CORTISOL LEVELS AND SHORT TERM OUTCOME IN HIV INFECTED PATIENTS WITH SEPSIS IN KENYATTA HOSPITAL
INVESTIGATOR

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DECLARATION

This study was done as part of fulfillment for my masters program at the department of clinical medicine and Therapeutics at the University of Nairobi.

This proposal was submitted for approval by the department of medical therapeutics and the ethics committee Kenyatta hospital.

Signed........ Date 16/11/09

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Acknowledgments

This is my opportunity to express my respect to the almighty God without whom we the members of this team would not have made it this far. This thesis is dedicated to my family who kept to my side thought the time I was working on the study. I am pleased to thank my supervisors and every one who formed the team that resulted to accomplishment of protocol and study results.

Dr Florence Keli-Kariithi
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<td>A1</td>
<td>adrenal insufficiency</td>
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<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
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<tr>
<td>ACTH</td>
<td>adrenal corticotrophic hormone</td>
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<td>CRH</td>
<td>corticotrophin release hormone</td>
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<tr>
<td>CNS</td>
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<td>cluster differentiation 4</td>
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<td>DTC</td>
<td>diagnostic testing and counseling</td>
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<tr>
<td>FAI</td>
<td>functional adrenal insufficiency</td>
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<td>HIV</td>
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<td>MAC</td>
<td>mycobacterium avium complex</td>
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<td>opportunistic infections</td>
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<td>hypothalamic pituitary adrenal axis</td>
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<td>american college of chest physicians/society of critical care Medicine</td>
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<td>SIRS</td>
<td>systemic inflammatory response syndrome</td>
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<tr>
<td>APACHE</td>
<td>acute physiology and chronic health evaluation</td>
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<td>SAPS</td>
<td>simplified acute physiology score</td>
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<td>statistical package for the social services</td>
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ABSTRACT

Introduction

Adrenal insufficiency occurs in Human immunodeficiency virus (HIV)/ Acquired Immunodeficiency Syndrome (AIDS) and causes morbidity and mortality in HIV patients.

Objective

To determine cortisol levels and short term outcome at 2 weeks in HIV infected and HIV uninfected patients admitted with sepsis in Kenyatta National hospital.

Design

This was a Cross Sectional Comparative study.

Settings

Medical wards, Intensive Care Unit, Renal Units Kenyatta National Hospital.

Subjects

Patients admitted with sepsis.

Method

Consecutive HIV infected admitted with sepsis as defined by a tool adopted from the consensus conference held 2008 were recruited. Male or female HIV infected patients aged more than 13 yrs and their age and sex matched comparative HIV negative patients were included. A baseline cortisol test was done. Synthetic cosynthropin was given intravenously to stimulate the adrenal glands and serum cortisol levels at 30 and 60 minutes done following the stimulation. Patients were then followed until 2 weeks after admission to establish their outcome. Expected outcomes were either discharge from the hospital or death. P values of 0.005 were considered significant at confidence intervals of 95%. Adrenal insufficiency was defined as baseline cortisol levels < 130nmol/l and or failure to achieve cortisol levels of > 414nmol/l post stimulation.

Results

A total of 94 HIV infected and HIV uninfected patients were recruited in the study 47 patients in each group. The mean age was 36±12.2 in the HIV infected group and 37±13.4 HIV uninfected group. There was no statistically significant difference in the proportions of patients with adrenal insufficiency in the two groups. The prevalence of
primary adrenal insufficiency in the study and comparative groups was 19% and 25.5% respectively.

There were more deaths in the comparative group 31.9% compared to the study group at 24%.

Conclusion
There was no significant difference of adrenal insufficiency in the study group and comparative group in the comparative group.
LITERATURE REVIEW

BACKGROUND

INTRODUCTION
The joint United Nations Program on HIV/AIDS (UNAIDS) and World Health Organization (WHO) global estimates that more than 33.1 million people in the world had HIV/AIDS in 2007. More than 1.3 million people are currently living with HIV in Kenya. HIV was first described in 1981 in a group of homosexual men who presented with an illness that was similar to infectious mononucleosis in America. In 2005 prevalence of HIV in Kenya was found to be 4.6%- 5% during Adult HIV prevalence survey. HIV affects all systems in the body the endocrine system being one.

Adrenal insufficiency was first described by a British physician Dr Thomas Addison in 1885. In Addison’s disease patients produce low amounts of cortisol sometimes production of mineral corticoids is affected. Addison’s disease is also referred to as chronic adrenal insufficiency. During acute critical illness some patients produce inadequate amounts of cortisol. This is referred to as functional adrenal insufficiency.

CLINICAL SIGNIFICANCE OF ADRENAL INSUFFICIENCY IN HIV
Patients with HIV/AIDS have an increased prevalence of Adrenal insufficiency and Functional Adrenal Insufficiency (FAI) which is a cause of morbidity and mortality. Adequate adrenal reserve is necessary during acute severe illness. Reduction of adrenal reserve results to inadequacy of combating inflammation during acute severe disease. The prevalence of Functional adrenal insufficiency in a study done in ICU patients admitted with sepsis by Marik and colleagues showed a prevalence of 75% in severely ill HIV patient. Functional adrenal insufficiency was demonstrated by basal stress total serum cortisol threshold of <69nmol/l critically ill HIV patients. The occurrence of functional adrenal insufficiency shows that hypo-adrenalism can occur without obvious structural defects in the hypothalamic–pituitary–adrenal axis (HPA).
Deficiency of cortisol during sepsis is associated with increased morbidity and mortality. In the study done by Marik and colleagues the mortality rate was 47% with the 75% prevalence of adrenal insufficiency. Use of corticosteroids at physiological doses improves the outcome. The use of steroids is best if given early especially in Gram negative infections. Adrenal Insufficiency and functional adrenal insufficiency in critically ill patients may be difficult to diagnose. This may be due to lack of sufficient history and overlap of symptoms, delay or unavailable laboratory reports.

Clinical signs and symptoms of adrenal insufficiency include weakness, nausea, fatigue, anorexia, vomiting, weight loss, cutaneous and mucosal pigmentation, hypotension and hypoglycemia.

**THE HYPOTHALAMIC PITUITARY ADRENAL AXIS AND FUNCTIONS OF CORTISOL**

The Hypothalamic Pituitary axis (HPA) functions by interaction of the nervous and endocrine systems. The nervous system regulates the endocrine system activities. The hypothalamus releases Corticotrophin Release Hormone (CRH) which then stimulates the pituitary to release Adrenal Cortical Release Hormone (ACTH). ACTH stimulates the adrenal gland to release glucocorticoids, mineralcorticoids and sex hormones.

The adrenal gland consists of a cortex and medulla. The cortex is divided into an outer zona glomerulosa, intermediate zona fasciculata and inner zona reticularis. Glomerulosa synthesizes mineralcorticoids while fasciculate and reticularis secrete glucocorticoids and sex steroids. The secretion of glucocorticoids, mineralcorticoids and sex hormones is controlled by ACTH. ACTH secretion is in turn controlled by Corticotrophin Release Hormone (CRH) produced in the hypothalamus.

Cortisol is the predominant corticosteroid secreted from the adrenal cortex in humans. Physiologic concentrations are necessary for normal function of all body cells. The basal secretory rate of cortisol is 10 to 30 mg per day. In a healthy, unstressed person, cortisol
is secreted in a diurnal pattern under the influence of ACTH released from the pituitary gland. The hormone level is highest in the early morning hours. ACTH secretion occurs under the influence of hypothalamic CRH, and both hormones are subject to negative feedback control by cortisol.

Circulating cortisol is bound to corticosteroid-binding globulin, with less than 10 percent in the free, bio available form. During severe infection, sepsis, trauma, burns, illness, or surgery, there is an increase in cortisol production by a factor of six or in levels roughly proportional to the severity of the illness. Diurnal variation in cortisol secretion is also lost. These effects are due to increased production of CRH and ACTH and a reduction in negative feedback from cortisol.

Stimulation of the hypothalamic–pituitary axis during severe illness is caused by elevated levels of circulating cytokines, among other factors. Cortisol increases protein breakdown, nitrogen excretion, hepatic gluconeogenesis, extracellular fluid, appetite, fat deposition in the upper body. It decreases Leukocyte adhesion and diapedesis, inflammation, bacterial lysis in leukocytes, numbers of T-cells, and inhibits migration of water into cells and chance of infection. The overall effect is reduction of the inflammatory process.

**HIV INFECTION AND ADRENAL GLANDS**

HIV infection has complex effects on the hypothalamic–pituitary–adrenal axis. Potential mechanisms for the development of adrenal insufficiency in patients with HIV infection are varied. They include HIV infection of the adrenals or co-infection with cytomegalovirus or mycobacterium. The adrenals may be destroyed by tumors such as lymphomas and Kaposi's sarcoma.

Adrenal insufficiency may occur in adrenocortical hemorrhage secondary to coagulopathy, or during sepsis due to the cytokines produced, such as tumor necrosis factor-alpha. Drugs that are sometimes used for treatment of opportunistic infections such as ketoconazole inhibit 11-β hydroxylase enzyme necessary for steroid synthesis.
Other drugs use in other HIV related morbidities include: phenytoin, megesterol, opiates, anticoagulants and rifampicin stimulate cytochrome P-450 enzyme increasing metabolism of cortisol. In HIV/AIDS, the adrenal glands are frequently a site of opportunistic infection, most commonly with CMV, Mycobacterium avium-complex (MAC), Mycobacterium tuberculosis, Cryptococcus neoformans, Toxoplasma gondii, Pneumocystis carinii, and Histoplasma capsulatum have also been found on pathologic examination of the adrenal glands.

CORTISOL AND SEPSIS
Adequate adrenal function is essential in patients with sepsis and acute severe illness. Deficiency of cortisol during sepsis is associated with morbidity and mortality. Cortisol facilitates the delivery of glucose to cells making it an essential hormone in the metabolic response to stressful conditions as in sepsis. Sepsis has been defined by several teams. A consensus conference was held to define sepsis in 2008 by the American College of Chest Physicians and Society of Critical Care Medicine (ACCP/SCCM). Sepsis was defined as Systemic Inflammatory Response Syndrome (SIRS) resulting from proven or suspected infection (bacterial, viral, fungal, or parasitic). In conditions where sepsis is not corrected micro vascular damage takes place leading to tissue hypoxia and tissue damage and multiple organ dysfunction septic shock and death occurs there after. SIRS is a reference for systemic response to activation of the innate immune response, due to infectious or noninfectious causes. SIRS includes the presence of more than one of the following manifestations (list is not exhaustive of all parameters used to define SIRS):

- Fever ≥38°C or ≤36°C
- Heart rate ≥90 beats/min
- Tachypnea, of ≥20 breaths/min
- Alteration of white blood cell count ≥12,000 cells/mm³, ≤4,000 cells/mm³, or the presence of ≥10% immature neutrophils
- Arterial systolic pressure ≤90 mmHg despite adequate fluid resuscitation
Production of low cortisol amounts during sepsis, so called functional adrenal insufficiency (FAI), is associated with increased morbidity and mortality. Cortisol facilitates the delivery of glucose to cells making it an essential hormone in the metabolic response to stress. Administration of hydrocortisone at dosages of 200-300mg/24 hours of hydrocortisone improves the prognosis of patients, if given early during the course of Gram negative infections. In the CORTICUS study steroids were shown to shorten the time to vasopressin response.

CLINICAL FEATURES OF ADRENAL INSUFFICIENCY

Adrenal insufficiency in HIV patients with sepsis may be difficult to diagnose due to lack of sufficient history and overlap of symptoms, delay or unavailable laboratory reports. Adrenal gland involvement is commonly found in late stages of HIV infection and thus found in WHO Stage IV disease. Adrenal insufficiency may be divided into three general categories. It may be associated with primary inability to elaborate sufficient quantities of cortisol. It may be secondary to inadequate ACTH formation or release. It can occur in chronic adrenal insufficiency which is not adequately replaced, especially in the presence of hemorrhage and pituitary apoplexy.

AI may follow a progressive or acute destruction of adrenals. The clinical presentation of adrenal insufficiency may be acute or insidious and thus difficult to recognize. The manifestations of AI are often non-specific. They need not to be present for the disease to be diagnosed. AI is clinically characterized by weakness, nausea, fatigue, anorexia, vomiting, and weight loss, hyper pigmentation of skin, asthenia, salt craving, wasting, arterial hypotension and hypoglycemia.

The patients may develop a tan in exposed body parts, and in areas that suffer chronic friction and trauma such as the elbows, knuckles and the belt line. The buccal mucosa may be pigmented at sites of dental occlusion. Other symptoms include personality changes, irritability, restlessness, enhanced sensory modalities such as change in taste.
olfaction and hearing which reverse with therapy. Pubic and axillary hair may also reduce. These symptoms may be easily mistaken for clinical presentation of AIDS.

Studies have demonstrated both diminished cortisol levels without clinical features in AIDS patients. The incidence of adrenal insufficiency in critically ill HIV-infected patients is unclear, partly because different criteria are used to diagnose adrenal insufficiency. The adrenal gland is the endocrine organ most commonly involved in patients infected with (HIV). It is important to recognize patients with adrenal insufficiency, as it is a cause of morbidity and mortality.

**MANAGEMENT OF ADRENAL INSUFFICIENCY**

Patients with clearly documented AI should be treated by steroid replacement therapy. Regimens that have been used include glucocorticoids replacement therapy consisting of oral hydrocortisone at 200-300 mg/day especially if given early during the course of Gram negative infections. To simulate the normal diurnal rhythm two thirds of the dose is given in the morning and a third in the late afternoon. Patients are thereafter maintained on hydrocortisone at doses between 15 and 20 mg per day.

Patients with primary adrenal insufficiency may require the addition of mineralcorticoids if hyperkalemia or symptoms of volume depletion persist despite glucocorticoids replacement. Mineralcorticoids replacement is done with oral fludrocortisone acetate at a typical dose of 0.05 to 0.1 mg per day orally. Patients should maintain an ample intake of sodium such as 3 to 4 g/day. Under conditions of moderate stress such as a low-grade fever, patients require increases of up to 2 to 3 times their maintenance doses.

The overall maintenance dose of adrenal steroid replacement should be that which is needed to alleviate those symptoms attributable to the adrenal insufficiency, including hemodynamic and electrolyte abnormalities. Doses higher than usual maintenance doses should be avoided because of their potential risk of enhancing immunosuppression consequently exacerbating underlying opportunistic infections due to steroid therapy in patients with HIV disease and AIDS.
JUSTIFICATION OF THE STUDY

More than 1.3 m people live with HIV in Kenya. HIV infected patients have a high degree of adrenal insufficiency with a prevalence of 18%- 22% with some authorities reporting a prevalence of up to 75%. The adrenal glands are frequently affected by opportunistic infections and malignancies with a risk factor of developing adrenal insufficiency. Deficiency of cortisol during sepsis is associated with a high morbidity and mortality. There is no local data about prevalence of adrenal insufficiency and the relationship to outcome in patients with sepsis.

STUDY OBJECTIVES

General objective
To determine cortisol levels in HIV infected patients admitted with sepsis and short term outcome at 2 weeks in Kenyatta National Hospital.

Secondary Objectives
1. To compare baseline cortisol level in HIV infected and uninfected patients admitted with sepsis
2. To compare cortisol levels of synthetic ACTH stimulated adrenal glands of HIV infected and uninfected patients admitted with sepsis
3. To correlate the cortisol levels and reserve with the outcome in weeks of hospitalization.

METHODS

Study Design
This study was a cross sectional comparative study in patients admitted in Kenyatta National Hospital with sepsis.

Inclusion criteria
1. Age above 13 years
2. HIV infected and HIV uninfected admitted in medical wards, renal and intensive care units with sepsis during the period of August 2008 and November 2008
3. Patients with sepsis as identified by a tool adopted form the Consensus Conference criteria for definition of Sepsis held in 2008. The screening tool is attached as appendix II.

4. Consent to participate

Exclusion Criteria

1. Patients previously known to have primary adrenal insufficiency by documented laboratory tests
2. Pregnant and lactating patients
3. Patients on steroid therapy
4. Alcoholics: by patients and relatives report
5. Patients with documented diabetes mellitus, thyroid, Cushing’s or phaeochromocytoma
6. Those who did not consent to participate
7. Patients who had received steroids one month before the study or were on steroids at the time of the study

Study Area

The study was conducted in medical wards, intensive care unit and the renal units in Kenyatta National Hospital.

Study population

HIV infected and uninfected patients admitted with sepsis in Kenyatta National Hospital.

Study participants

Study participants included HIV infected and uninfected patients admitted with sepsis in Kenyatta National Hospital. They were matched for sex and age to the nearest 5 years. HIV infected patients formed the study group while HIV uninfected patients formed the controls.
Patients suspected to have sepsis are screened for sepsis

Patients found to have sepsis are tested for HIV

HIV positive

Baseline and post stimulation cortisol

Outcome at 2 weeks

HIV negative

Baseline and post stimulation cortisol

Outcome at 2 weeks
Sample size

Using a prevalence of 21% of AI in patients with HIV and 1% in patients with AI without HIV, the sample size was calculated. The study targeted a 95% confidence level and power of 80%. The minimum sample size calculated using the formula below was 47 for each group.

For unequal groups of size \( n_1 \) and \( n_2 \), where \( r = n_2 / n_1 \), is

\[
n_1 = \frac{z_{\alpha/2} \sqrt{(r+1)pq} + z_s \sqrt{rp_1q_1 + p_2q_2}}{rd^2}
\]

where \( p = \frac{p_1 + rp_2}{r+1} \) and \( n_2 = rn_1 \).

For small samples, employ a "continuity correction"

\[
n_1 = \frac{n_1}{4} \left( 1 + \sqrt{1 + \frac{2(r+1)}{n_1rd}} \right)^2
\]
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<tr>
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<tr>
<td>Probability of ADRENAL FAILURE in observation group</td>
<td>p1</td>
<td></td>
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<tr>
<td>Probability of ADRENAL FAILURE in control group</td>
<td>p2</td>
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<td>47</td>
</tr>
<tr>
<td>Continuity correction for n2'</td>
<td>n2</td>
<td>47</td>
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**Total sample size 94; 47 in the observation group and 47 in the control group.**
**Sampling Method and Clinical Assessment**

Patients with suspected sepsis were identified in the medical wards, ICU and renal unit. Consecutive sampling was done. Using a tool adopted from the consensus conference held 2008 to define sepsis, appendix III, patients were screened for sepsis. Consecutive HIV infected patients were selected and recruited. Age and sex matched HIV uninfected comparative patients with sepsis were included in the study for comparison. A clinical examination was conducted on the recruited individuals. Blood pressure, temperature, pulse rate, respiratory rate and a general physical examination were done. Chest ray of patients who had pneumonia and other radiological images that were available were reviewed. Blood cultures and microscopy reports of body fluids were obtained as appropriate for the clinical conditions of each patient.

Sepsis was defined by suspected or proven infection with SIRS. SIRS was presence of any of the 2 of the following: temperature of 38°C, hypothermia of 36°C, tachycardia of ≥90 beats/min or Tachypnea, manifested by a respiratory rate ≥20 breaths/min and arterial systolic pressure ≤ 90 mmHg.

In order to enroll 97 patients, 200 patients were screened at acute and emergency department. Patients or guardians provided informed consent as appropriate. All HIV infected patients were staged by WHO staging criteria.

Blood was drawn for baseline cortisol at 8 am by venous puncture after application of a tourniquet. Stimulation of adrenal glands was done using 1ug of synthetic ACTH. Blood was drawn for cortisol level assay at 30 and 60 minutes post stimulation. The outcome of the patients enrolled in the study was established at two weeks. Patients were followed up daily to keep an update of whether they were still in the units they had been admitted to.
**ASSAYS**

Normal cortisol was defined by a range of 138-690 nmol/l. Normal response to stimulation with synthetic ACTH was defined as an increase of cortisol level equal or > 414 nmol/l.

**Primary adrenal insufficiency** was defined as cortisol levels <138 mmol/l at baseline and failure to increase cortisol levels to achieve a post stimulation cortisol equal to or > 414 nmol/l. **Secondary adrenal insufficiency** was defined as baseline cortisol level > 138 nmol/l and post stimulation increase of cortisol < 414 nmol/l. Functional adrenal insufficiency was defined as baseline cortisol > 138nmol/l and post stimulation cortisol of > 414nmol/l.

**Clinical Methods and assessment of study participants**

Patients were screened at acute and emergency, renal unit and intensive care departments by a tool to define sepsis adopted from a consensus conference held 2008. Consent forms were signed by patient’s relatives at the respective units if they were too sick to consent. Patients were reviewed again the following morning consent forms signed for those who had not signed at initial review. A second clinical examination was done and data collected in a study proforma included in this report as appendix III. Blood was then drawn before and two further times after stimulation with synthetic ACTH.

Blood specimens were transported in a cool box at a temperature of 2-8°C. Samples were stored at the -80°C while waiting to be assayed. Cortisol levels were determined by an ELISA test which was performed at the laboratory of the department of clinical medicine and therapeutics. The ELISA test is an assay based on competitive interaction of cortisol and the hormone enzyme conjugate of monoclonal anti cortisol antibodies. The results were automatically analyzed by a computer and were expressed in nmol/l.

To differentiate primary form secondary adrenal failure cortisol levels were assayed after stimulation with Adrenal cortical Trophic Hormone (ACTH). Cosyntropin studies in
patients with HIV disease have frequently detected a range of cortisol levels from subclinical alterations in cortisol levels to frank primary adrenal insufficiency.

Quality assurance
Control assays and observation of protocol were done every morning to ensure quality control. Commercial reagents kits were used with internal quality samples. Samples were run in the same assay to minimize inter assay variation.

DATA COLLECTION AND ANALYSIS
Data was collected and entered into the study pro forma. cleaned and verified. It was entered into SPSS version 15 and Statistical analysis was then done. Descriptive characteristics of the study population were summarized using means and standard deviations for continuous variables and proportions for categorical variables. Comparisons of means of cortisol levels, duration before death/discharge were done using t test and associations between categorical data were analyzed using Chi-square.

ETHICAL CONSIDERATION
The study was conducted after approval by the Department of clinical Medicine and therapeutics and the Ethical and Scientific Review Board Kenyatta national hospital. Patients or guardians signed an informed consent for participation in the study after explanation of procedures.
Fig 2 Age distribution study group and comparative group

Percentage number of patients

Age in years

Study group
Control group

0.0% 5.0% 10.0% 15.0% 20.0% 25.0%
RESULTS

In order to enroll 94 patients 200 patients were screened. All the 200 patients that were seen were potential participants in that they fulfilled criteria definition of sepsis as defined for the study. Out of the 200 patients screened 106 were excluded due to several reasons. During the night of admission 43 died. 30 declined to consent. By the time of enrollment 30 had no HIV results and 3 of them could not be traced to the units that they were admitted to. There were 47 patients who were HIV infected and 47 others who were HIV uninfected that finally enrolled into the study.

HIV infected patients in this study formed the study group while the HIV negative patients were the comparative group. The baseline characteristics are shown in table 2 below.

**Table 2 age and gender of the study group and control with sepsis**

<table>
<thead>
<tr>
<th></th>
<th>Study group n=47</th>
<th>Comparative n=47</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>23 (51.1%)</td>
<td>23 (51.1%)</td>
</tr>
<tr>
<td>Female</td>
<td>24 (49.9%)</td>
<td>24 (49.9%)</td>
</tr>
<tr>
<td>Mean Age years</td>
<td>36±12</td>
<td>37±13.4</td>
</tr>
<tr>
<td>Range in years</td>
<td>14-69</td>
<td>15-72</td>
</tr>
</tbody>
</table>

The mean age in the study group was 36.6± 12.2 while in the comparative group was 37 ±13.4. The gender proportions and mean ages of the study group and the comparative group were similar. The distribution of the patient’s age is shown in figure 2 below.
Fig 2 Age distribution study group and comparative group
Table 3 Clinical diagnosis at hospitalization study and comparative groups

<table>
<thead>
<tr>
<th>Category</th>
<th>Study group n=47</th>
<th>Comparative group n=47</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>22(46.8%)</td>
<td>26(55.3%)</td>
<td>.409</td>
</tr>
<tr>
<td>Meningitis</td>
<td>16(34%)</td>
<td>8(17%)</td>
<td>.058</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>1(2.1%)</td>
<td>4(8.5%)</td>
<td>.168</td>
</tr>
<tr>
<td>Infect. Endo.</td>
<td>1(2.1%)</td>
<td>2(4.3%)</td>
<td>.557</td>
</tr>
<tr>
<td>Not known</td>
<td>7(14.9%)</td>
<td>7(14.9%)</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3 shows the various diagnoses of patients at admission. Pneumonia and meningitis were the most common cause of sepsis in the two groups. In the study group 46.8% patients had pneumonia while 55.3% had pneumonia in the comparative group. Meningitis was detected in 34% of the study group while in the comparative group at 17%. The other conditions occurred at fairly small proportions in the two groups. In 14.9% patients there was no clear cause of sepsis.

The WHO clinical staging of the HIV of the study group patients is shown in figure 3 below. Majority of the patients in the study group (80.9%) were in clinical stage 4 disease. The mean CD4 cell count in the last 3 months was 144 ± 111 in the study group.
Only 8.5% patients in the study group were on antiretroviral medication at the time of admission to the hospital. Majority of the patients in the two groups (96%) had not been treated for TB in the previous 5 yrs.

**Table 4 Clinical characteristics study patients based on parameters defined in the consensus conference criteria for sepsis held 2008**

<table>
<thead>
<tr>
<th></th>
<th>Study group n=47</th>
<th>Comparative group n=47</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>36 (76.6%)</td>
<td>32 (68.1%)</td>
<td>0.356</td>
</tr>
<tr>
<td>Septic shock</td>
<td>5 (11.6%)</td>
<td>8 (17.0%)</td>
<td>0.370</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>6 (12.8%)</td>
<td>7 (14.9%)</td>
<td>0.765</td>
</tr>
</tbody>
</table>

The severity of sepsis is shown in table 4 above. In the study group 12.8% patients had severe sepsis in the study group while in the comparative group it was 14.9% shown in table 5. There were more patients with severe disease in the comparative group compared to the study group. The difference in the two groups did not reach statistical significance.
Table 5 Clinical characteristic study group control based on consensus conference criteria for diagnosis of sepsis 2008

<table>
<thead>
<tr>
<th>Category</th>
<th>Study group BP mmHg</th>
<th>Control group BP mmHg</th>
<th>Study group Pulse /min</th>
<th>Control group Pulse /min</th>
<th>Study group Temp °C</th>
<th>Control group Temp °C</th>
<th>Study group resp/min</th>
<th>Control group resp/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>89.1 ± 3.1</td>
<td>88.8 ± 3.4</td>
<td>108.9 ± 23</td>
<td>101.0 ± 12.7</td>
<td>37.7 ± 0.8</td>
<td>37.6 ± 1.1</td>
<td>37.7 ± 0.8</td>
<td>26.8 ± 3.2</td>
</tr>
<tr>
<td>Severe Sepsis</td>
<td>87.0 ± 4.5</td>
<td>88.5 ± 3.5</td>
<td>114.6 ± 12</td>
<td>106.0 ± 18.9</td>
<td>38.1 ± 0.9</td>
<td>37.3 ± 0.8</td>
<td>38.1 ± 0.9</td>
<td>26.0 ± 4.3</td>
</tr>
<tr>
<td>Septic shock</td>
<td>87.2 ± 4.5</td>
<td>89.4 ± 1.5</td>
<td>119.0 ± 7.1</td>
<td>98.1 ± 10.7</td>
<td>37.9 ± 1.1</td>
<td>37.2 ± 0.8</td>
<td>37.9 ± 1.1</td>
<td>26.9 ± 3.0</td>
</tr>
</tbody>
</table>

Table 5 above shows various vital signs that were observed from the study. The mean BP in those who had sepsis was 89.1 ± 3.1 in the study group while in the control group was 88.8 ± 3.4.

Table 6 Creatinine and electrolyte levels in study and control group

<table>
<thead>
<tr>
<th></th>
<th>Study group n=47</th>
<th>Comparative n=47</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium mmol/l</td>
<td>3.95 ± 0.52</td>
<td>4.10 ± 0.55</td>
<td>0.17</td>
</tr>
<tr>
<td>Sodium mmol/l</td>
<td>136.2±6.23</td>
<td>137.1±4.2</td>
<td>0.37</td>
</tr>
<tr>
<td>Creatinine umol/l</td>
<td>138=150.7</td>
<td>170.3±209.5</td>
<td>0.40</td>
</tr>
</tbody>
</table>

The patient’s renal indices were as shown in table 6. Majority of the patients had normal potassium, sodium and creatinine levels. There was no difference of statistical significance in creatinine and electrolytes in the two groups.

Table 7 Mean Cortisol levels at baseline

<table>
<thead>
<tr>
<th></th>
<th>Study group</th>
<th>Comparative group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Percentage</td>
<td>Mean cortisol levels (nmol/l)</td>
</tr>
<tr>
<td>Adrenal Ins.</td>
<td>13</td>
<td>27.7</td>
<td>85.2±22.8</td>
</tr>
<tr>
<td>Normal adrenals</td>
<td>34</td>
<td>74.3</td>
<td>331.1±200.1</td>
</tr>
</tbody>
</table>
Fig. 4 Proportions of patients cortisol levels at baseline for study and comparative groups

Figure 5 Mean baseline mean cortisol levels of patients in the study and comparative groups
The prevalence of low cortisol levels at baseline was higher in the comparative group at 38.2% higher than 27.7% in the study group shown in table 7 above and figure 4 below. The absolute baseline cortisol levels were lower in the study group than that in the comparative group at baseline cortisol levels. The difference in absolute mean cortisol levels in those who had adrenal insufficiency in the two groups was not statistically significant p=0.63.

There were more patients with normal cortisol level in the study group at baseline at 74.3% compared to 61.6% in the comparative group. The difference in proportions between the two groups was not significant.
Table 8 Interpretation of response to ACTH stimulation

<table>
<thead>
<tr>
<th>Response to ACTH</th>
<th>Study group</th>
<th>Comparative group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Percentage</td>
<td>Mean absolute cortisol change</td>
</tr>
<tr>
<td>Abnormal</td>
<td>12</td>
<td>25.5</td>
<td>86.8 ±56.7 nmol/l</td>
</tr>
<tr>
<td>Normal</td>
<td>1</td>
<td>0.02</td>
<td>856.7 nmol/l</td>
</tr>
</tbody>
</table>

The cortisol levels of the patients who had low baseline cortisol level are shown in table 8 above. The maximum response in the study group in those who had low baseline cortisol was achieved by one patient. The cortisol level of this patient rose above the target 414 nmol which is the expected minimum rise in cortisol level post stimulation. Nearly all the patients in the study group who had low baseline cortisol level did not achieve maximal response to ACTH stimulation. Based on this finding there were 24% patients in the study group who had primary adrenal. Secondary adrenal insufficiency occurred in 2.1% of patients in the study group.

Maximal response was achieved by 2 patients in the comparative group in those who had low baseline cortisol levels. The level of cortisol in these two patients rose by 844.3 ±66.1 a level above the target 414 nmol/l minimum level expected post stimulation. Majority patients in the comparative group did not achieve expected rise in cortisol after stimulation of their adrenal glands with synthetic ACTH. Therefore primary adrenal insufficiency occurred in 34% in while secondary adrenal insufficiency occurred in 4.2% in the comparative group.

It was noted that in the two groups of patients the levels of cortisol were lower than target levels of cortisol at 60 minutes post stimulation with ACTH. It was expected that those who had not achieved maximum response at 30 minutes would achieve it at 60 minutes.
The patients who had a rise at 60 minute were noted to have drops in cortisol levels. Those who had achieved minimal response at 30 minutes were noted to have a fall in cortisol levels at 60 minutes. Since all the had achieved a response in cortisol levels at 30 minutes ACTH response was analyzed with cortisol levels at 30 minutes.

Table 9 Outcome of study patients at 2 weeks follow up

<table>
<thead>
<tr>
<th>Category</th>
<th>Study group n=47</th>
<th>Comparative group n=47</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total alive</td>
<td>34</td>
<td>28</td>
<td>0.192</td>
</tr>
<tr>
<td>Mean number of days before discharge days</td>
<td>11.3</td>
<td>7.7</td>
<td>0.005</td>
</tr>
<tr>
<td>Total died</td>
<td>11</td>
<td>15</td>
<td>0.356</td>
</tr>
<tr>
<td>Mean number of days before death</td>
<td>8.7</td>
<td>6.1</td>
<td>0.28</td>
</tr>
</tbody>
</table>

The mean number of days patients stayed in hospital before discharge was 11.3±5.5 in the study group and 7.7±4.1 in the comparative group shown in table 9. The study group patients stayed longer than the comparative group. The difference in duration of stay was statistically significant p= 0.005.

In the study group 72.3% and 59.6% patients in the comparative group were alive by 2 weeks of stay in the hospital the difference was not significant.

The maximum duration of stay in the hospital in the study group was 11.3 days while in the comparative group was 7.7 days and the difference was significant p= 0.005.

There were more deaths in the comparative group at 2 weeks.
In the comparative group 34% patients died before 2 weeks while in the study group 24% died. The difference in the number of deaths was not significant.

There were 11 deaths in the study group. Among the patients that died in this group 2 had primary adrenal insufficiency. The absolute mean increase in cortisol level of these
two was 96.9 nmol/l \(\pm 35.5\). The rest of the 9 patients that died had functional adrenal insufficiency. The mean change in cortisol level in these patients was 133.1 \(\pm 18\) nmol/l.

The total number of patients that died in the comparative group was 16. In this group, 5 patients that died had had primary adrenal insufficiency. The mean change in cortisol level was 127.8 \(\pm 72.6\) nmol/l. The remaining 11 patients that died had functional adrenal insufficiency. The mean increase in cortisol level in this group was 96.4 \(\pm 21.2\) nmols/l.

**DISCUSSION**

Adrenal insufficiency is a common condition in patients hospitalised with sepsis. The prevalence varies from 19% found by Meya et al among critically ill HIV patients admitted in Mulago to 75% found by Marik et al in severely ill admitted in ICU. HIV infected patients are at higher risk of adrenal insufficiency. Potential mechanisms for the development of adrenal insufficiency in patients with HIV infection include:

- HIV infection of the adrenals or co-infection with cytomegalovirus or mycobacteria
- Destruction of the adrenal glands by tumor (lymphoma, Kaposi’s sarcoma)
- Adrenocortical hemorrhage secondary to coagulopathy
- Diminished adrenal secretion as an effect of cytokines such as tumor necrosis factor-\(\alpha\) Inhibition of the 11-\(\beta\) hydroxylase enzyme necessary for steroid synthesis by drugs such as ketoconazole and rifampicin
- Stimulation of cytochrome P-450 enzyme activity with increased metabolism of cortisol

The patients in this study had a mean age of 36 \(\pm 12\) in the study group. This is the age group likely to be infected with HIV in the local epidemiological pattern. The commonest cause of sepsis was pneumonia or chest infection at 46.8% in the study group. This is within the range observed in other studies where the cause of sepsis was pulmonary infections in 57% HIV admitted with critical illness in Mulago hospital.
There were more patients with primary adrenal insufficiency in the comparative group. The prevalence of primary adrenal insufficiency at was 25.5% in the study group and 34% in the comparative group.

The prevalence of primary adrenal insufficiency in the study group was higher than the 19% found by Meya and colleagues in HIV infected in patients admitted in Mulago hospital with critical illness. These patients were similar to those that Meya et al included in their study in that they were HIV infected. The patients in this study were HIV infected admitted with sepsis. In the study done in Uganda HIV patients admitted with critical illness were included in the study. Meya’s group used the modified Patient at Risk Team criteria to select patients with critical illness. The study group patients were identified by a tool adopted from consensus conference to define sepsis held 2008. It is possible that the clinical states of patients in the two studies were different. The study group patients may have been in poor clinical state compared to those in Meya et al study.

In this study the adrenal glands of the study group patients were stimulated with synthetic ACTH. Meya and colleagues did not stimulate their study patient with synthetic ACTH. The prevalence of adrenal insufficiency was based on baseline cortisol level and presence of eosinophilia. These differences in the mode of establishment of adrenal insufficiency accounts further for the differences of prevalence observed in the two studies.

The prevalence of adrenal insufficiency was 34% in the comparative group was much lower than that found by Marik and colleagues. Marik and colleagues conducted a study in patients admitted with sepsis in ICU uninfected with HIV. Marik and his team found the prevalence of adrenal insufficiency to be 61% much higher than that found in the control group in this study. Marik and colleagues conducted their study in intensive care setting in Washington center hospital. The diagnosis of sepsis was based on
consensus criteria by the Society of critical care Medicine /American college of Chest Physicians criteria for septic shock similar to what was used to identify the comparative group in this study. The clinical severity of disease in the comparative group by available scoring systems as Acute Physiology and Chronic Health Evaluation (APACHE) was not done. This was because some of the parameters used in evaluation were not determined for logistic reason. Marik et al patients were scored by APACHE score although the scores of the patients are not included in his report. It is possible that the clinical severity of patients involved in these two studies was different.

The mean level of cortisol in the study group was 85.2 ±22.8 nmols and 90.2 ± 31.3 nmol in the comparative group. These levels of cortisol in the two study groups in this study compares with 121.4±19 nmols found in the Brazilian study done by Rosita and colleagues. Rosita Fontes and colleagues conducted a study in Brazil among patients with acquired immunodeficiency syndrome to study endocrine disorders in HIV infected. The control group included by Rosita et al consisted of healthy HIV uninfected volunteers while the study group consisted of HIV infected patients with mixed clinical presentation attending an out patient endocrine clinic. Rosita et al did not quantify the prevalence of adrenal insufficiency before and post stimulation. These mixed clinical presentations of patients studied by Rosita et al were: with no symptoms, with opportunistic infections, neoplasm and non specific symptoms associated with adrenal insufficiency. The patients in these two studies were different in that Rosita conducted a study in stable out patients while this study focused on patients admitted with sepsis.

There were more deaths in the control group compared to the study group. In the comparative group 15 (31.9%) patients died in the control group while in the study group to 11 (24 %) died. The high number of deaths in the control group may have occurred because of complicated sepsis occurring in the study group. Clinical severity of participants was not scored it could be that there were more sick patients in the control group. The prevalence of death among the comparative group compares closely with 47 % found by Marik and colleagues. The prevalence of adrenal insufficiency in those who died in the comparative group was 23.4% which is lower than 42% found by Marik et al.
Marik et al patients were selected similarly to the comparative group of patients although they were all ICU. Meya et al conducted a study in Mulago hospital in HIV infected critically ill patients. In the study conducted by David Meya 30% patients died. This is slightly higher than the 24% death in the study group. All the patients that died in that study had normal adrenal function. The 19.1% patients who died in this study were found to have functional adrenal insufficiency. More than half of the patients with adrenal insufficiency were discharged while half the patients with normal adrenal function died.

Patient’s cortisol levels were found to be decreasing one hour post stimulation. There were more patients with cortisol levels below the target 414 nmols at 60 minutes post stimulation. In this study 1 ug/1.73m2 of synthetic ACTH was used similar to the study conducted by Rasmuen et al. These results agree with the observations made by Rasmuson et al. Rasmuson conducted a study to evaluate the HPA axis in patients admitted in medical wards with 1ug/1.73m2. He found that 96% patients had maximal stimulation at 30 minutes with only 4% having maximal stimulation after 60 minutes. The observation in the study done by Rasmusons’ and colleagues correlated highly with serum cortisol levels done during a concurrent Insulin Tolerance Test ($r's = 0.91 - 0.93; P< 0.0001$) which is considered the gold standard for testing the hypothalamic pituitary adrenal axis. The standard 250ug of synthetic ACTH has been found to be supra physiological and causes a serum cortisol rise which is incomplete at 30 minutes in a study done by Wood and colleagues in who had just undergone major surgery. It has been postulated that high (ACTH 250mg) levels induce further mobilization or synthesis of cortisol from other pools as observed in a study done by Wood and colleagues.
CONCLUSION

There was an apparent difference in adrenal sufficiency in the two groups of patients involved in this study.

Majority of the study group patients were in WHO stage 4 HIV disease. HIV patients admitted in Kenyatta hospital present in late stage HIV disease. These late stage HIV patients were not on anti retroviral medication at the time of admission.

Pneumonia and meningitis were common presentation and cause of sepsis in patients admitted in Kenyatta hospital.

There were more deaths in the control group compared to the study group.

There is a significant difference in duration of stay in hospital. HIV infected patients with sepsis patients stayed longer in hospital than HIV uninfected. This is may due to severe degree of sepsis in the HIV although this can to be attributed to findings in this study since clinical scoring of disease was not done.

RECOMMENDATIONS

1. The prevalence of adrenal insufficiency is high in patients admitted with sepsis in KNH. Studies should be conducted in future looking at adrenal insufficiency and appropriate interventions provided to patients admitted with sepsis and outcome.

2. There were more deaths in the control group compared to the study group. The patients in this study were not scored by clinical scoring criteria for disease severity. We postulate that the clinical condition of the patients in the study group may have been worse than that of the study group. In order to compare the study groups adequately in subsequent similar studies scoring for severity of disease is essential.

3. The peak time point for cortisol levels after stimulation with ACTH seems to be different from that found when 250ug of synthetic ACTH is administered. Further studies to evaluate peak time for Low dose ACTH stimulation test should be conducted and response to ACTH stimulation is assayed at 30 minutes 45 and 60 minutes to establish when optimal stimulation is achieved by the majority.
STUDY LIMITATIONS

The patient's clinical severity of disease was not established by existing clinical scoring tools such as APACHE II scores. It is therefore not known whether the two groups were different by clinical severity of disease.

The study did not establish the types of treatment that were administered in the two groups of patients. There is a possibility that the treatments provided in the two groups were different explaining the apparent differences in the prevalence of adrenal insufficiency and outcome at 2 weeks.
STUDY PROFORMA (APPENDIX 1)

1) Baseline characteristics

Date.../...../......
Hospital No
Study No
Age ________ years
BMI: ________ kg/m2 B/P
Temp deg cent
Weight ________
Height:
Systolic - Diastolic -
Resp Rate/min
Heart rate/min
HIV state:
Year tested for HIV
WHO stage of HIV if HIV positive

2) Clinical History

History of
Yes No
Diarrhea
Nausea
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amenorrhea</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Previous anti-tuberculosis treatment: no
(In the previous 5 years)

Current anti-tuberculosis regimen

Current use of ARVs: yes no

Hyper pigmentation of skin present yes no

Current use of phenytoin

Ketoconazole
Mesesterol

Opiates

Anticoagulants

Presence of diabetes mellitus, thyroidism
Specify

Use of immunosuppressive medications

3) Final diagnosis

4) Laboratory results

4) Laboratory results

4) Laboratory results
d) Current CD4 levels previous 3 months

Cortisol assay

<table>
<thead>
<tr>
<th></th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>nmol/l</td>
</tr>
<tr>
<td>Baseline cortisol</td>
<td></td>
</tr>
<tr>
<td>Cortisol 30 min after stimulation</td>
<td></td>
</tr>
<tr>
<td>Cortisol 60 min after stimulation</td>
<td></td>
</tr>
<tr>
<td>Difference in response</td>
<td></td>
</tr>
<tr>
<td>Electrolytes</td>
<td>Results</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Baseline Potassium mmol/l</td>
<td></td>
</tr>
<tr>
<td>Baseline Sodium mmol/l</td>
<td></td>
</tr>
<tr>
<td>Baseline creatinine mmol/l</td>
<td></td>
</tr>
</tbody>
</table>

4) Condition of adrenal glands

- Functional Adrenal Failure
- Normal adrenal function

OUTCOME

Date.../....../.....
dd/mm/yy

Name

Study No

Outcome Discharged

- Yes
- No

How many days did the patient stay in before discharge from hospital? ..................

If no, did the patient die is it death? Yes

How many days did the patient stay in hospital before death? ..................
Screening Patients for Severe Sepsis

A patient who meets the following 3 criteria has a positive screen suggestive of severe sepsis:

**INFECTION**—Does your patient have one or more of the following infection criteria?

- DOCUMENTED OR SUSPECTED—Does the patient have positive culture results from blood, sputum, urine, etc.?
- ANTI-INFECTIVE THERAPY—Is the patient receiving antibiotic, antifungal, or other anti-infective therapy?
- PNEUMONIA—Is there documentation of pneumonia (x-ray, etc.)?
- WBCs—Has WBCs been found in normally sterile fluid (urine, CSF, etc.)?
- PERFORATED VISCUS—Does the patient have a perforated hollow organ (bowel)?

► DID YOU CHECK ANY BOXES ABOVE?

**SIRS**—Does your patient have two or more of the following SIRS criteria?

- TEMPERATURE—Is the patient’s temperature ≥ 38°C (≥ 100.4°F) or ≤ 36°C (≤ 96.8°F)?
- HEART RATE—Is the patient’s heart rate > 90 bpm?
- RESPIRATORY RATE—Is the patient’s respiratory rate ≥ 20 breaths/min?
- WBC COUNT—Is the patient’s WBC count ≥ 12,000/mm³ ≤ 4000/mm³, or are there > 10% immature neutrophils (left shift)?

► DID YOU CHECK TWO OR MORE BOXES ABOVE?

**ACUTE ORGAN DYSFUNCTION**—Does your patient have one or more of the following organ dysfunction criteria?

- CARDIOVASCULAR—Does the patient have a systolic BP ≤ 90 mm Hg or mean arterial pressure ≤ 70 mm Hg for at least 1 hour despite fluid resuscitation or require vasoressor support?
- RESPIRATORY—Does the patient have a PaO₂/FiO₂ ratio ≤ 250, PEEP > 7.5 or require mechanical ventilation?
- REMAL—Does the patient have low urine output (eg, < 0.5 mL/kg/hr for 1 hour despite adequate fluid resuscitation), increased creatinine (> 50% increase from baseline) or require acute dialysis?
- HEMATOLOGIC—Does the patient have a low platelet count (< 100,000/mm³) or PT/PTT > upper limit of normal?
- METABOLIC—Does the patient have a low pH with high lactate (eg, pH ≤ 7.30 and plasma lactate ≥ upper limit of normal)?
- HEPATIC—Are the patient's liver enzymes > 2x upper limit of normal?
- CNS—Does the patient have altered consciousness or a reduced Glasgow Coma score?

► DID YOU CHECK ANY BOXES ABOVE?

**IF YOU CHECKED:**

A) INFECTION + B) SIRS + C) ORGAN DYSFUNCTION = POSITIVE SCREEN SUGGESTIVE OF SEVERE SEPSIS

Lilly Acute Care
Definitions for Sepsis-related Clinical Conditions

SIRS  Systemic inflammatory response to an insult or injury, independent of cause, with more than one of the following manifestations:\footnote{1}
- Temperature $\geq 100.4^\circ\text{F}$ or $\leq 96.8^\circ\text{F}$ ($\geq 38^\circ\text{C}$ or $\leq 36^\circ\text{C}$)
- Heart rate $\geq 90$ beats/min
- Tachypnea, as manifested by a respiratory rate $\geq 20$ breaths/min or hyperventilation, as indicated by a PaCO$_2 \leq 32$ mm Hg
- Alteration of white blood cell count $\geq 12,000$ cells/mm$^3$, $\leq 4000$ cells/mm$^3$, or the presence of $> 10\%$ immature neutrophils

Sepsis  SIRS resulting from infection (bacterial, viral, fungal, or parasitic)\footnote{1}

Severe sepsis  Sepsis associated with signs of at least one acute organ dysfunction, hypoperfusion, or hypotension\footnote{1}

Septic Shock  Sepsis-induced hypotension persisting despite adequate fluid resuscitation\footnote{1}

MODS  Multiple Organ Dysfunction Syndrome. Presence of altered function of two or more organs in an acutely ill patient such that homeostasis cannot be maintained without intervention\footnote{1}

This document lists some [but not all] common clinical criteria that may be used to screen patients for severe sepsis. It is intended for healthcare professional educational purposes only. By providing this document, Lilly is not making recommendations on diagnosis or treatment of any particular patient. The judgment of the physician/clinician, based on knowledge of the specific patient, should always be the deciding factor.

Reference:

Lilly
Study Consent Form
CONSENT FORM FOR PARTICIPATION IN THE STUDY

Principal investigator Dr Florence Keli 0722 362 377
Department of clinical and Therapeutic Medicine

Introduction
Adrenal glands are small organs located above the kidneys. Patients with HIV-infection may suffer failure of adrenal glands leading to inability in to handle severe infections. Patients may then feel tired, weak with general body pain, abdominal pain, vomit, cough and colour of the lighter parts of the body may change to become darker.

Objectives
We can only tell those affected after we measure the levels of a certain chemical (cortisol) in the blood of these patients. The level of the chemical goes down in affected patients. This study will involve taking a medical history from you, checking your medical records, doing a physical examination including taking your weight and taking blood from you three times.

Procedure and ethical issues
The first time only 1 ml of blood will be taken from a vein in your forearm and this will be used to measure the level of the chemical in your blood. You will then be given an injection of a drug that will make your body to produce the chemical we are studying. We will then take an ml of blood after 30 minutes and 60 minutes from the time you received the drug. Your doctor will be provided with your investigation reports. You will then be managed depending on the outcome of the results.

Risks
You will feel slight pain as blood is drawn for the investigations above.

Benefits
Participation in this study will help in early detection and early intervention of failing adrenal glands. The primary cause of failure of the gland will be managed where possible.

**Participant’s Rights**

Participation in the study is a matter of choice and it is your right to choose to participate or fail to. If you choose not to participate your medical care will not change. Confidentiality will be maintained at all times. At the end of the study, I will hand over the study findings to the medical department in the University of Nairobi. Any useful information that will improve the quality of care will be shared with the caregiver for appropriate action.

**Consenting**

All patients will receive a copy of the consent form to read and keep for further reference. All correspondence can be done through the following

**Patients signature** .................................................. **Date** ......................

**Researchers signature** .................................................. **Date** ......................

Dr Florence Keli- Kariithi  
Clinical Medicine and Therapeutics  0722 362 377

Proff Bhatt  
Chairperson Ethics review committee  
Prof Bhatt  
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