The Absence of Adrenal Gland Enlargement during Septic Shock Predicts Mortality
A Computed Tomography Study of 239 Patients

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ABSTRACT

Background: Assessment and management of septic shock associated adrenal function remain controversial. The aim of this study was to explore the prognostic value of adrenal gland volume in adults with septic shock.

Methods: A short cosyntropin test and determination of adrenal volume by computed tomography were performed within 48 h of shock in patients with septic shock (n = 184) and in 2 control groups: 40 ambulatory patients and 15 nonseptic critically ill patients. The primary endpoint was intensive care unit mortality.

Results: At intensive care unit discharge, 59 patients with septic shock died. Adrenal volume was 12.5 cm³ [95% CI, 11.3–13.3] and 8 cm³ [95% CI, 6.8–10.1] in the nonseptic group (P < 0.05 with both septic cohorts) and 7.2 cm³ [95% CI, 6.3–8.5] in the ambulatory patient group (P < 0.05 in patients with septic shock). In patients with septic shock, adrenal volume less than 10 cm³ was associated with higher 28-day mortality rates with an area under the receiver operating curve of 0.84 [95% CI, 0.78–0.89]. Adrenal volume above 10 cm³ was an independent predictor of intensive care unit survival (hazard ratio = 0.014; 95% CI [0.004–0.335]).

Conclusion: A total adrenal gland volume less than 10 cm³ during septic shock was associated in univariate and multivariate analysis with mortality at day 28 in patients with septic shock. Whether adrenal gland volume can be a surrogate of adrenal gland function and used to guide hydrocor-

What We Already Know about This Topic
• The use of low dose steroids in patients with septic shock appears to improve mortality in subgroups of patients, but identification of patients who will benefit is difficult

What This Article Tells Us That Is New
• Computed tomography identification of adrenal gland volume may be helpful in identifying septic patients who might benefit from steroid therapy

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This article is accompanied by an Editorial View. Please see: Ekermann M, Schmidt U: Does adrenal size matter? Anesthesiology 2011; 115:223–5.
tisone therapy in septic shock patients needs to be further investigated.

BUNDLE therapy of septic shock, a disease with a mortality rate ranging from 30 to 50%,1–5 may include low-dose steroid.6–11 Indeed, independent factors of poor outcome include hypothalamic–pituitary–adrenal axis impairment resulting in critical illness-related corticosteroid insufficiency.8,9,11–16 Several studies have reported that daily treatment of certain patient subgroups presenting with septic shock with a prolonged (5–7 days) low dose (200–300 mg) of hydrocortisone offers potential benefits of reduced intensive care unit (ICU) length of stay or mortality.6,8,13,14,17 However, one multiple center study failed to confirm the effect of such treatment on mortality18 and the recent international consensus conference on critical illness-related corticosteroid insufficiency management in the ICU setting recommended considering low-dose steroid therapy only for vasopressor-dependent patients with septic shock.15 Key patient selection criteria may include diagnosis of impaired hypothalamic–pituitary–adrenal axis or a poor response to endogenous steroids.10,11 However, currently there is no absolute plasma cortisol concentration that distinguishes adequate and inadequate adrenal response.11,12,15 More sophisticated tests are not routinely performed and are therefore not recommended to guide treatment.11,15 In a pilot study using computed tomography (CT), we previously reported an increased adrenal gland volume, unrelated to adrenal hemorrhage, in patients with septic shock.19,20

The aim of the current study was to describe adrenal gland volume and its accuracy as a prognostic value in septic shock. We hypothesized that the absence of adrenal gland volume enlargement could be associated with mortality in patients with septic shock.

Materials and Methods

Study Design

This study was conducted from January 2005 to January 2009 in a 16-bed medical–surgical ICU. In accordance with French law, informed consent was not mandatory, given that this observational study did not modify current diagnostic or therapeutic strategies. The study design is represented in figure 1. Our study followed the Standards for Reporting Diagnostic Accuracy (STARD) recommendations concerning the report of studies of diagnostic accuracy.21,22 This study was approved by the Montpellier University Hospital Institutional Review Board, Montpellier, France.

Study Population

Septic Shock

Consecutive patients were included if they presented with septic shock23 and had been explored, within the first 48 h of shock, with an abdominal CT and measurements of basal and response plasma cortisol concentrations, before and after a short cosyntropin test with 250 µg cosyntropin intravenous injection (fig. 1). In our ICU, it is part of the standard of care to order a body CT scan in the early phase of septic shock to rule out any surgical or interventional radiology treatment for source control but also to assess the initial pattern of an acute lung injury. Thus, more than 70% of the

![Fig. 1](https://example.com/fig1.png)

**Fig. 1.** Design of the study. Cosyntropin test was done at the time of the shock onset. Hydrocortisone treatment was started once the test had been done. To be included in the study, patients needed to be explored with an abdominal computed tomography (CT) scan within the first 48 h of the shock onset.
CT scans performed combine both lung and abdominal CT. CT may be delayed or not performed when the cause of sepsis is obvious and/or its risks overwhelm its benefits. In this study, patients younger than 18 yr, who are pregnant, with pituitary or adrenal disease, or with a history of steroid use were excluded.

During the study period, septic shock management followed the 2004 Surviving Sepsis Campaign guidelines. All patients were treated with intravenous hydrocortisone, 50 mg four times a day, during 5–7 days regardless of the result of the cosyntropin stimulation test.

Control Subjects
Patients without sepsis admitted to the ICU (ICU nonseptic group, n = 15) and 40 consecutive ambulatory patients who had a normal virtual colonoscopy served as control subjects (control group, n = 40).

Measurements and Clinical Evaluation
We collected data for sex, age, date, reason for ICU admission, and Simplified Acute Physiology Score II for all ICU patients (tables 1 and 2).

Laboratory Variables
No laboratory variables were collected in the control group. In the ICU groups, cortisol was assayed at baseline and 60 min after cosyntropin stimulation. Plasma cortisol concentration was measured using immunoradiology assay (SP2100, Beckman Coulter SAS, Roissy, France). Response to cosyntropin stimulation was considered to be positive if T60-T0 was above 9 g/dl. In the septic shock group, we also recorded serum protein and albumin concentrations and the results of the blood cultures as well as plasma creatinine, bilirubin, lactate, platelets, leukocytes, hemoglobin, and procalcitonin (tables 1, 2).

CT Scan of the Adrenal Glands
Semiautomatic measurement of the adrenal glands by CT scan was performed as previously described by our group in a pilot study. The measurement technique was reproducible as we reported in the pilot study a concordance correlation coefficient between the radiologist and the intensivist of 0.87 (95% CI, [0.76–0.93]) for the total gland volume measurement. The adrenal contour was semiautomatically traced by one radiologist (SN), who was unaware of the clinical status of the subjects, every 3-mm section. The scanner software automatically calculated the adrenal volume by summing the area on each slice. Adrenal gland volume between control and septic shock groups were compared.

Table 1. Characteristics of the 239 Studied Patients (184 Septic Shock, 15 Nonseptic ICU, and 40 Control Patients)

<table>
<thead>
<tr>
<th></th>
<th>Septic Shock Group (n = 184)</th>
<th>Nonseptic ICU Group (n = 15)</th>
<th>Control Group (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>64 [61–67]</td>
<td>60 [41–74]</td>
<td>57 [53–61]*</td>
</tr>
<tr>
<td>Male sex</td>
<td>128 (70)</td>
<td>10 (67)</td>
<td>22 (55)</td>
</tr>
<tr>
<td>Type of admission</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Medical</td>
<td>85 (46)</td>
<td>6 (40)</td>
<td>NA</td>
</tr>
<tr>
<td>Surgical</td>
<td>99 (54)</td>
<td>9 (60)</td>
<td>NA</td>
</tr>
<tr>
<td>Type of septic shock</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Lung</td>
<td>41 (22)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Abdominal</td>
<td>88 (48)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Both</td>
<td>66 (36)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Positive blood cultures</td>
<td>22 (12)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>16 (9)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Gram-positive cocci</td>
<td>6 (3)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Proven samples with encapsulated organisms</td>
<td>7 (4)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>1 (1)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Streptococcus pneumonia</td>
<td>6 (3)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Plasma cortisol concen. (µg/dl)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Before corticotropin test</td>
<td>19.8 [20.9–25.6]</td>
<td>ND</td>
<td>NA</td>
</tr>
<tr>
<td>60 min after corticotropin test</td>
<td>29.7 [28.8–33.9]</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cosyntropin test responders</td>
<td>84 (46)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Total adrenal gland volume (cm³)</td>
<td>12.3 [12.0–13.4]</td>
<td>8 [6.8–10.1]†</td>
<td>7.2 [6.3–8.5]*</td>
</tr>
<tr>
<td>ICU length of stay (days)</td>
<td>11.0 [13.9–24.7]</td>
<td>4 [1–15]†</td>
<td>NA</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>59 (32)</td>
<td>3 (20)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Data are median and 95% confidence interval or n (%). Cosyntropin test responders were patients with a Δ plasma cortisol concentration 60 min after a short corticotropin test of more than 9 µg/dl. (To convert values for cortisol to nM/l, multiply by 27.6.) *P < 0.05 between septic shock and control groups. †P < 0.05 between septic shock and nonseptic ICU groups.

ICU = intensive care unit; NA = not applicable; ND = not done; SAPS II = Simplified Acute Physiology Score.
Data are represented as mean ± SD or median and 95% CI or n (%).

COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; SAPS II = Simplified Acute Physiology Score.

**Study Outcomes**

The main endpoint was mortality in the ICU in relation to adrenal gland volume. The secondary endpoints were to analyze total adrenal gland volume in relation to septic shock, and to the cosyntropin stimulation test results.

Assumptions for the sample size calculation were based on previous studies on septic shock performed in our ICU. Assuming a 40% mortality in the ICU in the group with adrenal gland volume above 10 cm³ during septic shock, we calculated that 154 patients would need to be studied to detect a 50% absolute increase in mortality if the adrenal gland volume was less than 10 cm³; with 80% statistical power and a one-sided α value of 0.05.

**Statistical Analysis**

Data are represented as mean ± SD or median and 95% CI. Continuous data were compared with Student t test or Mann-Whitney U test when appropriate. Categoric data were analyzed with chi-square and Fisher exact test. The Pearson correlation coefficient was used to assess the correlation between the cosyntropin test results and adrenal gland volume measurement. Sensitivity and specificity of adrenal volume and basal/response plasma cortisol concentration curves to predict mortality were assessed using receiver operating characteristic (ROC) curves and compared with the Mann-Whitney U test. The cutoff point for ROC was determined by the statistics software to automatically minimize the mathematic distance between the ROC curve and the ideal point as a method to minimize misclassification of patients. As previously reported, we also determined two cutoff points to detect volume, which predicts mortality with the best sensitivity and the best specificity. Survival at day 28 was estimated by the Kaplan–Meier method and compared between groups with the log-rank test. A theory-driven logistic regression model was also developed in three steps.

*Fig. 2.* Flow chart of the study. ACTH = adrenocorticotropic hormone; CT = computed tomography; ICU = intensive care unit.
colinearity among the candidate variables and selected the more clinically relevant variable in case of high correlation. Finally, we constructed a full multivariable model forcing all selected predictors (age, sex, Simplified Acute Physiology Score II, comorbidities, plasma creatinine and lactate, basal and random plasma cortisol concentration) and adding the total adrenal gland volume during septic shock. Two-way multiplicative interactions were systematically evaluated. The statistical significance of predictors was assessed using bootstrap resampling with replacement (200 samples). Odds ratio of dying was calculated along with 95% CI. All values were two-tailed and \( P < 0.05 \) was considered significant. Statistical analysis was performed with SAS v9 (Cary, NC) and checked by an independent statistician (GM).

Results

Patients

During the study period, among 1,462 patients admitted to the ICU, 470 presented with septic shock. Among these 470, 266 either did not have a cosyntrropin test or CT scan or had CT but not in the first 48 hours of septic shock. Thus, 184 consecutive patients meeting the inclusion criteria were analyzed (fig. 2). Table 1 shows the main characteristics of the patients with septic shock (\( n = 184 \)), the ICU patients without sepsis (ICU nonseptic group, \( n = 15 \)) and the control...
group (n = 40). Table 2 shows the comparison between survivors and nonsurvivors in the 184 patients with septic shock.

### Adrenal Gland Volume in Control, Nonseptic, and Septic Shock ICU Groups

In the septic shock group, CT was performed 1 day [95% CI, 1–2 days] after the cosyntropin test, which was performed in the first 12 hours [95% CI, 8 to 16 h] after the administration of vasopressors for septic shock. Total adrenal gland volume of the 184 patients in the septic shock group (12.4 cm³ [95% CI, 11.3–13.3]) was significantly higher in comparison with the 15 patients in the nonseptic ICU group (8.0 cm³ [95% CI, 6.8–10.1]; P < 0.0001 for both comparison), and with the 40 patients in the control group (7.2 cm³ [95% CI, 6.3–8.5], P < 0.0001 for both comparison). There was no significant difference in total adrenal gland volume between the nonseptic ICU and control groups (table 1).

Among the 184 patients with septic shock who had a CT scan and cosyntropin test, 100 were also explored before and during septic shock, adrenal glands volume increased more during shock in the survivors (P = 0.0001) (fig. 3).

### Adrenal Gland Volume and Cosyntropin Test Results

There was no evidence for a correlation between adrenal gland volume measurement during septic shock and baseline cortisol concentration (r = 0.09; [CI 95%, −0.11–0.29], P = 0.36) and a weak correlation with the Δ cortisol (r = 0.34 [CI 95%, 0.15–0.51], P < 0.001).

### Adrenal Gland Volume, Cosyntropin Test Response and Outcome

In septic shock, total adrenal gland volume during shock was 13.8 cm³ [95% CI, 13.0–15.1] in the 125 survivors compared with 9.7 cm³ [95% CI, 8.8–9.9] (P < 0.0001) in the 59 nonsurvivors. In the 100 patients who had a CT scan before and during septic shock, adrenal glands volume increased more during shock in the survivors (+33 ± 24%) than in the non survivors (+8 ± 7%) (P < 0.0001) (fig. 4).

In the 184 patients with septic shock,ROC analysis identified a total adrenal gland volume of 10 cm³ as the best predictor of death with a sensitivity of 70% [95% CI, 56–81], a specificity of 92% [95% CI, 86–96], a positive predictive value of 82%, an accuracy of 84%, and an area under the ROC curve of 0.84 [95% CI, 0.78–0.89] (fig. 5). Using this threshold, the likelihood ratio of death in the ICU was 8.7 times greater if the total adrenal gland volume was less than 10 cm³. To convert values for cortisol to nM/l, multiply by 27.6.

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Table 3. Multivariate Logistic Regression Analysis of Risk Factors for Mortality in the 184 Septic Shock Patients

<table>
<thead>
<tr>
<th>Factor</th>
<th>Approximate Coefficient</th>
<th>Approximate Standard Error</th>
<th>Approximate Odds Ratio</th>
<th>Approximate Lower Confidence Limit</th>
<th>Approximate Upper Confidence Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.018</td>
<td>0.020</td>
<td>1.019</td>
<td>0.976</td>
<td>1.059</td>
</tr>
<tr>
<td>SAPS II on admission</td>
<td>0.018</td>
<td>0.020</td>
<td>1.019</td>
<td>0.977</td>
<td>1.059</td>
</tr>
<tr>
<td>Plasma creatinine on ICU admission</td>
<td>0.005</td>
<td>0.003</td>
<td>1.005</td>
<td>0.998</td>
<td>1.009</td>
</tr>
<tr>
<td>Plasma lactate on ICU admission</td>
<td>0.056</td>
<td>0.072</td>
<td>1.058</td>
<td>0.911</td>
<td>1.209</td>
</tr>
<tr>
<td>Cosyntropin test responders</td>
<td>1.071</td>
<td>0.613</td>
<td>2.920</td>
<td>0.743</td>
<td>8.229</td>
</tr>
<tr>
<td>Total adrenal gland volume during shock greater than 10 cm³</td>
<td>−4.210</td>
<td>1.113</td>
<td>0.014</td>
<td>0.004</td>
<td>0.339</td>
</tr>
</tbody>
</table>

ICU = intensive care unit; SAPS II = Simplified Acute Physiology Score.
than 10 cm$^3$. To better describe the ROC analysis, we also determined the cutoff value that resulted in the best sensitivity (15 cm$^3$ allowing a sensitivity of 98% [95% CI, 91–99] but a specificity of 41% [95% CI, 32–50]) and in the best specificity (7.3 cm$^3$ allowing a specificity of 98% [95% CI, 93–99] but a sensitivity of 25% [95% CI, 15–38]).

The best cutoff value for baseline plasma cortisol concentration was 32 µg/dl with a sensitivity of 33% [95% CI, 20–47], a specificity of 79% [95% CI, 70–86] and an area under the ROC curve of 0.52 [95% CI, 0.44–0.59] and 2.7 µg/dl for response cortisol concentration with a sensitivity of 44% [95% CI, 30–60], a specificity of 73% [95% CI, 63–82] and an area under the ROC curve of 0.55 [95% CI, 0.46–0.63].

The area under the ROC curves was significantly higher for total adrenal gland volume than basal cortisol concentration ($P < 0.001$) and than peak cortisol concentration ($P < 0.001$). Figure 6 shows the survival curves in the sepsis validation for total adrenal gland volume (≤ or more than 10 cm$^3$) (fig. 6A), basal plasma cortisol concentration (≤ or more than 32 µg/dl) (fig. 6B), and response cortisol concentration (≤ or more than 2.7 µg/dl) (fig. 6C) and Δ cortisol (≤ or more than 9 µg/dl)$^9$ (fig. 6D). Total adrenal gland volume was strongly associated with 28-day survival (hazard ratio 5.0 [95% CI, 4.3–14.1]; $P < 0.0001$) (fig. 6A). Although Simplified Acute Physiology Score II, lactate, platelets, plasma creatinine, and total bilirubin concentration were associated with mortality on univariate analysis (table 2), multivariate analysis showed that adrenal gland volume was the sole independent risk factor of mortality at day 28 (table 3). Interestingly, 68% of the patients with Δ cortisol less than 9 µg/dl and a total adrenal gland volume of less than 10 cm$^3$ died before day 28, whereas only 14% of the patients with a total adrenal gland volume higher than 10 cm$^3$ and a Δ cortisol higher than 9 µg/dl died before day 28 ($P < 0.0001$) (table 4). Four representative patients are presented in figures 7 and 8.

In a multiple regression model including sex, age, Simplified Acute Physiology Score upon ICU admission, admission category, sepsis source, and total hydrocortisone dose as independent data and adrenal gland volume as the dependent data; male sex and total hydrocortisone dose were statistically associated with adrenal gland volume (table 5). There were 3 of 15 deaths (20%) at 28 days in the nonseptic ICU patient group. In this group, adrenal gland volume was not associated with 28-day mortality.

**Discussion**

This study shows that, in septic shock, total adrenal gland volume measured by CT scan was an independent prognostic factor for 28-day mortality. Adrenal gland volume was nearly doubled in septic shock groups in comparison with the nonseptic ambulatory group, and was increased by 35% in comparison with the nonseptic ICU group. Second, in hydrocortisone–treated septic shock, the cosyntropin test result was poorly correlated with adrenal gland volume. Finally, by multivariate analysis, we report for the first time that total adrenal gland volume less than 10 cm$^3$ during septic shock may represent a mortality risk factor.

Adrenal glands volume was evaluated with a semiautomated organ volumetric technique by a radiologist (SN) by CT and dedicated software (Myrian®, Intrasense, Montpellier, France). This software is widely available
and is certified for organ volume measurement. The use of semiautomated organ volumetry technique has become part of a routine process in radiology for various situations, such as liver or gastric surgery, but volumetry has been poorly studied in intensive care medicine and was used only once for adrenal gland volume measurement, in a pilot study. Adrenal gland volume has been previously shown to increase in stress conditions such as depression and Cushing disease.

In this study, adrenal gland volume was not correlated with basal cortisol but showed some correlation with cortisol response to cosyntropin. These findings suggested that morphologic assessment of the adrenal glands may provide additional information on adrenal function to improve the diagnosis of critical illness-related corticosteroid insufficiency, which remains challenging. In practice, patients with adrenal gland volume less than 10 cm³ had higher risk of death (fig. 5 and 6). In the current study, every patient

Fig. 8. Representative patients included in this study. (A and B) A patient who survived septic shock. His total adrenal gland volume was 22 cm³. (C and D) A patient who died of septic shock. His total adrenal gland volume was 9.7 cm³. A control patient (E) was explored by virtual colonoscopy as well as a nonseptic intensive care unit (ICU) patient (F). Total adrenal gland volume was similar in those 2 patients with a volume of 6.9 cm³ and 7.3 cm³, respectively.
with septic shock was treated with hydrocortisone. Multiple regression showed that a higher total dose of hydrocortisone was associated with a smaller adrenal gland (table 5). More than a very unlikely direct effect of a very short hydrocortisone treatment on adrenal gland, this association may be interpreted as the sicker the patients, the longer they were treated with hydrocortisone and the smaller the adrenal gland volume.

The mechanisms leading to the increased volume did not include adrenal gland hemorrhage or necrosis. Furthermore, there was no sign of excess fluid loading between septic shock groups on CT (such as ascites or bowel edema) and it is then unlikely that adrenal gland enlargement could be related to a gland edema. Interestingly, in 16 patients who had been evaluated before, during, and after recovery of sepsis, we were able to demonstrate that the morphologic changes in adrenal glands were reversible (fig. 3).

This study has some limitations. Although the external validity of this study may be limited because of its single center and observational design, we included all consecutive patients in whom a CT and a cosyntropin test were prescribed within the 48 h of septic shock onset, representing 40% of patients with septic shock (fig. 2). All patients with septic shock received hydrocortisone as part of routine management. Therefore, we could not analyze the effect of this treatment on both adrenal morphology and patient outcome or speculate on the adrenal gland volume in patients with septic shock who were not treated with hydrocortisone. In this first study showing the association between adrenal gland volume and mortality, we did not include patients who did not have septic shock or those acutely treated with steroids, which could represent a limitation to our study. Finally, although we clearly demonstrated a link between adrenal gland volume and mortality, our study was not designed to explain the potential pathophysiologic pathways. However, according to the gland density profile similar to normal parenchyma, the radiologist did not observe any sign of gland edema, hemorrhage or necrosis.

In conclusion, our findings show that in septic shock, CT of the adrenal gland may contribute to assess adrenal function and a total adrenal gland volume less than 10 cm³ may identify high-risk patients. Further studies may evaluate the adrenal gland volume in association with the cosyntropin stimulation test in other populations at high risk of critical illness-related corticosteroid insufficiency such as brain dead or multiple trauma patients and whether assessment of adrenal gland morphology on CT may identify patients likely to respond to corticosteroids.

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### References