Original Article

THAI J GASTROENTEROL 2007
*Vol. 8 No. 3*
Sept. - Dec. 2007
109

# The Adrenal Insufficiency and Cortisol Response after ACTH Stimulation Test in Non-highly Stressed Patients with Cirrhosis

***Sanpajit T, M.D.***
***Chutaputti A, M.D.***

## ABSTRACT

***Objective:*** Adrenal insufficiency is common in critically ill patients, particularly those with septic shock. Patient with liver failure and sepsis shared many clinical features, including hyperdynamic circulation. In critically ill patients, adrenal insufficiency is associated with hemodynamic instability and poor outcome. This study examined the functional adrenal reserve by using ACTH stimulation test in fifteen non-highly stressed patients with cirrhosis.

***Patients and Methods:*** A low-dose (1 μg) ACTH (corticotropin) test was done in non-highly stressed patients with cirrhosis who were admitted due to various causes within 5 days of admission.

***Results:*** The result of ACTH stimulation test of fifteen patients revealed that 6/15 (40%) patients were classified as adrenal insufficiency reserve and 9/15 (60%) were indicated as normal adrenal function. Among those with impaired adrenal reserves five of six patients displayed basal and stimulated cortisol values of lower than 20 μg/dL. The LDL-cholesterol level at the time of adrenal testing was the variable predictive of adrenal insufficiency ($p = 0.035$).

The baseline basal cortisol were $16.4 \pm 5.5$ in the Child-Pugh score A and B compared with $19.1 \pm 6.5$ in the Child-Pugh score C ($p = 0.4$). The peak serum cortisol were $22.7 \pm 4.0$ in the Child-Pugh score A and B compared with $21.4 \pm 4.0$ in the Child-Pugh score C ($p = 0.69$). The increment in cortisol levels in the Child-Pugh score A and B ($6.4 \pm 2.5$ μg/dL) was significantly higher than in the Child-Pugh score C ($2.3 \pm 1.8$ μg/dL) ($p = 0.003$)

***Conclusions:*** Adrenal insufficiency assessed by the ACTH stimulation test is common in non-highly stressed patients with cirrhosis. It is more frequent in those with severe liver disease.

**Key words :** Adrenal insufficiency, Cirrhosis, Lipoproteins

*[Thai J Gastroenterol 2007; 8(3): 109-14]*

***Address for Correspondence:*** *Anuchit Chutaputti, M.D., Division of Digestive and Liver Disease, Department of Medicine, Phramongkutklao Hospital, Bangkok 10400, Thailand.*
*Division of Digestive and Liver Disease, Department of Medicine, Phramongkutklao Hospital, Bangkok, Thailand.*

## BACKGROUND

Patients with cirrhosis are susceptible to bacterial infection[1,2], which can result in hemodynamic instability, organ dysfunction, hepatic encephalopathy, and a decreased survival rate.

Severe sepsis and septic shock is frequently associated with adrenal insufficiency, which lead to a poor prognosis.

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[3-5], this study postulated that adrenal failure may be common in patients with liver disease.

Studies have shown that the liver is the primary site of metabolism of adrenal steroid hormone and synthesis of cholesterol, which is the major precursor of steroid. 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.[6] Experimental studies suggest that HDL-C, which is synthesized principally by the liver and to a lesser degree in the intestine, is the preferred lipoprotein source of steroidogenic substrate in the adrenal gland.[7] Therefore, preexisting liver dysfunction may further disturb the activation of the HPA axis during stress.

Few data support high rate of adrenal insufficiency in critically ill cirrhosis[18,19] and one study found benefit of corticosteroid administration on survival of cirrhotic patients with septic shock.

However, there is no study concerning the association between non-critically ill stressed cirrhotic patients and adrenal function.

This study aimed to examine the adrenal response to the ACTH stimulation test and the relationship between adrenal function and various patients parameter that help to predict adrenal insufficiency.

## PATIENTS AND METHODS

This study was conducted in fifteen patients with non-highly stressed cirrhosis who was admitted to Phramongkutklao Hospital and College of Medicine from February 2006 until February 2007 from various causes.

The clinical diagnosis of hepatic cirrhosis was made based on the presence of esophageal varices or ascites with no other cause, along with an unequivocal image on sonography or computed tomography.

Patients who admitted to medicine ward, adrenal function testing was performed as follows: patients with liver disease who met these inclusion criteria underwent an adrenal function testing, a low-dose (1 μg) ACTH (cosyntropin) stimulation test[8] within 5 days of admission.

In this test, 0.01 mg ACTH (cosyntropin) was given intravenously, and plasma cortisol levels were measured before and 30 and 60 minutes later. The peak cortisol level was defined as the highest cortisol level obtained after cosyntropin administration, either at 30 or 60 minutes. The increment was calculated as the difference between peak and baseline cortisol levels.

### Criteria for the diagnosis of adrenal insufficiency

a) Random plasma cortisol concentration of less than 15 μg/dL or b) a stimulated cortisol concentration below 20 μg/dL indicates adrenal insufficiency under stress conditions.[9-11]

The severity of liver disease on the day of the ACTH stimulation test was graded by the Child-Pugh system.[12]

Renal dysfunction was defined as a serum creatinine level of greater than 1.5 mg/dL on the day of the ACTH stimulation test. The cut-off value of 1.5 mg/dL was based on previous investigations showing glomerular filtration rate is distinctly decreased in patients with cirrhosis and a serum creatinine higher than this level.[13] Furthermore, this is also the cutoff value used to define hepatorenal syndrome.[14]

Inclusion criteria were as follows: cirrhotic patients aged 18-80 years admitted with hematemesis and/or melena, sepsis, spontaneous bacterial peritonitis or 2/3 of clinical SIRS; Temperature >38 ˚C or <36 ˚C, heart rate > 90 beats per minute, and respiratory rate >20 BPM.

Exclusion criteria were as follows: patients in critically ill state with hypoxemic respiratory failure or hypotension (systolic BP <90 mmHg or requiring vasopressor agents for blood pressure support), 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 10 to 30 days in the previous 6 months, as well as patients currently receiving glucocorticoids or who were treated with glucocorticoids

during their hospital stay, were excluded from the study. Patients with known HIV positive or malignancy, were excluded from study.

Patient's clinical and laboratory data including sex, age, causes of cirrhosis and causes of admission was collected. Routine biochemical analysis, hematological, lipoprotein profile, and coagulation profiles were obtained on the day of ACTH stimulation test. The plasma cortisol was measured by a competitive immunoassay using direct chemiluminescent technology (Cobas test, Roche). The values range between 0.018 and 63 μg/dL.

## Statistical Analysis

Descriptive statistics are expressed as mean ± SD. All variables were tested for normal distribution using the Kolmogorov-Smirnov test. The independent Student t test was used to compare the means of continuous variables and the normal distribution data.

Otherwise, the Mann-Whitney U test was used. Categorical data were tested using the chi-squared ($\chi^2$) test. Risk factors were assessed using univariate analysis, and variables that were statistically significant in the univariate analysis were included in the multivariate analysis by applying a multiple logistic stepwise.

The correlation between the results of the ACTH stimulation test and the disease severity scores was analyzed with linear regression procedure to obtain independent risk factors using the Pearson method. The statistical significance was considered when p value was less than 0.05.

# Results

## Patient Characteristics

Fifteen non-highly stressed patients with cirrhosis were reported in this investigation. Their biological profiles on the day of ACTH stimulation test are given in Table 1. The mean patient's age was 54 years. There were 13 men (86%) and 2 women (14%). The causes of liver cirrhosis included alcohol (n = 14), HBV plus alcohol (n = 1), HCV plus alcohol in (n = 1), and cryptogenic cirrhosis (n = 1).

Overall causes of hospital admission were upper

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

| | All patients (n = 15) | Adrenal insufficiency (n = 6) | Normal adrenal function (n = 9) | P-value |
|---|---|---|---|---|
| Age (yrs) | 54.1 ± 14.1 | 50.6 ± 18.6 | 56.4 ± 10.9 | 0.458 |
| Albumin (g/dL) | 2.5 ± 0.5 | 2.2 ± 0.6 | 2.7 ± 0.4 | 0.068 |
| Globulin (g/dL) | 3.9 ± 0.9 | 3.5 ± 1.0 | 4.1 ± 0.9 | 0.284 |
| AST (U/L) | 132.3 ± 83.2 | 102.5 ± 57.5 | 152.2 ± 94.5 | 0.272 |
| ALT (U/L) | 55.3 ± 36.3 | 50.7 ± 54.8 | 58.4 ± 20.1 | 0.700 |
| Total bilirubin (mg/dl) | 11.1 ± 10.4 | 12.4 ± 10.4 | 10.3 ± 11.0 | 0.716 |
| Alkaline phosphatase (mg/dL) | 145.0 ± 80.1 | 101.8 ± 22.8 | 173.8 ± 92.6 | 0.088 |
| PT (INR) | 1.7 ± 0.7 | 1.7 ± 0.3 | 1.7 ± 0.9 | 0.922 |
| Child-turcot | 9.8 ± 2.8 | 11.2 ± 3.0 | 8.9 ± 2.3 | 0.120 |
| Hematocrit | 29.8 ± 3.4 | 26.9 ± 3.3 | 30.1 ± 2.9 | 0.063 |
| WBC | 8933.3 ± 4626.0 | 9000.0 ± 4694.3 | 8888.9 ± 4865.3 | 0.966 |
| Total cholesterol (mg/dL) | 124.8 ± 64.0 | 83.6 ± 48.0 | 150.5 ± 61.2 | 0.063 |
| LDL cholesterol (mg/dL) | 69.7 ± 54.2 | 31.0 ± 37.8 | 93.9 ± 49.8 | 0.035 |
| HDL cholesterol (mg/dL) | 22.0 ± 17.4 | 17.0 ± 16.6 | 25.1 ± 18.2 | 0.436 |
| Triglyceride (mg/dL) | 103.4 ± 41.1 | 81.4 ± 28.4 | 117.1 ± 43.3 | 0.133 |
| Plasma BUN (mg/dL) | 23.0 ± 24.5 | 26.2 ± 33.2 | 21.2 ± 20.4 | 0.733 |
| Plasma Cr (mg/dL) | 1.4 ± 1.0 | 1.7 ± 1.3 | 1.3 ± 0.9 | 0.510 |
| Basal cortisol (μg/dL) | 18.0 ± 6.1 | 12.7 ± 2.6 | 21.6 ± 5.0 | 0.002 |
| Peak cortisol (μg/dL) | 22.0 ± 5.9 | 16.3 ± 2.8 | 25.7 ± 4.1 | <0.001 |
| Increment of cortisol (μg/dL) | 3.9 ± 2.9 | 3.7 ± 4.0 | 4.1 ± 2.1 | 0.767 |

gastrointestinal bleeding (n = 6), acute cholecystitis (n = 1), pneumonia (n = 1), sepsis and hepatic encephalopathy without identified source of infection (n = 4), empyema thoracis (n = 1), severe alcoholic hepatitis (n = 1), and necrotizing fasciitis (n = 1).

The result of ACTH stimulation test of fifteen patients revealed 6/15 (40%) patients were classified as adrenal insufficiency reserve and 9/15 (60%) were indicated as normal adrenal function. Among those with impaired adrenal reserve, five of six patients displayed basal and stimulated cortisol values of lower than 20 μg/dL.

There were no significant differences in baseline characteristics of all patients. All patients were normotensive and did not require artificial ventilation.

Mean Child-Pugh scores were 11.2 ± 3.0 and 8.9 ± 2.3 in the impaired adrenal reserve and the normal adrenal reserve groups, respectively (P = 0.12)

## Range of ACTH results

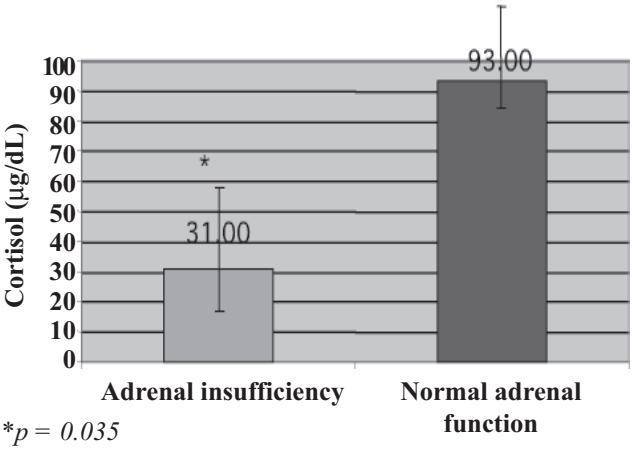
Mean values of basal cortisol were 12.7 ± 2.6 and 21.6 ± 5.0 μg/dL in the impaired adrenal reserve and the normal adrenal function, respectively (p = 0.002). Mean values of peak cortisol were 16.3 ± 2.8 in the impaired adrenal reserve s and 25.7 ± 4 in the normal adrenal function (p ≤0.0001). Mean values of incremented cortisol were 3.65 ± 4 in the impaired adrenal reserve s and 4.12 ± 2.18 in the normal adrenal function (p = 0.76).

Mean values of basal cortisol were 16.4 ± 5.5 in the Child-Pugh score A and B and 19.1 ± 6.5 in the Child-Pugh score C (p = 0.4 ). Mean values of peak cortisol were 22.7 ± 4.0 in the Child-Pugh score A and B and 21.4 ± 4.0 in the Child-Pugh score C (p = 0.69). Mean values of incremented cortisol were 6.4 ± 2.5 in the Child-Pugh score A and B and 2.3 ± 1.8 in the Child-Pugh score C (p = 0.003) (Figure 1).

Mean values of serum LDL-C were 31.0 ± 37.8 impaired adrenal reserve and 93.9 ± 49.8 in the normal adrenal function (p = 0.035) (Figure 2).

No significant different for baseline cortisol, peak cortisol, and increment in cortisol compared between s with serum HDL-C cut of values at 30 mg/dl[23] (Figure 3).

No different in renal dysfunction in both adrenal insufficiency and normal adrenal function (1.7 ± 1.3, 1.3 ± 0.9, P = 0.5)




*p = 0.035

**Figure 2** Mean values of serum LDL cholesterol in patients with adrenal insufficiency compared with normal adrenal function

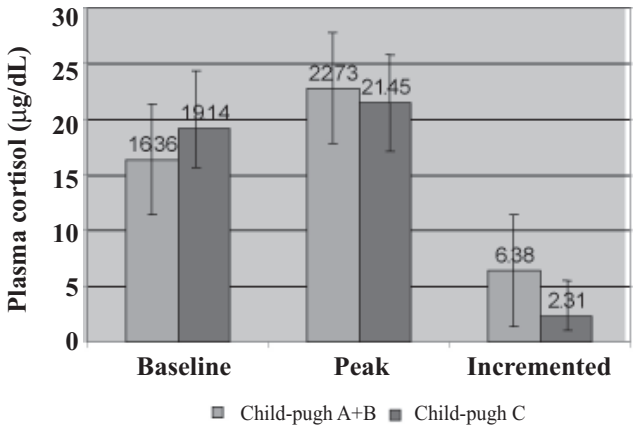



**Figure 1** Results of ACTH stimulation test in cirrhotic patients of Child-pugh A and B compared Child-pugh C

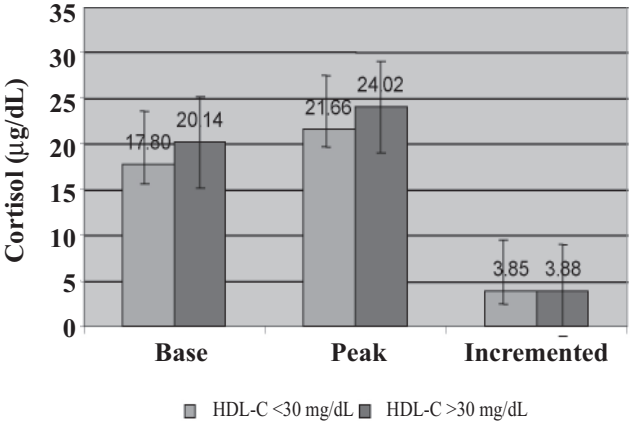



**Figure 3** Mean baseline cortisol peak cortisol and increment cortisol after ACTH stimulation test according to serum HDL cholesterol level

## DISCUSSION

The main finding of this study was that the incidence of adrenal failure was 40% in non-highly stressed patients with liver cirrhosis especially those of advanced stage. There was a negative correlation between the cortisol increment after ACTH stimulation test and Child-Pugh scores, suggesting that adrenal dysfunction is inversely related to liver function reserve. In this study, LDL-C is also found to be a predicting factor for adrenal dysfunction in addition to the degree of liver failure. Liver failure is well recognized to cause renal and pulmonary disease; however, the association between liver failure and adrenal insufficiency has not been well studied.

Harry and coworkers[15] demonstrated an abnormal high dose ACTH (cosyntropin) stimulation test in 28 of 45 (62%) patients with acute liver failure.

The study of McDonald, *et al*.[16] in 38 non-stressed end-stage liver disease patients found 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.

According to Paul E Marik[17] study in 340 patients with liver disease, it was reported that 245 (72%) were diagnosed with adrenal insufficiency. Among these included 8 (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.

Ming Hung Tsai[18] reported that adrenal insufficiency occurred in 51.48% of critically ill patients with cirrhosis and severe sepsis. The cumulative rates of survival at 90 days were 15.3% and 63.2% for the adrenal insufficiency and normal adrenal functions, respectively ($P < 0.0001$). The hospital survivors had a higher cortisol response to corticotropin ($16.2 \pm 8.0$ vs. $8.5 \pm 5.9$ μg/dL, $P < 0.001$). The cortisol response to corticotropin was inversely correlated with various disease severity, Model for End-Stage Liver Disease, and Child-Pugh scores. Acute physiology, age, chronic health evaluation III score, and cortisol increment were independent factors to predict hospital mortality.

Fernandez J[19] prospectively evaluated the effects of steroids on shock resolution and hospital survival in a series of 25 consecutive patients with cirrhosis and septic shock. It was found that adrenal dysfunction was frequent in patients with advanced cirrhosis (Child C: 76% vs. Child B: 25%, $P = 0.08$) and resolution of septic shock (96% vs. 58%, $P = 0.001$), survival in the intensive care unit (68% vs. 38%, $P = 0.03$), and hospital survival (64% vs. 32%, $P = 0.003$) were significantly higher in those who received corticosteroid.

The slightly low serum HDL levels and significantly low serum LDL in the adrenal insufficiency observed in this study further support the notion that liver disease may lead to impaired cortisol synthesis.

In Paul E Marik[17] study found the HDL level at the time of adrenal testing was the only variable predictive of adrenal insufficiency ($p < 0.0001$).

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[20]. Experimental studies suggest that HDL is the preferred lipoprotein source of steroidogenic substrate in the adrenal gland[21].

Cicognani and coauthor[20] demonstrated a striking decrease in the level of serum HDL in patients with cirrhosis that was related to the severity of disease (Childs class). Habib A and coauthors[22] found that HDL cholesterol in noncholestatic cirrhotic patients was a liver function test and an indicator of prognosis. HDL cholesterol below 30 mg/dL in cirrhotic patients was associated with 3.4-fold increase in the hazard ratio for cirrhotic death or transplantation at 6 or 12 months.

Van der Voort and coauthors[23] demonstrated that in critically ill patients, low HDL levels were associated with an attenuated response to cosyntropin.

Several mechanisms may be responsible for the impaired adrenal function. An increased level of cytokines has been shown to be a major determinant of the magnitude of cortisol response to corticotrophin[25]. Additionally, coagulopathy, which is common in patients with cirrhosis, may lead to adrenal hemorrhage and adrenal insufficiency[26]. Finally impaired synthesis of cholesterol, the most important precursor of steroid hormones in patients with cirrhosis and sepsis, may have an impact on the cortisol response.

Additional limitations include the free serum cor-

tisol, cortisol binding globulin, and aldosterone levels were not measured. Some would argue that the low cortisol levels in patients with liver disease are non-diagnostic, particularly in hypoalbuminemic patients, and therefore measureing serum free cortisol is needed[27].

In this study, a low dose, of 1.0 μg ACTH stimulation test, was used to routinely screen adrenal insufficiency for critically ill patients. It has long been known that the dose of cosyntropin used in the standard ACTH stimulation test-250 μg-is a large overdose. For this reason and to improve the test's sensitivity in detecting partial secondary or tertiary adrenal insufficiency, Dickstein, *et al*.[8] introduced the low-dose ACTH stimulation test with 1.0 μg of intravenous. Mayenkenecht J, *et al*.[27] showed that the cortisol level at 30 minutes during the standard ACTH stimulation test is similar to the result during the low dose test.

Some authors have reported that the low-dose test is more sensitive in detecting partial adrenal insufficiency in critically ill patients and they have suggested that more researches are needed[27]. Some clinicians have raised a concern about the possibility of error in administration in the low-dose test, since a 1.0 μg cosyntropin vial is not commercially available.

## REFERENCES

1. Wiest R, Garcia-Tsao G. Bacterial translocation in cirrhosis. Hepatology 2005; 41: 422-33.
2. Fernandez J, Navasa M, Gomez J, *et al*. Bacterial infection in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. Hepatology 2002; 35: 140-8.
3. van Leeuwen HJ, Heezius EC, Dallinga GM, *et al*. Lipoprotein metabolism in patients with severe sepsis. Crit Care Med 2003; 31: 1359-66.
4. 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;139:186-93.
5. 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: 1182-7.
6. 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.
7. 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: 1387-95.
8. Dickstein G, Shechner C, Nicholson WE, *et al*. Adrenocorticotropin stimulation test: effects of basal cortisol level, time of day, and suggested new sensitive low dose test. J Clin Endocrinol Metab 1991; 72: 773-8.
9. Marik PE, Zaloga GP. Adrenal insufficiency in the critically ill: A new look at an old problem. Chest 2002; 122: 1784-96.
10. Marik PE. Unraveling the mystery of adrenal failure in the critically ill. Crit Care Med 2004; 32: 596-7.
11. Cooper MD, Stewart PM. Corticosteroid insufficiency in acutely ill patients. N Engl J Med 2003; 348: 727-34.
12. Pugh RN, Murray-Lyon IM, Dawson JL, *et al*. Transection of the esophagus in the bleeding esophageal varices. Br J Surg 1973; 60: 648-52.
13. Bataller R, Gines P, Guevara M, *et al*. Hepatorenal syndrome. Semin Liver Dis 1997;17:233-47.
14. Arroyo V, Gines P, Gerbes A, *et al*. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. Hepatology 1996; 23: 164-76.
15. Harry R, Auzinger G, Wendon J. The clinical importance of adrenal insufficiency in acute hepatic dysfunction. Hepatology 2002; 36: 395-402.
16. McDonald JA, Handelsman DJ, Dilworth P, *et al*. Hypothalamic-pituitary adrenal function in end-stage non-alcoholic liver disease. J Gastroenterol Hepatol 1993; 8: 247-53.
17. Marik PE. The hepatoadrenal syndrome: a common yet unrecognized clinical condition. Crit Care Med 2005; 33: 1254-9.
18. Tsai MH, Peng YS, Chen YC, *et al*. Adrenal insufficiency in patients with cirrhosis, severe sepsis and septic shock. Hepatology 2006; 43: 673-81.
19. Fernandez 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: 1288-95.
20. 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: 1387-95.
21. 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: 792-6.
22. Habib A, Mihas AA, Abou-Assi SG, *et al*. High-density lipoprotein cholesterol as an indicator of liver function and prognosis in noncholestalic cirrhotics. Clin Gastroenterol Hepatol 2005; 3: 286-91.
23. 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: 2199-203.
24. Mastorakos G, Chrousos GP, Weber JS. Recombinant interleukin-6 activates the hypothalamic-pituitary-adrenal axis in humans. J Clin Endocrinol Metab 1993; 77: 1690-4.
25. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. N Engl J Med 2003; 348: 727-34.
26. Hamrahian AH, Oseni TS, Arafah BM. Measurement of serum free cortisol in critically ill patients. N Engl J Med 2004; 350: 1629-38.
27. Mayenknecht J, Diederich S, Bahr V, *et al*. Comparison of low and high dose corticotropin stimulation tests in patients with pituitary disease. J Clin Endocrinol Metab 1998; 83: 1558-62.