# Adrenal insufficiency in critically ill septic patients at Dr George Mukhari Hospital

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**Abstract**
**Rationale:** Adrenal insufficiency occurs with varying frequency in critically ill patients. It is usually associated with a high mortality and poor clinical outcome. **Objective:** To determine the incidence of adrenal failure in patients with severe sepsis and septic shock admitted to our intensive care unit. **Design:** Prospective observational study, over a two year period (June 2003 – June 2005). **Setting:** University hospital multi-disciplinary intensive care unit in South Africa. **Patients:** One hundred and fifty-two patients with severe sepsis and septic shock. Patients with a history of adrenal insufficiency, those on steroid therapy and all those who received etomidate within a week prior to enrollment were excluded. **Interventions:** None. **Measurements and main results:** A random plasma cortisol level was measured in consecutive patients with severe sepsis and septic shock. Adrenal insufficiency was defined as a cortisol level below 20μg/dL. The incidence of adrenal insufficiency was 26, 97% (CI: 19, 97% - 34, 03%). Patients with adrenal insufficiency had lower APACHE II scores and better short-term survival rates. The occurrence of adrenal dysfunction in patients with septic shock was low with an incidence of 15.6%. The type of infecting organism, site of infection and the origin of the sepsis were not associated with differences in the incidence of adrenal deficiency. **Conclusion:** Absolute adrenal insufficiency is not uncommon among our critically septic patients. The presence of adrenal failure was inversely correlated with illness severity and mortality.

**Keywords:** Adrenal insufficiency, Cortisol, Sepsis.

Hypothalamic-pituitary-adrenal dysfunction is common in critically ill patients. Its occurrence rate varies widely depending on the population of patients studied and the diagnostic criteria used.[1,2,3,4] The overall incidence approximates 30%, with an incidence as high as 50-60% in patients with septic shock.[5] It is important to recognize these patients since this disorder has a high mortality if untreated.[6]

The most common cause of adrenal insufficiency in critically ill patients is sepsis and the systemic inflammatory response syndrome (SIRS).[5,7] This is presumably due to the circulating suppressive factors released during systemic inflammation.[8] SIRS is associated with both primary and secondary adrenal insufficiency that is reversible with treatment of the inflammation.[9]

Clinically acute adrenal insufficiency presents with hypotension refractory to fluid therapy and requiring vasopressor agents. Laboratory assessment may demonstrate eosinophillia and hypoglycemia.

Hyponatremia and hyperkalemia are uncommon.

There has been much controversy regarding the criteria for the diagnosis of adrenal insufficiency.[10,11,12] The diagnosis would be best made using an end-organ marker of adrenal steroid action. No such marker is available at present. Free circulating cortisol may be a better measure of adrenal steroid availability, but its assays are not readily available. Thus at the present time, adrenal function is best assessed using total circulating cortisol levels. Random cortisol levels of <15μg/dl, <20μg/dl and <25μg/dl in severely stressed ICU patients have been suggested to denote impaired adrenal function and to best predict those patients, treated with glucocorticoids who can be withdrawn from vasopressors within 24hrs of steroid administration.[7,13,14,15] Both the standard (high dose) and low dose ACTH stimulation tests have been reported to lack adequate sensitivity for adrenal insufficiency.[7]

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### Study objective

To determine the incidence of adrenal insufficiency in critically ill septic patients in our Intensive Care Unit.

## Methods

This was prospective, observational study over a two year period (June 2003 and June 2005)

Consecutive adult subjects aged more than 17 years with severe sepsis or septic shock on admission to the ICU or developing these clinical diagnoses during their stay in the ICU formed the study population. Severe sepsis or septic shock was defined according the American College of Chest Physicians/Society of Critical Care Medicine consensus conference criteria.[16] The following data was recorded on all subjects: demographic details, vital signs, Inotropic support, site of sepsis, short-term (ICU) mortality rate, illness severity (APACHE II score), microbiological isolates and the length of stay in the intensive care unit. Plasma cortisol concentrations were determined by chemiluminescent immunoassay. Absolute adrenal insufficiency was defined by a random cortisol level of <20μg/dl. Patients with a history of adrenal insufficiency, those already on corticosteroids or those who had received etomidate within a week prior to the cortisol sample collection were excluded from the study.

Approval to conduct the study was granted by the Research, Ethics and Publications Committee of the University of Limpopo (MEDUNSA Campus).

## Statistics

Descriptive statistics are reported as mean ± SEM for normally distributed variables. Comparisons of categorical data were made using Fisher's exact test. For all comparisons, differences were considered significant when p<0, 05.

## Results

152 patients were studied (mean age 37 ± 17.4). 41 patients met our criteria for the definition of adrenal insufficiency, giving an occurrence rate of 26.97% (CI: 19.91% - 34.03%). Table I shows the incidence of adrenal insufficiency in our population if we were to use other proposed literature criteria. There is a wide variation in the incidence depending on the cut off point chosen.

**TABLE I : Incidence of adrenal insufficiency in our study population according to previously published criteria.**

| *Author* | *Defining cortisol level* | *Incidence* |
|---|---|---|
| Marik & Zaloga (2001) | <25μg/dl | 46% |
| Annane et al (2005) | <15μg/dl | 13% |

Sixty-four patients were in septic shock at the time of blood sampling. Only fifteen percent of these were confirmed to have adrenal insufficiency, compared to thirty-five percent of the cases that were not in septic shock. This difference was significant (p= 0,009). Patients with fluid-responsive shock had similar rates of adrenal failure to patients who required catecholamines for hemodynamic support (30% vs. 15.6%, p = 0.194).

The overall mortality was 24.3% (37/152). Only two of the deaths occurred in patients with confirmed adrenal failure. Forty-seven percent (30/64) of the cases with septic shock died. The mortality from all causes in the intensive care unit was significantly higher in patients without adrenal insufficiency (28.8% vs. 12, 2%, p = 0.035). The death rate in patients with community-acquired sepsis was similar to that of patients with nosocomial sepsis (26.8% vs. 22.2%, p = 0.052).

There was also no statistically significant difference in the mortality rate between bacteraemic and blood-culture negative cases (25.71% vs. 24.35%, p = 1,000).

The mean APACHE II score for the group was 14 ± 6.79. Non-survivors had significantly higher APACHE II scores compared to the survivors (18.49 ± 6.76 vs. 13.41 ± 6.34, p <0.0001). Patients with 'adequate' adrenal function had higher illness severity scores when compared to those with adrenal failure (15.42 vs. 12.58 , p = 0.023).

The yield of the microbiologic investigations is shown in tables II and III. Gram- negative pathogens accounted for 54% of the culture-positive cases. Eleven percent of the episodes were poly-microbial.

**TABLE II: Patients with documented infection and sites of infection.**

| *VARIABLE* | *TOTAL* |
|---|---|
| *PATIENTS* | *152* |
| • Who had positive documentation of infection | 81 (53) |
| • Who had positive blood culture results | 35 (23) |
| *SITES OF INFECTION* | *152* |
| • Lung | 54(35) |
| • Abdomino-perineal | 64(42) |
| • CNS | 6(0,4) |
| • Primary blood-stream | 19(13) |
| • (>1 site) | 11(0.1) |

Numbers in parentheses indicate percentages

34% of the patients with gram-negative sepsis were in septic shock compared to 45.4% of the cases with gram-positive sepsis. This difference was not significant (p = 0.43).

Patients with bacteraemic sepsis were no more likely to have adrenal insufficiency compared to those without bacteremia (37.1% vs. 23.9%, p = 0.1332). There was also no statistically significant difference in the incidence of adrenal dysfunction between cases with gram-negative and those with gram-positive sepsis (p = 1,000). Patients with pulmonary sepsis had similar rates of adrenal failure as those with abdomino-perineal sepsis (25.9% vs. 18.8%, p = 0.3796).

The mean duration of ICU stay for the group was 7.99 ± 7.64. The length of stay in the intensive care unit did not differ significantly between the patients with and those without adrenal failure (9.38 vs.7.32, p = 0.072).

**TABLE III: Pathogens isolated**

| *Gram-negatives* | *Gram-positives* | *Fungi* | *Mycobacteria* |
|---|---|---|---|
| Klebsiella species(18) | MSSA (7) | Candida albicans (2) | Mycobacterium tuberculosis (2) |
| Acinetobacter species(15) | MRSA (1) | Cryptococcus neoformans (11) | |
| Escherichia coli(7) | Enterecoccus species (7) | Pneumocystis jirovecil (1) | |
| Pseudomonas species(7) | Streptococcus species (9) | | |
| Other Enterobacter species (4) | | | |

Vasopressor therapy was required in forty-two percent of the patients. Table IV shows the frequency and types of vasoactive agents used for hemodynamic support.

**TABLE IV: Vasoactive agents used for hemodynamic support**

| *VASOACTIVE AGENTS* | *NO. OF PATIENTS* |
|---|---|
| Adrenaline | 26 |
| Dobutamine | 12 |
| Dopamine | 2 |
| Combination | 24 |

## Discussion

Based on this study adrenal insufficiency is probably not uncommon amongst our critically ill septic patients. A surprise finding was the relatively low occurrence rate of adrenal failure in patients with septic shock compared to other studies.[3,7,17] The explanation for this seemingly contradictory finding may lie in the fact that most of the septic shock cases in this study had raised cortisol levels (mean 827.58 mmol/l). Plasma cortisol levels have been found to be higher in patients with septic shock and, especially those with a higher risk of dying.[18,19,20]

Overall the mortality rate in patients with impaired adrenal function in this study was low. This disorder is said to be associated with a high mortality, particularly if left untreated or when it is associated with septic shock.[6,21,22] The death rate in patients with septic shock and adrenal failure in this study was low (0, 2%), but the small number of patients (10) suggests this to be a topic for further study. The prognostic value of secretory failure of the adrenal glands in patients with sepsis is still unclear.[19,20] Some authors believe that the conflicting reports reflect a bimodal distribution of mortality in relationship to the random cortisol level during sepsis, with patients having extremely low cortisol levels (<25μg/dl) and those who have very high levels (>45μg/dl) having the highest mortality.[23]

The diagnostic criteria for adrenal insufficiency remain unresolved. It is possible that the cut-off level for random cortisol used in our study is inappropriate, even though it has been used in other published reports.[19,20] A recent study by Venkatesh et al, demonstrated that although random cortisol measurements and the low dose corsyntropin test reliably reflected the 24 hour mean cortisol in critical illness, they do not take into account the pulsatile nature of cortisol secretion, with potential for erroneous conclusion about adrenal function based on a single measurement.[24] Of major concern is the marked difference in the incidence of adrenal failure in this study when the different criteria are used. Plasma cortisol determination is rapid and easy to perform (turn around time is less than half and hour).

Its advantage would be the ability of clinicians to introduce gluco-corticoid therapy early, and in appropriate patients. This would be provided a specific serum cortisol level has been validated for the diagnosis of adrenal failure. We are unaware of such a study. The use of 'rapid' shock reversal upon administration of exogenous steroids may not be a reliable means of evaluating adrenal insufficiency as corticosteroids have additional physiologic effects.

Our study suggests that gram-negative sepsis is still the more common in our intensive care unit patients. The occurrence rate of gram-negative sepsis is believed to have diminished over the years.[15] The trend observed in many recent sepsis studies is that gram-positive bacteria have surpassed gram-negative pathogens as aetiologic agents for sepsis.[26,27,28] The importance of local surveillance cultures cannot be over-emphasized.

Epinephrine was the vasoactive agent most often used in this study. It has been recommended that its use in septic shock be limited because of its potential negative effects, with dopamine and/or nor-adrenaline being recommended for initial therapy.[25] The use of vasoactive agents in this unit is not protocol-directed, and individual clinicians choose agents based on personal experience. Recommendations about the use of vasopressor agents in septic shock have been made difficult by the paucity of controlled trials and by the clinical reality that agents are frequently used in combination. The unit has no access to nor-epinephrine.

More than half of the infections were nosocomial in origin and accounted for half of the deaths observed in this study. The problem of hospital-acquired sepsis has become a cause for concern all over the world. It is believed to occur in 5-15% of hospital admissions, it is costly, and is estimated to account for a sizable number of deaths.[29,30,31] These infections occur more frequently among patients in intensive care units.[32] Accordingly, infection control measures are to be viewed as a priority and have to be integrated into the continuous process of improvement of quality of care.

The principles of infection control are simple and basic and easy to implement.

Some limitations of this study should be noted. Survival was restricted to survival at ICU discharge. Substantial long-term consequences have been reported for critically ill patients. As a result long-term survival and attainable quality of life have gained ground as outcome measures.[33,34] Stimulation tests were not performed as this was an observational study. Whether these tests would have enhanced our study is a matter of conjuncture as their validity remains questionable.

In summary, using a threshold value of <20μg/dl for random plasma cortisol we were able to establish that adrenal failure is not uncommon in our critically ill septic patients. Consensus on the definition of adrenal failure is paramount to guide glucocorticoid therapy in critically ill patients.

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## References

1. *Soni A, Pepper GM, Wyrwinski PM, et. al. Adrenal insufficiency occurring during septic shock: incidence, outcome and relationship to peripheral cytokine levels. Am J Med 1995; 98: 266-271.*
2. *Schein RMH, Spring CL, Marcial E. Plasma cortisol levels in patients with septic shock. Crit Care Med 1990; 18: 259-263.*
3. *Briegel J, Scheelling G, Haller M, et. al. A comparison of the adrenocortical response during septic shock and after complete recovery. Intensive Care Med 1996; 22: 894-899.*
4. *Barquit E, Kirton O. Adrenal insufficiency in the surgical intensive care unit patient. J. Trauma 1997; 42: 27-31.*

5. Zaloga G P, Marik P. Hypothalamic-pituitary adrenal insufficiency. Crit Care Clin 2001; 17: 25-42.
6. Annane D, Sébille 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.
7. Marik PE, Zaloga GP. Adrenal insufficiency during septic shock. Crit Care Med 2003; 31(1): 141-5.
8. Zaloga GP. Sepsis-induced adrenal deficiency syndrome. Crit Care Med 2001; 29: 688-690.
9. Briegel J, Fort H, Haller M, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock, a prospective randomized, double-blind, and single center study. Crit Care Med 1999; 27: 7230732.
10. Ligtenberg JJ, Zijlstra JG. The relative adrenal insufficiency syndrome revisited, which patients will benefit from low-dose steroids. Curr Opin Crit Care 2004; 10(6): 456-60.
11. Annane D. Time for a consensus definition of corticosteroid insufficiency in critically ill patients. Crit Care Med 2003; 31: 1868.
12. Shenker Y, Skatrud BJ. Adrenal insufficiency in critically ill patients. AJRCCM 2001; 163: 1520-1523.
13. Braams R, Kopperschaar HPF, van de Pavoordt HDWM, van Vroonhoven TJMV. Adrenocortical function in patients with ruptured aneurysm of the abdominal aorta. Intensive Care Med 1998; 24: 124-127.
14. Rivers EP, Blake HC, Dereczyk B, Ressler JA, et al. Adrenal dysfunction in hemodynamically unstable patients in the emergency department. Acad Emerg Med 1999; 6: 626-630.
15. Annane D, Belissant E, Cavailon J-M. Septic shock. Lancet 2005; 365: 63-78.
16. American College of Chest Physicians/Society of Critical Care Medicine consensus conference. Definition for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992; 20: 864-875.
17. Moran JL, Chapman MJ, O'Fathartaigh MS, et al. Hypocortisoleamia and adrenocortical responsiveness at onset of septic shock. Intensive Care Med 1994; 20: 489-495.
18. Schein RMH, Sprung CL, Marcial E, Napolitano I, Chernow B. Plasma cortisol levels in patients with septic shock. Crit Care Med 1990; 18: 259-263.
19. Annane D, Sébille V, Troche G, Raphael JC, Gajdos P, Bollisant E. A 3-level classification of septic shock based on cortisol levels and cortisol response to corticotropin. JAMA 2000; 283: 1038-1045.
20. Rothwell PM, Lawler PG. Prediction of outcome in intensive care patients using endocrine parameters. Crit Care Med 1995; 274:78-83.
21. Schroeder S, Wichers M, Klingmuller D, et al. The hypothalamic-pituitary-adrenal axis of patients with severe sepsis: altered response to corticotrophin-releasing hormone. Crit Care Med 2001; 29: 310-316.
22. Rivers EP, Gaspari M, Abi Saad G, et al. Adrenal insufficiency in high-risk surgical ICU patients. Chest 2001: 119: 889-896.
23. Marik PE, Zaloga GP. Adrenal insufficiency: A new look at an old problem. Chest 2002; 122: 1784-1796.
24. Venkatesh B, Mortimer RH, Couchman B, Hall J. Evaluation of random plasma cortisol and the low dose corticotrophin tests as indicators of adrenal secretory capacity in critically patients: a prospective study. Anaesth Intensive Care 2005; 33: 201-9.
25. Beale J, Hotlenberg SM, Vincent JL, Parrilo E. Vasopressor and inotropic support in septic shock: An evidence-based review. Crit Care Med 2004; 32(suppl): S455-S465.
26. Martins GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N. Engl J. Med 2003; 348: 1546-54.
27. Annane D, Aegerter P, Jars-Guincestre MC, Guidet B. Current epidemiology of septic shock: the CURB-Rea Network. Am J. Respir Crit Care Med 2003; 1687: 165-172.
28. Alberti C, Bru-Buisson C, Burchardi H, et al. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. Intensive Care Med 2002; 28: 108-121.
29. Brennan TA, Leape LL, Laird NM, et al. Incidence of adverse events and negligence in hospitalized patients: results of the Harvard Medical Practice Study. N. Engl J. Med 1991; 324: 370-376.
30. Thomas EJ, Studdert DM, Burstin HR, et al. Incidence and types of adverse events and negligent care in Utah and Colorado. Med Care 2000; 38: 261-271.
31. Leape LL, Brenick DM. Safe health care: are we up to it. BMJ 2000; 320: 725-726.
32. Eggimann P, Pittet D. Infection control in the ICU. Chest 2001; 120: 2059-2093.
33. Kaarlola A, Pettilä V, Kekki P. Quality of life six years after intensive. Intensive Care Med 2004; 29: 1294-1299.
34. Angus DC, Carlet J: on behalf of the 2002 Brussels Round-table participants. Surviving intensive care: a report from the 2002 Brussels Round-table. Intensive Care Med 2003; 29: 368-377.