 24 h and with a lower mortality ($P = 0.02$), whereas in those patients without AI hydrocortisone did not affect the norepinephrine dose.

Fernández *et al*[13], in a prospective but non-randomized study have evaluated adrenal function by SD-SST and the effects of low-dose hydrocortisone in 25 patients with advanced cirrhosis and septic shock. Patients with AI received intravenous hydrocortisone (50 mg every 6 h) and results were compared with those obtained from a retrospective 50 cirrhotic patients with septic shock in whom adrenal function was not investigated and who did not receive corticosteroid therapy. Results showed that hydrocortisone therapy was associated with a significant increase in shock resolution and hospital survival rate. Authors suggested that all cirrhotic patients with AI should be treated with hydrocortisone.

Recently, Arabi *et al*[29] in a randomized controlled trial, have shown that low dose hydrocortisone therapy in cirrhotic patients with septic shock had a significant reduction in vasopressor doses and higher rates of shock reversal, but it did not reduce mortality and was associated with an increase in adverse effects (gastrointestinal bleeding) and shock relapse.

Based on the above mentioned studies, there are still several unsolved problems and questions awaiting answers. Thus, re-evaluation of both doses and duration of corticosteroid therapy is necessary. Obviously, further prospective randomized clinical studies are needed to assess the effect of corticosteroid therapy in critically ill cirrhotic patients with AI.

CONCLUSION

AI occurs frequently in patients with liver cirrhosis both during critical illness and in stable disease. Studies, however, do not agree on the prevalence of AI in cirrhotic patients, mostly because of the different criteria and the methodology used to define AI. Diagnosis of AI in patients with liver cirrhosis remains controversial (particularly in those critically ill) as all diagnostic tests proved their limitations. Pathogenesis of AI in liver cirrhosis is still unknown, although decreased levels of cholesterol (mainly HDL cholesterol) and increased levels of pro-inflammatory cytokines and circulating endotoxin have been put forward. Some data suggest that AI may be a feature of cirrhosis *per se*, with a pathogenesis subtly different from that occurring in septic shock from other causes. Yet, there is still controversy in what concerns treatment with corticosteroids, although some cirrhotic patients with vasopressor resistant shock may benefit. However, further prospective, randomized clinical trials are necessary to assess the effect of corticosteroid therapy in critically ill patients with cirrhosis.

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