

# The hepatoadrenal syndrome: A common yet unrecognized clinical condition\*

Paul E. Marik, MD, FCCM; Timothy Gayowski, MD, FACS; Thomas E. Starzl, MD, FACS, PhD; for the Hepatic Cortisol Research and Adrenal Pathophysiology Study Group

**Objective:** Adrenal failure is common in critically ill patients, particularly those with sepsis. As liver failure and sepsis are both associated with increased circulating levels of endotoxin and proinflammatory mediators and reduced levels of apoprotein-1/high-density lipoprotein, we postulated that adrenal failure may be common in patients with liver disease.

**Design:** Clinical study.

**Setting:** Liver transplant intensive care unit.

**Patients:** The study cohort included 340 patients with liver disease.

**Interventions:** Based on preliminary observational data, all patients admitted to our 28-bed liver transplant intensive care unit (LTICU) undergo adrenal function testing. An honest broker system was used to extract clinical, hemodynamic, medication, and laboratory data on patients admitted to the LTICU from March 2002 to March 2004. A random (stress) cortisol level  $<20 \mu\text{g/dL}$  in a highly stressed patient (respiratory failure, hypotension) was used to diagnose adrenal insufficiency. In all other patients, a random cortisol level  $<15 \mu\text{g/dL}$  or a 30-min level  $<20 \mu\text{g/dL}$  post-low-dose (1  $\mu\text{g}$ ) cosyntropin was considered diagnostic of adrenal insufficiency. Patients were grouped as follows: a) chronic liver failure; b) fulminant hepatic failure; c) patients immediately status post-orthotopic liver transplantation receiving a steroid-free protocol of immunosuppression; and d) patients status post-remote liver transplant ( $\geq 6$  months). The decision to treat patients with stress doses of hydrocortisone was at the discretion of the treating intensivist and transplant surgeon.

**Measurements and Main Results:** Two-hundred and forty-five (72%) patients met our criteria for adrenal insufficiency (the hepatoadrenal syndrome). Eight (33%) patients with fulminant hepatic failure, 97 (66%) patients with chronic liver disease, 31 (61%) patients with a remote history of liver transplantation,

and 109 (92%) patients who had undergone liver transplantation under steroid-free immunosuppression were diagnosed with adrenal insufficiency. The high-density lipoprotein level at the time of adrenal testing was the only variable predictive of adrenal insufficiency ( $p < .0001$ ). In vasopressor-dependent patients with adrenal insufficiency, treatment with hydrocortisone was associated with a significant reduction ( $p = .02$ ) in the dose of norepinephrine at 24 hrs, whereas the dose of norepinephrine was significantly higher ( $p = .04$ ) in those patients with adrenal failure not treated with hydrocortisone. In vasopressor-dependent patients without adrenal insufficiency, treatment with hydrocortisone did not affect vasopressor dose at 24 hrs. One hundred and forty-one patients (26.4%) died during their hospitalization. The baseline serum cortisol was  $18.8 \pm 16.2 \mu\text{g/dL}$  in the nonsurvivors compared with  $13.0 \pm 11.8 \mu\text{g/dL}$  in the survivors ( $p < .001$ ). Of those patients with adrenal failure who were treated with glucocorticoids, the mortality rate was 26% compared with 46% ( $p = .002$ ) in those who were not treated. In those patients receiving vasopressor agents at the time of adrenal testing, the baseline cortisol was  $10.0 \pm 4.8 \mu\text{g/dL}$  in those with adrenal insufficiency compared with  $35.6 \pm 21.2 \mu\text{g/dL}$  in those with normal adrenal function. Vasopressor-dependent patients who did not have adrenal failure had a mortality rate of 75%.

**Conclusions:** Patients with liver failure and patients post-liver transplantation have an exceedingly high incidence of adrenal failure, which may be pathophysiologically related to low levels of high-density lipoprotein. Treatment of patients with adrenal failure may improve outcome. High baseline serum cortisol levels may be a maker of disease severity and portend a poor prognosis. (Crit Care Med 2005; 33:1254-1259)

**KEY WORDS:** adrenal insufficiency; cirrhosis; liver transplantation; cortisol; high-density lipoprotein; liver failure

Once considered a rare diagnosis in the intensive care unit (ICU), adrenal failure is being reported with increased frequency in critically ill patients with

sepsis, HIV infection, and head injury and following cardiac surgery (1-4). Adrenal failure may be associated with structural damage to the adrenal gland, pituitary gland, or hypothalamus; however, many critically ill patients develop reversible failure of the hypothalamic-pituitary-adrenal axis (5). Activation of the hypothalamic-pituitary-adrenal axis with the release of cortisol is an essential component of the general adaptation to illness and stress and contributes to the maintenance of cellular and organ homeostasis. This is clearly demonstrated in adrenalectomized animals, who succumb rapidly to hemorrhagic and septic shock, with steroid replacement being protective against these challenges (6, 7). Furthermore, Anane and colleagues (8) demonstrated that treatment with stress doses of hydrocortisone (and supplemental mineralocorticoid) improved survival in a subgroup of septic shock patients with adrenal failure.

The fact that adrenal failure is common in critically ill patients and that treatment with stress doses of glucocorticoids may be beneficial is difficult to

\*See also p. 1431.

From the Division of Pulmonary and Critical Care Medicine, Thomas Jefferson University, Philadelphia, PA (PEM); and Thomas E. Starzl Transplantation Institute, Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA (TG, TES).

Copyright © 2005 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins

DOI: 10.1097/01.CCM.0000164541.12106.57

dispute. What remains controversial at this time is the diagnosis of this disorder (9). Circulating cortisol is bound to corticosteroid-binding globulin with <10% in the free bioavailable form. During acute illness, there is an acute decline in the concentration of corticosteroid-binding globulin as well as decreased binding affinity for cortisol, resulting in an increase in the free biologically active fraction of the hormone (10, 11). Corticosteroid-binding globulin is also reduced in liver disease (12). In addition, both the number and affinity of the intracellular glucocorticoid receptor may be down-regulated (tissue resistance) during acute illness (13–16). These data suggest that a serum cortisol (total) level may not be an accurate reflection of glucocorticoid activity at the cellular level. Notwithstanding these limitations, and in the absence of a readily available diagnostic test with greater specificity, we and others have demonstrated that the baseline serum cortisol level may be useful for diagnosing adrenal failure in the critically ill as well as being a prognostic marker (1, 17, 18). There appears to be general consensus that a random cortisol level (total) <15 µg/dL in an ICU patient is diagnostic of adrenal insufficiency (19). In addition, we contend that a level <20 µg/dL in a highly stressed patient (hypotensive, hypoxic) is abnormal (1, 5, 9).

The incidence of adrenal failure in septic shock has been reported to be as high as 61% (1). As sepsis and end-stage liver disease have a number of pathophysiologic mechanisms in common (endotoxemia, increased levels of proinflammatory mediators, decreased levels of apoprotein-A/high-density lipoprotein), we speculated that adrenal failure may be common in patients with end-stage liver disease (20–22). Indeed, in preliminary data we have observed a high incidence of adrenal failure in patients with end-stage liver disease and patients post-liver transplantation (23). Furthermore, we and others have noted an association between low levels of high-density lipoprotein (HDL) and adrenal failure (23, 24). Based on these observations, we currently routinely assess adrenal function in patients in our liver transplant ICU (LTICU).

## MATERIALS AND METHODS

This study was conducted in the 28-bed LTICU in Montefiore Hospital, University of Pittsburgh, Pittsburgh, PA. Patients who have undergone liver transplantation as well as pa-

tients with acute and chronic liver failure and patients with gastrointestinal bleeding are admitted to the LTICU. Based on preliminary data, all patients (except those concurrently receiving glucocorticoids) admitted to the LTICU from March 2002 underwent adrenal function testing (as outlined subsequently) (23). The University of Pittsburgh Medical Center has a comprehensive electronic medical record system that archives patient clinical and laboratory data in a number of separate database systems. An honest broker system was used to retrospectively extract clinical and laboratory data on patients who underwent adrenal function testing from March 2002 to March 2004. An honest broker system uses a third party not involved in the study to extract, collate, and de-identify data files. De-identified data files that included diagnoses, transplant status, medication, physiologic, and hemodynamic data from the ICU information system as well as laboratory data were linked to form a relational database. The laboratory data included cortisol levels, liver function tests, coagulation profile, serum electrolytes, and lipid profile. The data extracted from the ICU information system included the hourly hemodynamic profile, use and dosages of vasopressor agents (norepinephrine), and medications. The honest broker validated the extracted data on all patients included in the study from a review of the primary source (i.e., the patients' electronic medical records). Permission to perform this study was obtained from the University of Pittsburgh Institutional Review Board. During the study period, patients undergoing liver transplantation (cadaveric, living related, and non-heart-beating donors) were treated with a steroid-sparing regimen of immunosuppression. Patients received Campath (Alemtuzumab/anti-CD 52 monoclonal antibody, Berlix Laboratories, Richmond CA) or thymoglobulin. Patients included in this protocol received 1 g of methylprednisolone to limit/prevent the cytokine reactions following the infusion of the lymphoid-depleting agents. Postoperative immunosuppression included oral FK 506 (tacrolimus) started on postoperative day 1, with the dose adjusted to obtain a whole blood trough level between 6 and 12 µg/mL as clinical circumstances dictated. Glucocorticoids were not used in the postoperative immunosuppressive regimen unless biopsy-proven rejection was demonstrated.

As part of the routine diagnostic workup of patients admitted to the LTICU, adrenal function testing was performed as follows: a) In patients requiring vasopressor agents, hypotensive patients undergoing volume resuscitation, and patients with hypoxic respiratory failure, a random ("stress") cortisol level (total serum cortisol) was obtained on admission to the LTICU; b) patients with liver disease who did not meet these criteria (as listed previ-

ously) underwent a low-dose (1 µg) cosyntropin stimulation test within 24 hrs of admission to the LTICU (1); and c) in patients post-liver transplantation, serum "cortisol" levels were measured daily from the second postoperative day and a low-dose cosyntropin stimulation test was performed when the serum cortisol level was <15 µg/dL. Patients who did not meet our criteria for adrenal insufficiency (discussed subsequently) and who either had a low level of high-density lipoprotein (HDL) (<20 mg/dL) or had a progressive deterioration in liver function underwent repeat adrenal function testing.

The serum cortisol results were available within 24 hrs of testing (usual delay of approximately 6 hrs except on weekends). The decision to treat patients with stress doses of hydrocortisone was at the discretion of the treating intensivist and/or transplant surgeon. When treatment was initiated, a standard dose of 100 mg of hydrocortisone intravenously every 8 hrs was used; this was then weaned as clinically indicated.

The cortisol was measured by a competitive immunoassay using direct chemiluminescent technology (Centaur Analyzer, Bayer). Total cholesterol and triglyceride were measured by a colorimetric assay (cholesterol oxidase and lipase-glycerol-kinase, respectively), whereas the HDL was measured by dextran sulfate extraction followed by the cholesterol oxidase reaction (Vitros Analyzer, Ortho Clinical Diagnostics). Low-density lipoprotein was calculated from the total cholesterol, HDL, and triglyceride concentration.

**Data Analysis.** Patients who had received systemic glucocorticoids for >30 days during the previous year were excluded from this study. Similarly, patients who had received systemic glucocorticoids for between 10 and 30 days in the previous 6 months, as well as patients concurrently receiving glucocorticoids or who were treated with glucocorticoids during their hospital stay, were excluded from the study (5). For the purposes of this study, we used the following conservative criteria for the diagnosis of adrenal failure: a) a random (stress) cortisol level of <20 µg/dL in patients with hypoxemic respiratory failure, with hypotension (systolic blood pressure <90 mm Hg), or requiring vasopressor agents for blood pressure support (5, 9); and b) a random level of <15 µg/dL or a 30-min post-low-dose cosyntropin stimulation test level of <20 µg/dL in non-highly stressed patients (5, 9, 19). Patients were grouped as follows: a) chronic liver failure; b) fulminant hepatic failure; c) patient status post-orthotopic transplant receiving steroid-free immunosuppression; and d) patient status post-remote liver transplant (≥6 months).

**Statistical Analysis.** Summary statistics were compiled to allow a description of the patient population and the predefined subgroups. Statistical analysis was done using

NCSS 2004 (Kaysville, UT). Chi-square analysis was used to compare categorical data. Continuous data were compared using Student's *t*-test. The Mann-Whitney U test was used for data that failed tests of normality. Pearson's correlation coefficient was used to determine the association between the stress cortisol level and serum albumin. Unless otherwise stated, all data are expressed as mean  $\pm$  SD, with statistical significance declared for probability values  $\leq .05$ .

## RESULTS

During the period under study, 452 patients underwent adrenal function testing. Sixty-two patients had undergone small bowel, multivisceral, pancreas, or kidney transplant and were excluded. A further 50 patients had received systemic corticosteroids in the 12 months preceding admission to the LTICU or during their current admission and were excluded. The study cohort comprised 340 patients with a history of liver disease. Twenty-four (7%) patients had fulminant hepatic failure, 146 (43%) had chronic liver disease, 51 (15%) had undergone remote liver transplantation, and 119 (35%) had recently undergone liver transplantation under steroid-free immunosuppression. Of the patients with chronic liver disease, 76 (52%) had ethanolic liver disease, 23 (16%) had hepatitis C, and 14 (10%) had nonalcoholic steatohepatitis. The mean age of the cohort was  $53 \pm 11$  yrs (fulminant liver failure  $39 \pm 16$  yrs; all other  $54 \pm 10$  yrs). There were 175 (58%) male patients.

Two-hundred and forty-five (72%) patients met our criteria for adrenal insufficiency. Eight (33%) patients with fulminant hepatic failure, 97 (66%) patients with chronic liver disease, 31 (61%) patients with a remote history of liver transplantation, and 109 (92%) patients who had undergone recent liver transplantation (with a steroid-sparing immunosuppressive regimen) were diagnosed with adrenal insufficiency. The random serum cortisol levels as well as the liver function tests, serum creatinine concentration, and cholesterol levels in the patient subgroups stratified by adrenal function are listed in Table 1. The HDL level at the time of adrenal testing was the only variable predictive of adrenal insufficiency ( $p < .0001$ ). The correlation coefficient between the random serum cortisol level and the serum albumin concentration was .02 ( $r^2 = .0004$ ,  $p = .83$ ).

One hundred and sixty-six patients were being treated with pressor agents at

the time of adrenal testing. Seventy-five percent of the pressor-dependent patients had adrenal insufficiency. The baseline serum cortisol was  $16.8 \pm 12.6$   $\mu\text{g/dL}$  in the pressor-dependent patients compared with  $13.1 \pm 11.4$   $\mu\text{g/dL}$  (nonsignificant) in those patients not receiving pressor agents. In those patients receiving vasopressor agents at the time of adrenal testing, the baseline cortisol was  $10.0 \pm 4.8$   $\mu\text{g/dL}$  in those with adrenal insufficiency compared with  $35.6 \pm 21.2$   $\mu\text{g/dL}$  in those with normal adrenal function. The pressor requirements in the vasopressor-dependent patients at baseline and after 24 hrs of hydrocortisone treatment, and the comparable pressor requirements of those patients who did not receive hydrocortisone, stratified by adrenal function are listed in Table 2.

Of the 119 patients undergoing transplantation with steroid-free immunosuppression, 109 (92%) were diagnosed with adrenal insufficiency. Following the large intraoperative dose of methylprednisolone, the serum "cortisol" level fell to a nadir of  $9.2 \pm 5.2$   $\mu\text{g/dL}$ . Fifty-one patients demonstrated a rapid postoperative recovery of hepatic function along with an increase in HDL and cortisol levels, and the remaining 68 (57%) were treated with hydrocortisone. Eleven of these patients had depressed left ventricular function (low cardiac index, high systemic vascular resistance) as determined by invasive hemodynamic monitoring.

One hundred and forty-one patients (26.4%) died during their hospitalization, and the mortality rate for each subgroup was as follows: fulminant hepatic failure 30%, chronic liver disease 56%, remote liver transplantation 62%, and recent liver transplantation 18%. The mortality rate was 59% in the patients receiving vasopressor agents at the time of adrenal testing compared with 28% in the vasopressor independent patients ( $p < .001$ ). The baseline serum cortisol was  $18.8 \pm 16.2$   $\mu\text{g/dL}$  in the nonsurvivors compared with  $13.0 \pm 11.8$   $\mu\text{g/dL}$  in the survivors ( $p < .001$ ). The mortality rate was 38.8% for patients diagnosed with adrenal failure compared with 55.9% ( $p = .005$ ) with normal adrenal function. Of those patients with adrenal failure who were treated with glucocorticoids, the mortality rate was 26% compared with 46% ( $p = .002$ ) in those who were not treated with glucocorticoids. The mortality rate was 75% in those vasopressor-dependent patients who did not have adrenal failure.

## DISCUSSION

The main finding of our study was the surprisingly high incidence of adrenal failure in critically ill patients with liver disease, an entity for which we have coined the term "hepatoadrenal syndrome." Liver failure is well recognized to cause renal (hepatorenal syndrome) and pulmonary (hepatopulmonary syn-

Table 1. Clinical data and laboratory data grouped according to adrenal function

	Adrenal Failure (n = 245)	Normal Adrenal Function (n = 95)	<i>p</i> Value
Age, yrs	54 $\pm$ 11	52 $\pm$ 12	.32
MAP, mm Hg	76 $\pm$ 17	82 $\pm$ 17	.14
Mechanical ventilation, n (%)	179 (73)	73 (77)	.58
Vasopressor agent, n (%)	124 (51)	42 (44)	.54
Random cortisol, $\mu\text{g/dL}$			
All patients	9.3 $\pm$ 4.1	30.4 $\pm$ 19.5	<.001
Fulminant	11.6 $\pm$ 2.7	29.6 $\pm$ 9.6	<.001
Chronic LD	10.8 $\pm$ 4.1	32.6 $\pm$ 22.8	<.001
Transplant	8.0 $\pm$ 3.8	29.3 $\pm$ 20.0	<.001
SP, Transplant	8.3 $\pm$ 3.7	21.2 $\pm$ 8.1	<.001
Total bilirubin, $\mu\text{mol/L}$	9.5 $\pm$ 9.6	8.2 $\pm$ 9.4	.31
INR	1.7 $\pm$ 0.9	1.8 $\pm$ 0.8	.20
Serum albumin, g/L	2.3 $\pm$ 0.7	2.5 $\pm$ 0.6	.37
Serum creatinine, $\mu\text{mol/L}$	1.8 $\pm$ 3.7	2.0 $\pm$ 2.9	.56
LDL cholesterol, mg/dL	55.8 $\pm$ 32.5	65.8 $\pm$ 54.3	.38
HDL cholesterol, mg/dL	8.2 $\pm$ 7.6	28.4 $\pm$ 14.4	<.0001
Mortality, n (%)	95 (39)	53 (56)	.005
Treated with steroids	41/156 (26)	—	
Not treated with steroids	41/89 (46) <sup>a</sup>	—	

MAP, mean arterial pressure; LD, liver disease; SP, steroid-sparing immunosuppression; INR, international normalized ratio; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

<sup>a</sup> $p = .002$  for treatment with steroids compared with no steroids.

Table 2. Baseline and 24-hr norepinephrine dose stratified by adrenal function and treatment with hydrocortisone in vasopressor-dependent patients

	Baseline Norepinephrine Dose, $\mu\text{g}/\text{kg}/\text{min}$	24-Hr Norepinephrine Dose, $\mu\text{g}/\text{kg}/\text{min}$	<i>p</i> Value
Normal adrenal function			
All (n = 42)	0.17 $\pm$ 0.16	0.18 $\pm$ 0.15	.76
Treated with steroids (n = 11)	0.24 $\pm$ 0.15	0.28 $\pm$ 0.22	.62
No steroids (n = 31)	0.15 $\pm$ 0.19	0.14 $\pm$ 0.16	.82
Adrenal insufficiency			
Treated with steroids (n = 98)	0.17 $\pm$ 0.19	0.11 $\pm$ 0.18	.02
No steroids (n = 26)	0.07 $\pm$ 0.06	0.17 $\pm$ 0.24	.04

drome) disease; however, the association between liver failure and adrenal insufficiency has not been well studied. Singh and colleagues (25) reported a single case of adrenal insufficiency following liver transplantation. Harry and coworkers (26) demonstrated an abnormal high-dose cosyntropin stimulation test in 28 of 45 (62%) patients with acute liver failure. In a cohort of 38 "nonstressed" patients with end-stage liver disease, McDonald et al. (12) reported a 64% reduction in peak plasma cortisol following insulin-induced hypoglycemia and a 39% reduction following a high-dose cosyntropin test when compared with healthy controls.

In patients with adrenal insufficiency, the mortality rate was lower in those patients treated with glucocorticoids. Although this was a nonrandomized study, these data support the contention that treatment of critically ill patients with adrenal insufficiency (low baseline cortisol level) may improve outcome (5, 19). Furthermore, as noted previously by Anan and colleagues (18), a very high serum cortisol was associated with a high mortality rate. Hence, untreated patients with adrenal insufficiency (low cortisol levels) and patients with a very high cortisol level may have a high mortality rate.

In our study, we used a stress (random) cortisol level to diagnose adrenal insufficiency in highly stressed critically ill patients and performed a low-dose (1- $\mu\text{g}$ ) cosyntropin test in less severely stressed ICU patients (5, 9). We believe this to be the most practical approach to the diagnosis of adrenal insufficiency in critically ill patients at this time. Using this diagnostic approach, 72% of the patients studied had adrenal insufficiency. Some would argue that the low cortisol levels in patients with liver disease are nondiagnostic, particularly in hypoalbuminemic patients, and of little clinical significance (11, 27). We disagree with

this contention. Few would argue that a serum cortisol level of 8  $\mu\text{g}/\text{dL}$  in a critically ill ICU patient is normal. We found no correlation between the serum cortisol and serum-albumin levels, negating the postulate that low cortisol levels may merely be a function of low levels of cortisol binding globulin with normal free cortisol levels (11). Furthermore, the hemodynamic response to hydrocortisone (Table 2) provides compelling evidence to support the contention that low cortisol levels are clinically relevant and that treatment with hydrocortisone may be beneficial.

The association between low serum HDL levels and adrenal insufficiency that we observed in this study further supports the notion that liver disease may lead to impaired cortisol synthesis. The adrenal gland does not store cortisol; increased secretion arises due to increased synthesis under the control of adrenocorticotropin. Cholesterol is the principal precursor for steroid biosynthesis in steroidogenic tissue. At rest and during stress, about 80% of circulating cortisol is derived from plasma cholesterol, the remaining 20% being synthesized *in situ* from acetate and other precursors (28). Experimental studies suggest that HDL is the preferred lipoprotein source of steroidogenic substrate in the adrenal gland (29). Recently, mouse SR-B1 (scavenger receptor, class B, type 1) and its human homolog (CLA-1) have been identified as the high-affinity HDL receptors mediating selective cholesterol uptake (30–32). These receptors are expressed at high levels in the parenchymal cells of the liver and the steroidogenic cells of the adrenal glands, ovary, and testis (33). CLA-1 messenger RNA is highly expressed in human adrenals, and the accumulation of CLA-1 messenger RNA is regulated by adrenocorticotropin in primary cultures of normal human adrenocortical cells (34).

Apolipoprotein (apo)A-1, the major protein component of HDL, is synthesized principally by the liver and to a lesser degree in the intestine. Cicognani and coauthors (35) demonstrated a striking decrease in the level of serum HDL in patients with cirrhosis that was related to the severity of disease (Childs class). We therefore suggest that the low levels of HDL in patients with liver disease may be pathogenetically linked to the high incidence of adrenal failure in this group of patients. Indeed, van der Voort and colleagues (24) demonstrated that in critically ill patients, low HDL levels were associated with an attenuated response to cosyntropin. ApoA-1 has been reported to have a plasma half-life of 5.8 days (36). The half-life of apoA-1 may explain the lower incidence of adrenal failure in patients with acute as opposed to chronic liver failure and may also explain the delayed recovery of adrenal function after tolerogenic transplant. The very high incidence of adrenal insufficiency immediately after liver transplantation may also be ascribed to the fact that the apoA-1 factory (liver) is removed for a number of hours during surgery (anhepatic phase) as well as the fact that the transplanted liver suffers both an ischemic and reperfusion injury. However, the large dose of methylprednisolone given intraoperatively may have contributed to the blunting of the hypothalamic-pituitary-adrenal axis. Before the use of steroid-sparing immunosuppression, the standard immunosuppressive regimen included glucocorticoids, which serendipitously treated the concomitant adrenal insufficiency until both hepatic and adrenal function normalized.

Apart from low HDL levels and the reduced delivery of substrate for cortisol synthesis, other mechanisms may contribute to the pathophysiology of the hepatoadrenal syndrome. Patients with acute and chronic liver disease have increased levels of circulating endotoxin (lipopolysaccharide) and proinflammatory mediators such as tumor necrosis factor (TNF)- $\alpha$  (21, 22). It is postulated that intestinal bacterial overgrowth with increased bacterial translocation together with reduced Kupffer cell activity and porto-systemic shunting results in systemic endotoxemia with increased transcription of proinflammatory mediators (21, 22). In addition, our group has previously demonstrated that serum endotoxin levels increase further during the anhepatic phase of liver transplantation

**P**atients with liver failure and patients post-liver transplantation have an exceedingly high incidence of adrenal failure, which may be pathophysiologically related to low levels of high-density lipoprotein.

and remain high for several days following transplantation (37–39). Lipopolysaccharide as well as TNF- $\alpha$  may inhibit cortisol synthesis. Endotoxin has been shown to bind with high affinity to the HDL receptor (Cla-1) with subsequent internalization of the receptor (40, 41). Lipopolysaccharide may therefore limit the delivery of HDL cholesterol to the adrenal gland. Furthermore, TNF- $\alpha$  as well as interleukin-1 $\beta$  and interleukin-6 has been demonstrated to decrease hepatocyte synthesis and secretion of apoA-1 (42). In critically ill surgical patients, Gordon and colleagues (43) demonstrated an inverse relationship between interleukin-6 levels and apoA-1. In addition to its effects on apoA-1, TNF- $\alpha$  has been demonstrated to directly inhibit cortisol synthesis in a dose-dependent manner (44). TNF- $\alpha$  may also cause tissue resistance to cortisol by decreasing the number of glucocorticoid receptors or by up-regulating FK binding protein 51, which prevents the cortisol/cortisol receptor/heat shock protein-90 complex from moving into the nucleus (15, 16, 45–49).

Our study is limited by the fact that it is an observational, noninterventive study. Additional limitations include the fact that the free serum cortisol, cortisol binding globulin, and aldosterone levels were not measured. Nevertheless, using “conservative” diagnostic criteria, we report a surprisingly high incidence of adrenal insufficiency in a large cohort of critically ill patients with liver disease. We believe that treatment with hydrocortisone is indicated in hemodynamically unstable patients with the hepatoadrenal syndrome. In addition, hydrocortisone may be beneficial in patients with the hepatoadrenal syndrome with unex-

plained altered mental status or unexplained fever.

## ACKNOWLEDGMENTS

We are exceedingly grateful to Kyrie Gault for tireless help with this project and the outstanding care delivered by the LTICU nurses, which made this project possible.

## REFERENCES

1. Marik PE, Zaloga GP: Adrenal insufficiency during septic shock. *Crit Care Med* 2003; 31:141–145
2. Marik PE, Kiminyo K, Zaloga GP: Adrenal insufficiency in critically ill HIV infected patients. *Crit Care Med* 2002; 30:1267–1273
3. Kilger E, Weis F, Briegel J et al: Stress doses of hydrocortisone reduce severe systemic inflammatory response syndrome and improve early outcome in a risk group of patients after cardiac surgery. *Crit Care Med* 2003; 31:1068–1074
4. Dimopoulou I, Tsagarakis S, Kouyialia AT, et al: Hypothalamic-pituitary-adrenal axis dysfunction in critically ill patients with traumatic brain injury: Incidence, pathophysiology and relationship to vasopressor dependence and peripheral interleukin-6 levels. *Crit Care Med* 2004; 32:404–408
5. Marik PE, Zaloga GP: Adrenal insufficiency in the critically ill: A new look at an old problem. *Chest* 2002; 122:1784–1796
6. Hinshaw LB, Beller BK, Chang AC, et al: Corticosteroid/antibiotic treatment of adrenalectomized dogs challenged with lethal *E. coli*. *Circ Shock* 1985; 16:265–277
7. Darlington DN, Chew G, Ha T, et al: Corticosterone, but not glucose, treatment enables fasted adrenalectomized rats to survive moderate hemorrhage. *Endocrinology* 1990; 127:766–772
8. Annane D, Sebille V, Charpentier C, et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288: 862–871
9. Marik PE: Unraveling the mystery of adrenal failure in the critically ill. *Crit Care Med* 2004; 32:596–597
10. Beishuizen A, Thijs LG, Vermes I: Patterns of corticosteroid-binding globulin and free cortisol index during septic shock and multi-trauma. *Intensive Care Med* 2001; 27: 1584–1591
11. Hamrahian AH, Oseni TS, Arafah BM: Measurement of serum free cortisol in critically ill patients. *N Engl J Med* 2004; 350: 1629–1638
12. McDonald JA, Handelsman DJ, Dilworth P, et al: Hypothalamic-pituitary adrenal function in end-stage non-alcoholic liver disease. *J Gastroenterol Hepatol* 1993; 8:247–253
13. Sun X, Fischer DR, Pritts TA, et al: Expression and binding activity of the glucocorticoid receptor are upregulated in septic muscle. *Am J Physiol Regulatory Integrative Comp Physiol* 2002; 282:R509–R518
14. Liu DH, Su YP, Zhang W, et al: Changes in glucocorticoid and mineralocorticoid receptors of liver and kidney cytosols after pathologic stress and its regulation in rats. *Crit Care Med* 2002; 30:623–627
15. Ali M, Allen HR, Vedeckis WV, et al: Depletion of rat liver glucocorticoid receptor hormone-binding and its mRNA in sepsis. *Life Sci* 1991; 48:603–611
16. Scammell JC, Denny WB, Valentine DL, et al: Overexpression of the FK506-binding immunophilin FKBP51 is the common cause of glucocorticoid resistance in three New World primates. *Gen Comparat Endocrinol* 2001; 124:152–165
17. Rivers EP, Gaspari M, Abi Saad G, et al: Adrenal insufficiency in high-risk surgical ICU patients. *Chest* 2001; 119:889–896
18. Annane D, Sebille V, Troche G, et al: A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. *JAMA* 2000; 283:1038–1045
19. Cooper MD, Stewart PM: Corticosteroid insufficiency in acutely ill patients. *N Engl J Med* 2003; 348:727–734
20. van Leeuwen HJ, Heezius EC, Dallinga GM, et al: Lipoprotein metabolism in patients with severe sepsis. *Crit Care Med* 2003; 31: 1359–1366
21. Rasaratnam B, Kaye D, Jennings G, et al: The effect of selective intestinal decontamination on the hyperdynamic circulatory state in cirrhosis. A randomized trial. *Ann Intern Med* 2003; 139:186–193
22. Mookerjee RP, Sen S, Davies NA, et al: Tumour necrosis factor alpha is an important mediator of portal and systemic haemodynamic derangements in alcoholic hepatitis. *Gut* 2003; 52:1182–1187
23. Marik PE: Adrenal insufficiency: The link between low apolipoprotein A-1 levels and poor outcome in the critically ill? *Crit Care Med* 2004; 32:1977–1978
24. van der Voort PH, Gerritsen RT, Bakker AJ, et al: HDL-cholesterol level and cortisol response to synacthen in critically ill patients. *Intensive Care Med* 2003; 29:2199–2203
25. Singh N, Gayowski T, Marino IR, et al: Acute adrenal insufficiency in critically ill liver transplant recipients. Implications for diagnosis. *Transplantation* 1995; 59:1744–1745
26. Harry R, Auzinger G, Wendon J: The clinical importance of adrenal insufficiency in acute hepatic dysfunction. *Hepatology* 2002; 36: 395–402
27. Loriaux L: Glucocorticoid therapy in the intensive care unit. *N Engl J Med* 2004; 350: 1601–1602
28. Borkowski AJ, Levin S, Delcroix C, et al: Blood cholesterol and hydrocortisone production in man: Quantitative aspects of the utilization of circulating cholesterol by the adrenals at rest and under adrenocorticotropin stimulation. *J Clin Invest* 1967; 46: 797–811

29. Yaguchi H, Tsutsumi K, Shimono K, et al: Involvement of high density lipoprotein as substrate cholesterol for steroidogenesis by bovine adrenal fasciculo-reticularis cells. *Life Sci* 1998; 62:1387-1395
30. Acton S, Rigotti A, Landschultz KT, et al: Identification of scavenger receptor SR-BI as a high density lipoprotein receptor. *Science* 1996; 271:518-520
31. Calco D, Gomez-Coronado D, Lasuncion MA, et al: CLA-I is an 85-kD plasma membrane glycoprotein that acts as a high affinity receptor for both native (HDL,LDL, and VLDL) and modified (OxLDL and AcLDL) lipoproteins. *Arterioscler Thromb Vasc Biol* 1997; 17:2341-2349
32. de la Llera-Moya M, Connelly MA, Drazul D, et al: Scavenger receptor class B type 1 affects cholesterol homeostasis by magnifying cholesterol flux between cells and HDL. *J Lipid Res* 2001; 42:1969-1978
33. Liu J, Heikkila P, Meng QH, et al: Expression of low and high density lipoprotein receptor genes in human adrenals. *Eur J Endocrinol* 2000; 142:677-682
34. Liu J, Voutilainen R, Heikkila P, et al: Ribonucleic acid expression of the CLA-1 gene, a human homolog to mouse high density lipoprotein receptor SR-BI, in human adrenal tumors and cultured adrenal cells. *J Clin Endocrinol Metab* 1997; 82:2522-2527
35. Cicognani C, Malavolti M, Morselli-Labate AM, et al: Serum lipid and lipoprotein patterns in patients with liver cirrhosis and chronic active hepatitis. *Arch Intern Med* 1997; 157:792-796
36. Eisenberg S: High density lipoprotein metabolism. *J Lipid Res* 1984; 25:1017-1058
37. Yokoyama I, Gavaler JS, Todo S, et al: Endotoxemia is associated with renal dysfunction in liver transplantation recipients during the first postoperative week. *Hepato-Gastroenterol* 1995; 42:205-208
38. Miyata T, Todo S, Imventarza O, et al: Endogenous endotoxemia during orthotopic liver transplantation in dogs. *Transplant Proc* 1989; 21:3861-3862
39. Yokoyama I, Todo S, Miyata T, et al: Endotoxemia and human liver transplantation. *Transplant Proc* 1989; 21:3833-3841
40. Vishnyakova TG, Bocharov AV, Baranova IN, et al: Binding and internalization of lipopolysaccharide by Cla-1, a human orthologue of rodent scavenger receptor B1. *J Biol Chem* 2003; 278:22771-22780
41. Baranova I, Vishnyakova T, Bocharov A, et al: Lipopolysaccharide down regulates both scavenger receptor B1 and ATP binding cassette transporter A1 in RAW cells. *Infect Immun* 2002; 70:2995-3003
42. Ettinger WH, Varma VK, Sorci-Thomas M, et al: Cytokines decrease apolipoprotein accumulation in medium from Hep G2 cells. *Arterioscler Thromb* 1994; 14:8-13
43. Gordon BR, Parker TS, Levine DM, et al: Relationship of hypolipidemia to cytokine concentrations and outcomes in critically ill surgical patients. *Crit Care Med* 2001; 29:1563-1568
44. Jaattela M, Ilvesmaki V, Voutilainen R, et al: Tumor necrosis factor as a potent inhibitor of adrenocorticotropin-induced cortisol production and steroidogenic P450 enzyme gene expression in cultured human fetal adrenal cells. *Endocrinology* 1991; 128:623-629
45. Molijn GJ, Spek JJ, van Uffelen JC, et al: Differential adaptation of glucocorticoid sensitivity of peripheral blood mononuclear leukocytes in patients with sepsis or septic shock. *J Clin Endocrinol Metab* 1995; 80:1799-1803
46. Liu LY, Sun B, Tian Y, et al: Changes of pulmonary glucocorticoid receptor and phospholipase A2 in sheep with acute lung injury after high dose endotoxin infusion. *Am Rev Respir Dis* 1993; 148:878-881
47. Molijn GJ, Koper JW, van Uffelen CJ, et al: Temperature-induced down-regulation of the glucocorticoid receptor in peripheral blood mononuclear leucocyte in patients with sepsis or septic shock. *Clin Endocrinol* 1995; 43:197-203
48. Melby JC, Spink WW: Comparative studies of adrenal cortisol function and cortisol metabolism in healthy adults and in patients with septic shock due to infection. *J Clin Invest* 1958; 37:1791-1798
49. Davies TH, Ning YM, Sanchez ER: A new first step in activation of steroid receptors: Hormone-induced switching of FKBP51 and FKBP52 immunophilins. *J Biol Chem* 2002; 277:4597-4600