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THE CORTICOSTEROIDS IN SEPTIC SHOCK CONTROVERSY

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Content

Introduction

Sepsis and septic shock are common in critically ill patients, and it is one of the leading causes of mortality in critical care units. The reported incidences ranged between 50 and 300 cases per 100 000, and this is expected to rise in the future (1) (2),potentially reflecting an increase in the immunocompromised population in society with aging and an increase in immunocompromising diseases such as HIV. Despite management directed at the infective organisms, such as early administration of an antimicrobial, fluid resuscitation, and cardiovascular and respiratory support, mortality due to sepsis remains high and could reach up to 70% when organ dysfunction and shock are present (3).

The initial definition of sepsis was developed in the 1991 consensus conference and defined sepsis as a "host's systemic inflammatory response syndrome (SIRS) to infection". Severe sepsis was defined as sepsis complicated by organ failure, such as hypoperfusion, hypotension or oliguria. This could proceed into septic shock, as evidenced by persistent hypotension despite fluid resuscitation (4). The 2001 task force definitions did not change significantly, only expanding the list of diagnostic criteria for severe sepsis, (5) until the publication of Sepsis-3). (6)**.** Sepsis-3 no longer referred to SIRS, removed the concept of severe sepsis, and now just referred to infection with organ dysfunction as sepsis. It also included hyperlactataemia of **>** 2 mmol/L as a mandatory component of the definition of septic shock. Sepsis is now defined as **"**life-threatening organ dysfunction due to a dysregulated host response to infection". Septic shock is “a subset of sepsis where underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality"

Endogenous corticosteroids are powerful anti-inflammatory agents that have a number of important regulatory functions. Corticosteroids modulate the inflammatory response by the inhibition of complement-induced granulocyte activation, reduce free arachidonic acid liberation and inhibit cytokine syntheses. In addition to influencing the distribution of fluid and electrolytes, corticosteroids maintain endothelial integrity and vascular permeability by suppression of inducible nitric oxide synthase. Corticosteroids also play an important role in restoring and maintaining myocardial function, vascular tone and responsiveness to adrenergic agents by attenuation of adrenergic receptor downregulation (7).

The important role of pro-inflammatory mediators in the pathophysiology of septic shock suggests a possible therapeutic role for steroid treatment to restore balance to an altered hypothalamic-pituitary-adrenal (HPA) axis and potentially improve patient outcome. This was supported by experimental animal studies that showed survival improvement in animals with reduced mortality even without antibiotic therapy (8, 9). The corticosteroids use in sepsis and septic shock has been controversial, and has fluctuated forth and back over the past 50 years. Although data supports a beneficial effect of steroids on systemic blood pressure and time of shock reversal, there were contradictory results from large multicentre trials about the ability of corticosteroid treatment to improve survival. Despite more than 5 decades of human trials, studies, debates and experimental animal studies, the role of corticosteroids, and even the evaluation of adrenal function, in sepsis is still controversial.

The controversy of corticosteroids in severe sepsis and septic shock is not as simple as whether corticosteroid therapy is beneficial to septic patients or not. Other important questions need to answered, such as which septic patients to be treated (severity of illness), corticosteroid drug, regime and dose, optimal duration of treatment, and whether the ACTH stimulation testing influences the steroid effects or not. Unfortunately, the current evidence and available clinical data do not answer all these important questions (8).

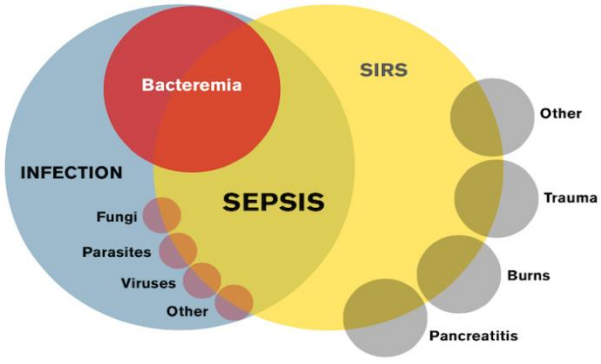

Figure 1 SIRS, infection and sepsis from 1992 consensus definition (4)

Pathophysiology of sepsis and septic shock

Severe infection triggers the immune system and inflammatory cascade after the recognition of pathogen associated molecular patterns (PAMPs), this occurs by stimulation of leukocytes and endothelium cells to release inflammatory mediators in the local infected area. The triggers can be a microorganism or a part of it such as a cell wall component, a DNA fragment or an exotoxin. Cytokines are inflammatory polypeptides that have effects on metabolic and endocrine function in addition to its immune role. TNF-α is the first pro-inflammatory cytokine to appear in the circulation, it stimulates phagocytosis, neutrophil adherence and degranulation (10). Interleukin (IL)-1 induces enzyme synthesis such as cyclooxygenase and nitric oxide synthase (NOS). IL-10 and IL-14 are anti-inflammatory cytokines, which are associated with downregulation of the immune response (7).

Although the proinflammatory response has an important role against infection and necrotic tissue to promote wound healing, dissemination of the inflammatory mediators into the systemic circulation, with a failure of anti-inflammatory responses to downregulate and balance the inflammation, leads to hemodynamic changes, microvascular abnormalities and mitochondrial dysfunction. This may culminate in tissue injury and organ failure by altering oxygen delivery, extraction and utilization (7, 11).

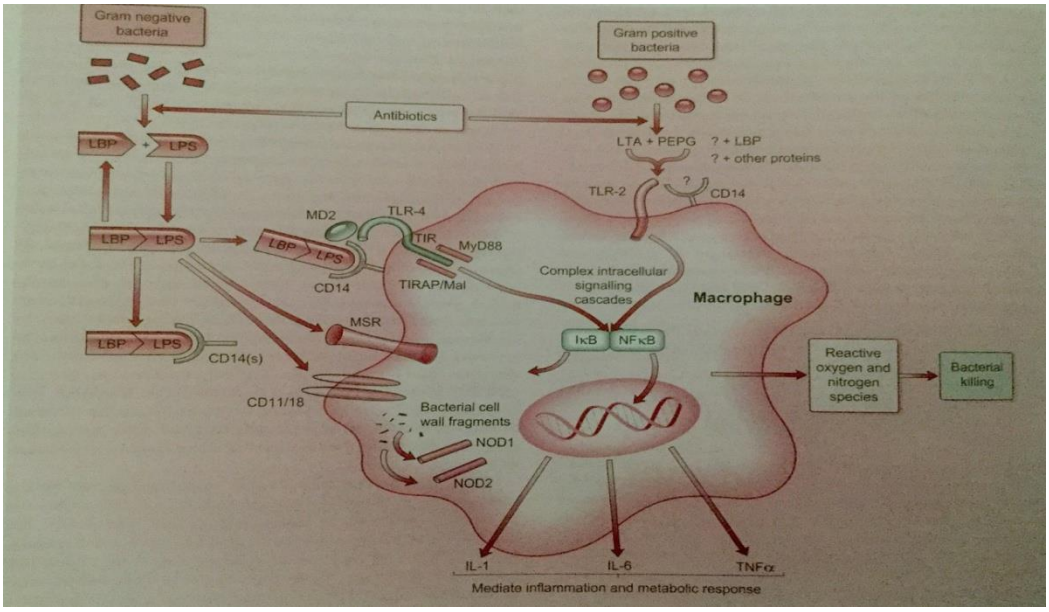

Figure 2 Immune system response to pathogens (7)

Effects of SIRS on the circulation

A drop in the systemic vascular resistance results from sustained generalized vasodilatation caused by vasodilator substances such as nitric oxide NO, this leads to hypotension, and intravascular pooling of blood, with hyporeactivity to adrenergic agents and loss of vasoregulation. Ventricular function may be negatively affected during sepsis by circulating myocardial depressant substances such as nitric oxide (NO), IL-6 and TNF-α. These lead to decreased ejection fraction and reduced left ventricular stroke work. All these potentially result in tissue hypoperfusion and tissue hypoxia (7, 12).

Effects of "SIRS" on endothelium and microvasculature

In health, the endothelium secretes vasoactive substances to regulate blood flow in the microvasculature, thus all organs are adequately perfused and oxygenated (12). Sepsis is associated with vascular endothelial damage, this leads to loss of endothelial regulatory mechanisms with an increase in extravascular leukocyte migration, leukocyte rolling and adherence. Large amounts of nitric oxide are produced as a result of an increase in inducible NOS (7), That increases microvascular permeability. This leads to a shift of fluid from the intravascular into the extra vascular space causing further hypotension and tissue edema, which causes mechanical compression of capillaries and increases diffusion distance. In addition to activation of the coagulation system, fluid shifts increase blood viscosity with haemoconcentration. All these changes lead to microvascular thrombosis with maldistribution of the blood flow and oxygen supply to tissues, which leads finally to tissue injury and organ failure (13).

Effects of "SIRS" on mitochondrial function and oxygen utilization

Mitochondria are the place where more than 85% of oxygen extracted by cells is used to produce energy (ATP) by oxidative phosphorylation. Mitochondria in sepsis are less able to use oxygen, which is seen as increased venous oxygen saturation and decreased oxygen content differences between arteries and veins. NO and reactive oxygen species (ROS) have direct inhibitory effects on the mitochondrial respiratory chain, with NO competing with oxygen in complex 4 and 1. There is also a decrease in NADH availability,

because cells use NADH in DNA damage repair caused by ROS (7). Mitochondria trigger cell apoptosis when mitochondrial function is disturbed, and this is worsened by mitochondrial lysis which releases proapoptotic factors. These factors lead to cellular death and enhance multi-organ dysfunction.

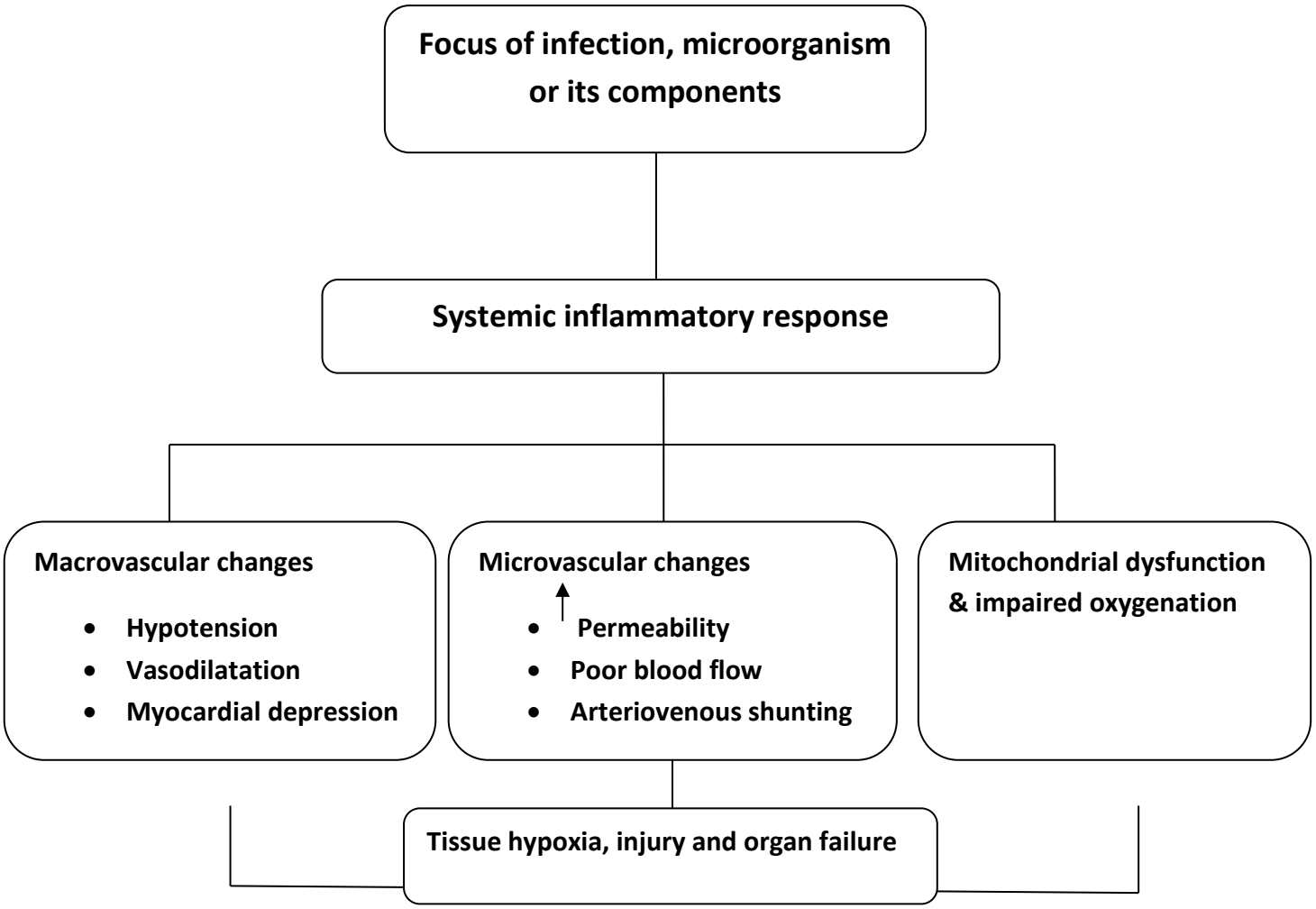

Figure 3: Pathphysiology of multiple organ dysfunction in sepsis and the effects of sepsis on organ function (7).

The hypothalamic pituitary adrenal HPA axis in septic shock

In a healthy unstressed person, serum cortisol levels range from 5 to 24 mcg/dl (138 – 662 nmol/l) (14). Cortisol is the main corticosteroid that is released from the adrenal glands under the influence of the pituitary gland according to a diurnal pattern. Complex sets of positive and negative signals and feedback control the HPA axis to regulate cortisol synthesis and release. The hypothalamus secretes corticotropin releasing hormone (CRH) to initiate the synthesis and stimulate the release of the adrenocorticotropic hormone (ACTH) from the anterior Pituitary. ACTH stimulate cortisol secretion from the adrenal glands. High level of circulating cortisol inhibits further production and release by a negative feedback control of both CRH and ACTH. Cortisol-binding globulin and albumin bind to the majority of cortisol in the circulation, leaving about 10% in the active, free form (15). During critical illnesses, such as severe infection and surgery, free cortisol level increases due to a rapid drop in corticosteroid-binding globulin and albumin (8).

Critical illness activates the HPA axis and lead to loss of the normal circadian rhythm and diurnal variation pattern (16). Circulating cytokines stimulate the release of CRH and ACTH with a reduction in the negative feedback. This leads to a marked increase in plasma cortisol, reaching levels up to 40 to 50 mcg/dl (15, 16). Cytokines can further alter peripheral cortisol metabolism and disable glucocorticoid inactivation. The amount and duration of the increase in cortisol levels are roughly proportional to the severity of the illness. The exact association between circulating levels of cortisol and outcomes remains unknown. Many studies have reported an association between higher plasma cortisol levels and a worse outcome (16, 17). In contrast, others have demonstrated that lower cortisol levels were found in non-survivors than in survivors (7).

Relative adrenal insufficiency

Relative, occult or functional adrenal insufficiency has been defined as suboptimal cortisol production during septic shock, and inadequate glucocorticoid activity in relation to the severity of the illness. This term "relative adrenal insufficiency" has changed recently to a more accurate term "critical illness related corticosteroid insufficiency (CIRCI)" (18, 19). The Consensus Task force of the American college of Critical Care Medicine defined

CIRCI as "a delta serum cortisol increase of less than 9 microgram per deciliter following administration of 250 microgram ACTH or a random total cortisol level of less than 10 mcg/dl" (19). Normal adrenal gland function is essential to survive critical illness. Animals that underwent adrenalectomy and were infected with live bacteria inevitably died, while there was outcome improvement in animals that received supplemental corticosteroids (20).

Many studies found that, in septic shock, suboptimal cortisol production and a maximum increase of serum cortisol of 9 mcg/dl or less after intravenous synthetic corticotrophin hormone might be common and associated with increased mortality. The mechanism of adrenal suppression during sepsis is not completely understood. Tissue resistance to glucocorticoid may be induced when high levels of inflammatory cytokines such as TNF-α compete with corticotrophin at its receptors. Adequate adrenocortical cells response to severe stress requires intact intra-adrenal cell-to-cell communication and crosstalk. High levels of circulating inflammatory cytokines, nitric oxide, superoxide and neuropeptides in sepsis may impair blood flow to the adrenal and pituitary gland. These can lead to pituitary and adrenal ischemia and necrosis (17, 21).

Etomidate and its effect on adrenal responsiveness

Many critically ill patients require emergency endotracheal intubation for airway control and mechanical ventilation. Etomidate is a carboxylated imidazole anesthetic agent that has been used widely to facilitate endotracheal intubation in patients with unstable haemodynamics, because of its low incidence of cardiovascular complications (22). Etomidate has been known to impair Corticosteroid synthesis by reversible inhibition of 11-β-hydroxylase. Following a single bolus, etomidate effect on adrenal function can last up to 30 hours (23). The effect of etomidate on adrenal function was first noticed when an excessive mortality rate was found in trauma patients who were sedated by etomidate infusion (24, 25). Now etomidate is recognized as an important cause of relative adrenocortical deficiency. A prospective observational study of 62 acutely ill patients who needed mechanical ventilation found the use of a single bolus of etomidate was

associated with an increased likelihood of relative adrenocortical deficiency (poor response to corticotrophin) for at least 24 hours after administration (22).

An a-priori sub-study of the CORTICUS trial analyzed the effects of etomidate on adrenal responsiveness and mortality in patients with septic shock and confirmed that a single bolus dose of etomidate was associated with an increased incidence of inadequate adrenal responsiveness, and increased mortality (23). Similarly, Annane et al showed that 94% of patients who received etomidate for facilitating intubation did not respond to the ACTH-stimulation test and had a higher mortality rate (23, 26). A possible explanation for this can be that etomidate was used more in more severely ill patients with co-morbidities and unstable haemodynamics. In support of this, other studies comparing etomidate to ketamine for rapid sequence intubation in acutely ill patients, showed that, despite a significant increase in the incidence of inadequate adrenal responsiveness in patients who received etomidate, it was not associated with worse clinical outcomes (27, 28).

Diagnostic assessment of adrenal reserve in patients with septic shock

Diagnosing relative adrenal dysfunction and assessing adrenal reserve in patients with septic shock still remains questionable. Until the present time, there is no consensus regarding the optimum diagnostic methods of adrenal function during critical illness. Evaluation of adrenal function in sepsis is affected by several factors (8): expected total plasma cortisol levels vary according to type and severity of illness making it difficult to estimate the normal range, especially given that extreme high and low cortisol levels were demonstrated in patients with most severe illness and were found to be associated with poor outcome (15, 17). Alteration in the levels of corticosteroid-binding globulin, changes in corticosteroid receptor affinity to cortisol, and a decrease albumin concentration during sepsis made it more difficult to estimate the accurate levels of free cortisol. Even if total and free cortisol levels can be measured accurately, changes in peripheral tissue sensitivity to corticosteroids lead to a variance in the optimal level of circulating corticosteroids according to the condition of patients (15).

The ACTH stimulation test with the administration of either 1 mcg or 250 mcg of corticotrophin has been the traditional assessment method in the intensive care unit. In patients with septic shock, adrenal insufficiently is identified when there is an increase of less than 9 mcg/dl after a 250 mcg ACTH stimulation test (19). The sensitivity and specificity of the ACTH stimulation test, however, remains questionable and likely to be unreliable (15). It should be considered that the ACTH stimulation test only tests the adrenal response to corticotrophin and does not evaluate the HPA axis. The changes in plasma cortisol concentration after the administration of corticotrophin is a measure of adrenal reserve and does not evaluate adrenal function (29).

Due to the association between cortisol levels and severity of illness, it is not easy to determine what consider to be an appropriate response in a critically ill patient. Thus, it is useful to identify a minimum and maximum threshold of cortisol level in which adrenal insufficiently is likely when plasma cortisol levels are below this minimal threshold. On the other hand, adrenal insufficiency is unlikely and can be excluded when plasma cortisol levels are above the maximum threshold. Many studies have proposed different threshold levels for the definition of adrenal insufficiency during acute illness, however, none have performed entirely satisfactorily (15).

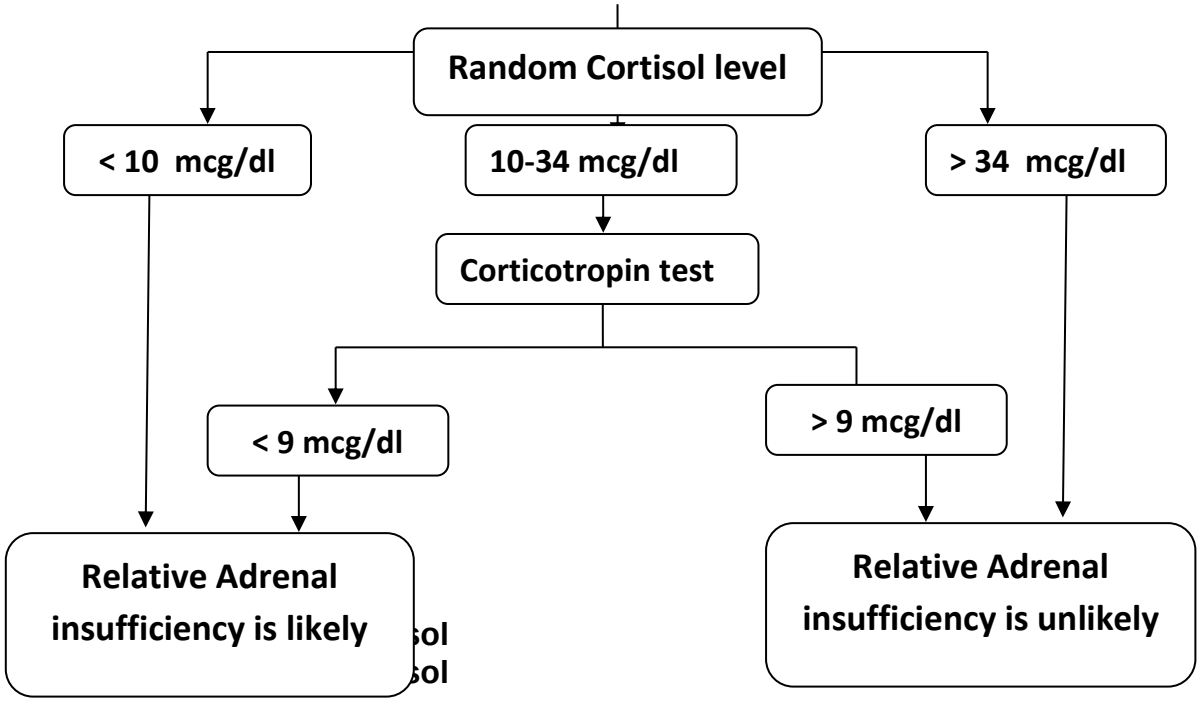

Figure 2: Diagnostic assessment of Adrenal reserve on basis of Cortisol levels and response to ACTH (15).

Random total serum cortisol

In septic shock, it is well known that total serum cortisol levels vary widely according to the severity of illness. This made many investigators try to find out if there is a predictive value of random cortisol levels on mortality. Random serum cortisol, in some studies, correlated with the severity of illness and mortality, with increased mortality associated with both low and high serum cortisol levels (30, 31). Conversely, other studies could not find any predictive value of cortisol levels on mortality.

Free cortisol

It has suggested that free cortisol might reflect HPA axis activation more accurately than total serum cortisol. During critical illness, there is a shift from the protein-bound inactive cortisol to the physiological active free cortisol. This occurs due to a marked drop in albumin and cortisol-binding globulin. In daily medical practice, plasma cortisol assays that measure total plasma cortisol are the standard assay, while free cortisol is not readily available because it is technically difficult and expensive.

In one study Ho and colleagues compared total and free plasma cortisol levels in patients with septic shock and sepsis (32). This prospective study included 74 patients, 45 patients had septic shock, 19 patients had sepsis and 10 were healthy controls. Total and free cortisol levels were measured before and after I.V administration of 250 mcg of corticotropin. They reported that free cortisol levels were likely to be a better indicator of, and corresponded more closely to the severity of illness than total cortisol levels. Basal free cortisol levels were much higher in patients with septic shock (186 nmol/l) in comparison to sepsis (29 nmol/l) or healthy controls (13 nmol/l). Another study compared total and free serum cortisol in 66 critically ill patients, of whom 18 had sepsis, to 33 healthy volunteers (33). Serum free cortisol concentrations were several times (up to 10-fold) higher in critically ill patients than healthy volunteers. This study was criticised for not documenting the degree of haemodynamic instability at the time of plasma cortisol sampling and not including any patients with septic shock.

A recent study compared total and free serum cortisol to interstitial tissue levels. Tissue levels were measured by using microdialysis catheters inserted into the subcutaneous adipose tissue of the thigh in mechanically ventilated septic patients (34). This study included a small number, only 35 ventilated, septic patients. They found that interstitial subcutaneous tissue cortisol was moderately correlated with total and free Serum cortisol. So far, the role of free cortisol levels in providing useful prognostic information in critically ill patients has not completely investigated and more studies are still needed.

ACTH stimulation test

The ACTH stimulation test has been the traditional assessment method of adrenal function in intensive care units. Pituitary ACTH consists of 39 amino acids, but the biological activity is presented in the N-terminal portion of the molecule. Synthetic ACTH is also known as cosyntropin, which consists of the first 24 amino acids of corticotropin (15, 16). There are two main types of ACTH stimulation tests, which are dependent on the dose of cosyntropin: the high-dose 250 mcg, and low-dose 1 mcg, ACTH stimulation tests. Before the administration of cosyntropin, a basal serum cortisol needs to be checked first, and after i.v. administration of cosyntropin, a serum cortisol level should be measured at 30 and 60 minutes later.

High-dose ACTH stimulation test

Numerous studies have used a high-dose ACTH stimulation test to identify patients with adrenal dysfunction in septic shock. They have, however, yielded variable results. Annane used a high-dose test to evaluate the prognostic value of cortisol levels and cortisol response to corticotropin in their prospective cohort study of 189 patients with septic shock (17). A maximum increase in cortisol of less than 9 mcg/dl and baseline serum cortisol level of more than 34 mcg/dl were identified as risk factors for death. They also identified 3 patterns of HPA axis activation, each one was associated with a different prognosis:

- In the first, 'best prognosis', group, 28-day mortality was only 26%, and it was associated with what was considered to be appropriate HPA axis activation: baseline plasma cortisol < 34 mcg/dl and a cortisol increase > 9 mcg/dl in response to cosyntropin.
- In the intermediate group, 28-day mortality was 67%. This group was defined by a baseline plasma cortisol < 34 mcg/dl and a cortisol increase < 9 mcg/dl in response to cosyntropin or a baseline plasma cortisol > 34 mcg/dl and a cortisol increase > 9 mcg/dl in response to cosyntropin "
- The third group had the worst prognosis, with a 28-day mortality rate of 82%. In these patients high basal cortisol levels (> 34 mcg/dl) were combined with low cortisol response (< 9 mcg/dl) to cosyntropin (17).

Another larger retrospective cohort study supported the findings of the Annane study: non-survivors had a lower cortisol response and higher baseline cortisol levels than survivors (35).

Table 1: Patterns of prognosis in Annane study. BC = Baseline cortisol, DC = delta cortisol (17)

Patterns	**28-mortality**	**Prognosis**
BC < 34 mcg/dl and DC > 9 mcg/dl	**26%**	**Good**
BC < 34 mcg/dl and DC < 9 mcg/dl or BC > 34 mcg/dl and DC > 9 mcg/dl	**67%**	**Poor**
BC > 34 mcg/dl and DC < 9 mcg/dl	**82%**	**Very poor**

Low-dose ACTH test

100 pg/ml of ACTH is enough to maximise stimulation of the adrenal cortex. Levels of ACTH after the use of high-dose ACTH increase markedly to reach up to 60,000 pg/ml, while using low-dose ACTH produces corticotropin levels of approximately 300 pg/ml (16, 29). This made some investigators think that 250 mcg of ACTH is supraphysiologic and can stimulate adrenal secretion of cortisol even when adrenal dysfunction exists (29). Patients who respond normally or adequately to high-dose ACTH may still have adrenal insufficiency when tested by insulin tolerance tests or metyrapone tests. Although these two dynamic tests are better and test the entire ACTH axis, they are not easy to perform during critical illness. Different studies have compared a low-dose, 1 mcg, corticotropin-stimulating test and the standard high 250 mcg dose for the diagnosis of relative adrenal insufficiency (21, 36):

The first study was a prospective cohort study that included 59 patients with septic shock, 29 of them were males, with a mean age 57 +/- 16.7 years (36). Patients were considered steroid-responsive if they could maintain their mean arterial pressure more than 65 mmHg without vasopressor agents within 24 hours of starting hydrocortisone. First, basal cortisol level was obtained, and then patients sequentially received an intravenous injection of 1 mcg and 250 mcg of corticotrophin at 60 minutes apart. Cortisol levels were measured 30 and 60 minutes after both high- and low-dose tests. All patients then received 100 mg hydrocortisone 3 times a day (36). In this study, adrenal insufficiency was defined as serum cortisol of < 18 mcg/dl after the use of the cosyntropin test. The low-dose ACTH test was able to detect adrenal insufficiency in 22% of patients, which was more than the high-dose ACTH test did, with only 8%. 22 patients (37%) were steroid responsive, 54% of them had a diagnostic 1mcg-cosyntropin test in comparison to 22% who had a diagnostic 250mcg-cosyntropin test. This suggests that the low-dose ACTH test was superior to the high-dose test in detecting adrenal insufficiency that responded haemodynamically to corticosteroids (36). A similar study compared low-dose and high-dose ACTH in 46 patients with septic shock and found that the low-dose test was able to identify a group of patients with insufficient adrenal reserve who could be missed by high-dose tests (21).

Limitations of the ACTH stimulation test

Several reasons made investigators question the reliability of ACTH stimulation tests in critically ill patients:

- Firstly, inconsistent results in the same patients were found when ACTH test was performed on more than one occasion (37).
- Second, the threshold of 9 mcg/dl increase in serum cortisol after the use of the ACTH test may not be clinically helpful, because some critically ill patients had spontaneous cortisol increases > 9 mcg/dl without receiving the ACTH stimulation test (38).
- Third, the use of etomidate to facilitate endotracheal intubation in patients with septic shock suppresses the HPA axis and may interfere with the results of the ACTH stimulation test.
- Fourth, cortisol immunoassay is the available cortisol measurement method in most clinical laboratories. Liquid chromatography–tandem mass spectrometry is the reference standard method. It is a time- and labour-intensive assay that is only available in central laboratories. Briegel and colleagues compared total cortisol measurement by these two methods by measuring serum cortisol from duplicate serum samples taken from patients included in the CORTICUS Study. They found a wide variation in cortisol immunoassay measurement that may over- or underestimate the actual cortisol levels (39).

Corticosteroid therapy for patients with sepsis and septic shock

The interest in the possible therapeutic role of cortisol in severe sepsis and septic shock has existed for a long time. The use of corticosteroids as an adjunctive therapy in severe sepsis and septic shock has been controversial, and has swung back and forth over the past 50 years.

High-dose corticosteroids

For many years, during the 1960s through to the 1980s, it was accepted practice to use a high-dose orticosteroid for a short period of 1 to 2 days as adjunctive therapy in patients with severe sepsis and septic shock (8). This therapeutic strategy of using high dose corticosteroids was supported by the results of Schumer's prospective and retrospective

studies (40). This study was done to assess the safety and efficacy of high dose steroids in septic shock. Part 1 of this study was a prospective, randomized, placebo-controlled, and double-blind trial that included 172 patients with septic shock. Half of them received dexamethasone 3 mg/kg or methylprednisolone 30 mg/kg, and the other half received normal saline. This study demonstrated a dramatic and significant survival benefit of the use of high-dose corticosteroids in septic shock. The overall mortality was significantly less in the steroid-treated group (10.4 %) in comparison to the control group (38.4%). Part 2 was retrospective and showed a similarly significant survival improvement (40).

Later in the 1980s several large, well-designed prospective, randomized, placebo-controlled clinical trials showed that high doses of methylprednisolone failed to demonstrate a survival benefit in severe sepsis and septic shock, even when steroids were administered early after diagnosis (41, 42, 43). Bone and colleagues performed a large, prospective, randomized, double-blind, placebo-controlled trial, in which 382 patients were enrolled (41). Patients were randomized to receive either placebo or 30 mg/kg of methylprednisolone sodium succinate within two hours of diagnosis. No significant differences were found in the prevention or the reversal of shock. This clinical trial also demonstrated that high-dose steroid did not improve mortality in severe sepsis and septic shock. In fact there was evidence that mortality might be increased in the steroid-treated group, because significantly more deaths were related to secondary infection in those who received steroids (41).

A meta-analysis investigated studies published before 1989 on the effects of short courses of high-dose corticosteroid in sepsis and reported that this regime increased mortality and worsened secondary infection (44). In 1995, another meta-analysis identified nine relevant randomized trials of high-dose steroids. This meta-analysis confirmed that high-dose corticosteroids did not improve mortality or survival rate, and suggested that their use might be harmful and tended to increase mortality from secondary infection (45). It is, however, important to note that short-course high-dose steroids may improve outcome in some specific infectious diseases such as severe typhoid fever, bacterial meningitis in children and pneumocystis jiroveci pneumonia in acquired immunodeficiency syndrome (46).

Low-dose corticosteroids

Since the publication of the well-designed clinical trials and meta-analyses in the 1980s and 1990s that demonstrated high doses of corticosteroids do not improve outcome and might be potentially harmful, it is has been generally accepted that high-dose corticosteroids should not be administered to patients in the early phases of sepsis. In the early 1990s, there was considerable interest in the possibility of the use of more physiologic steroid doses known as “low-dose”, “stress-dose” or “supraphysiological” steroid therapy. These doses are administered over a longer duration. In the late 1990s, data emerged from 3 small trials demonstrating that, in patients with septic shock, low-dose corticosteroid therapy (200 to 400 mg/day hydrocortisone equivalent), resulted in haemodynamic improvement, faster shock reversal and possibly an improved survival rate (47, 48, 49). Shock reversal in these studies was mainly defined as catecholamine weaning, which was a very strong predictor of survival.

Bollaert and colleagues suggested that the clinical benefits of low doses of corticosteroid are most likely more dependent faster weaning of catecholamine therapy than on the absolute haemodynamic improvement (47). Prolonged use of high doses of catecholamine could further complicate blood flow disturbances and exacerbate the already existing blood flow maldistribution, which could further aggravate tissue ischaemia. High doses of catecholamine have been found to cause myocardial damage in human and animals (47). In the VAAST trial, when low-dose corticosteroids were combined with low-dose vasopressin, this resulted in decreased mortality and organ dysfunction in comparison to the combination of corticosteroids and noradrenalin (50). Two additional small trials suggested that the use of physiological doses of steroids in sepsis had a tendency toward decreased mortality, reducing the time for shock reversal, number of organ failures, and duration of mechanical ventilation (48, 67).

These small trials prompted a larger randomized trial. Annane and colleagues performed a large, multicentre, prospective, double-blinded and placebo-controlled trial in France (26). 300 patients with vasopressor-dependent septic shock were randomised within 8

hours of presentation to receive either 50 mg i.v. hydrocortisone every 6 hours plus 50 mg fludrocortisone enterally once daily, or placebo, and treatment was continued for 7 days and stopped without tapering. All patients underwent a high-dose ACTH stimulation test at the time of enrollment for adrenal function evaluation. Patients were classified as having an inadequate adrenal reserve if delta cortisol increased less than 9 mcg/dl or adequate adrenal reserve if delta cortisol increased more than 9 mcg/dl at 60 minutes compared to basal cortisol level at enrollment time. The main outcome measure was 28-day survival in patients who did not respond to ACTH stimulation test. In addition to evaluating mortality, they also evaluated duration of vasopressor therapy and side effects of steroid replacement versus placebo (26):

- 76.5%, or 229 of 300 patients (114 Corticosteroid, 115 placebo) were non-responders to the corticotrophin test and met the criteria for adrenal dysfunction. Among those, low doses of hydrocortisone significantly reduced the 28-day mortality (53 % versus 63 % in placebo group), ICU mortality (58 % versus 70%), as well as resulting in faster vasopressor therapy withdrawal by 28 days (57% versus 40 %).
- Among all patients, low-dose steroid decreased mortality significantly: 55% versus 61% in placebo group.

The results of this trial produced an immediate impact on clinical practice and resurrected steroid therapy in patients with septic shock, especially as there was no significant increase in serious side effects associated with the hydrocortisone treatment. Survival improvement in the Annane trial was supported by other smaller studies, which led the Surviving Sepsis Campaign in 2004 to support the use of low-dose hydrocortisone for adult vasopressor-dependent septic shock patients, who are adequately fluid resuscitated (51). The Annane study has, however, been criticized for its high control group mortality 61% and the high rate of adrenal dysfunction compared to many clinical sepsis trials.

CORTICUS

Since the Annane study, the use of low-dose corticosteroid treatment for septic shock patients was supported by other smaller studies and was used widely until the results of

the CORTICUS study were published. Hydrocortisone therapy for patients with septic shock (CORTICUS), is a recent large, prospective, international, multicentre, randomized, double-blinded, placebo-controlled study of 499 adult patients with septic shock. For patients to be included in this study, they had to have hypotension for at least 1 hour, and the enrollment window was up to 72 hours. All patients underwent a high-dose 250 mcg ACTH stimulation test at the time of enrollment for adrenal function evaluation. Patients were classified as having an inadequate adrenal reserve if delta cortisol increased than 9 mcg/dl or adequate adrenal reserve if delta cortisol increased more than 9 mcg/dl at 60 minutes compared to basal cortisol level at enrollment time. Patients were administered 50 mg hydrocortisone intravenously every 6 hours for 5 days followed by a tapering regime or placebo. The main outcome measure was death at 28-days amongst patients who did not respond to the ACTH Stimulation test.

Hydrocortisone administration in this study did not improve 28-day mortality in patients with septic shock, and there was no a significant difference in mortality either in patients who did not respond to the ACTH test (39% hydrocortisone vs 36% placebo) nor in patients who responded to the ACTH test (28 % for both groups). Overall, mortality was 34% in the steroid group and 31% in the placebo group. Shock reversal was faster in the steroid group than the placebo group (3.3 days vs 5.8 days). There was, however, an increased frequency of super-infection, including new episodes of sepsis, hyperglycemia and hypernatremia in the corticosteroid-treated group (52). The negative results of CORTICUS conflicted with the Annane results. This produced an uncertainty about the use of low-dose steroid therapy in septic shock and made the Surviving Sepsis Campaign reassess the merits of using low-dose corticosteroids.

The CORTICUS study has been also criticized for its low placebo-group mortality of only 31.5%, rather than the expected 50 to 60%. The lack of corticosteroid benefit in the CORTICUS study might therefore be due to the enrollment of septic patients with lower disease severity, I whom the risks of hydrocortisone therapy exceed its potential benefits.

Table 2: Comparison between Annane and CORTICUS (26)(52)		
	Annane study	CORTICUS

Population study	300 vasopressor-dependent septic shock patients	499 septic shock patients
Enrolment time	8 hours	72 hours
Simplified acute physiology score	55.5	49
Non-responders to ACTH	76.5 %	46.7 %
28-day mortality in HC group: Overall Non-responders	 55 % 53 %	 34.3 % 39.2 %
28-day mortality in placebo group: Overall Non-responders	 61 % 63%	 31.5% 36.1%
Conclusion	Significant improvement in survival and shock reversal	No improvement in survival

HYPRESS trial (53)

HYPRESS is a recent large prospective, randomized, double-blind, placebo-controlled study testing the efficacy of steroid therapy in patient with severe sepsis to prevent the development of septic shock. 380 patients with severe sepsis were included, they were randomized to receive either a continuous infusion of 200 mg of hydrocortisone for 5 days or placebo. It showed that the use of hydrocortisone in patients with severe sepsis did not reduce the risk of developing of septic shock (53).

Meta-analyses

Meta-analyses have attempted to solve the contrast in the available data and provide clear guidance. Annane and colleagues identified and evaluated 17 randomized clinical trials. They demonstrated that, compared to the steroid-treated groups, there was a higher mortality in the placebo group (35.3% versus 38.5% in placebo). Subgroup meta-analysis of 12 trials showed a more favourable effect of low-dose steroids on mortality (44% in control group vs 37.6% in steroid group) (54).

Minneci and colleagues in their updated meta-analysis suggested that severely ill patients who are likely to die from sepsis were more likely to benefit from low-dose corticosteroid

therapy. In contrast, low-dose steroid in septic patients with less severe illness and who are likely to survive might be harmful to them and lead to worse outcomes (55). Another small meta-analysis which evaluated 6 clinical randomized trials demonstrated that corticosteroid therapy seemed to be safe in patients with septic shock, but it has no effect on mortality (56). All meta-analyses reported a reduction in the incidence of vasopressor-dependent shock and a decrease in time to shock reversal.

A recent network meta-analysis published in 2017 included 22 studies and partial data from 1 study, this was done to evaluate the use of different corticosteroid drugs and their regimes on the outcome in patients with septic shock. No drug or regime was superior to another in reducing mortality or GIT bleed (57).

A retrospective before and after study was published recently in 2017 compared the outcome of septic patients treated with a combination of I.V Vit C, hydrocortisone and thiamine with control group. It included a small number of 47 patients in each group. The hospital mortality was significantly less with 8.5% in treated group compared with 40.4% in the control group. It also showed a decrease in the progressive organ dysfunction including acute kidney injury (66)

Corticosteroid treatment, glycemic control and intensive insulin therapy

Stress hyperglycemia and insulin resistance are common in septic patients and are seen as a normal response to stress critically ill patients, even in those who are not known to be diabetic (58). Hyperglycemia is thought to be a powerful pro-inflammatory mediator. Acute hyperglycemia causes abnormal organ perfusion and abnormal vascular reactivity by reducing endothelial nitric oxide levels. Conversely, insulin has been proven to have potent anti-inflammatory effects. Insulin infusion is associated with a marked reduction in pro-inflammatory mediators with fibrinolytic and anti-thrombotic effects (59).

Tight glycaemic control “maintaining blood glucose at a level between 4.4 and 6.2 mmol/l” has been shown to reduce mortality and morbidity in critically ill patients in certain settings. Intensive insulin therapy also reduced acute renal failure requiring dialysis, blood transfusion, critical illness polyneuropathy and the duration of mechanical ventilation (60).

There is, however, a concern regarding the high risk of hypoglycemia and as such moderate glycaemic control is advocated in most settings.

Corticosteroids might induce hyperglycaemia, and as such the administration of low-dose hydrocortisone as an adjunctive therapy in septic shock may compromise glycaemic control strategies. An observational, prospective, pilot study investigated the effect of bolus doses of 50 mg of hydrocortisone on blood glucose levels in 16 patients with septic shock (61). It showed that a single bolus of 50 mg hydrocortisone increased blood glucose levels significantly with a highly variable individual response. A continuous hydrocortisone infusion appeared to be more preferable and practical than repetitive bolus doses (61). The COITSS trial investigated the efficacy of intensive insulin therapy in patients whose septic shock was treated with 50 mg of hydrocortisone every 6 hours and 50 mcg fludrocortisone once daily (62). 509 patients were enrolled in this trial and were randomly assigned to one of four treatment groups: intensive glucose control with insulin infusion plus hydrocortisone, intensive glucose control with insulin infusion plus hydrocortisone plus fludrocortisone, conventional insulin therapy with hydrocortisone, or conventional insulin infusion plus hydrocortisone and fludrocortisone. They found that compared to conventional insulin therapy, intensive insulin therapy did not improve mortality in patients treated with corticosteroids (42.9% Vs 45.9%). Episodes of severe hypoglycemia (<40 mg/dl) were more frequent with intensive insulin therapy than conventional insulin therapy. Enteral fludrocortisone did not improve mortality and was associated with an increased risk of secondary infection, especially urinary tract infection (62).

Surviving Sepsis Campaign (SCC)

The Surviving Sepsis Campaign is an organisation with the stated aim of reducing mortality from severe sepsis and septic shock worldwide. The Surviving Sepsis Campaign Guidelines are the gold-standard for the management of patients with sepsis (63).

A large observational database is provided by SSC (64). 17,847 patients of 27,836 met the recommendation for low-dose steroids and needed vasopressor therapy despite adequate resuscitation and 50% of those received low-dose steroids. Hospital mortality

was greater in steroid-treated groups compared to those without. Although this is a large data set, the observational nature limits its conclusions. Taking the available data into account the, the most recent Surviving Sepsis Campaign recommendations are as follows:

1. “We suggest against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest IV hydrocortisone alone at a dose of 200 mg per day (65).
2. We suggest not using the ACTH stimulation test to identify the subset of adults with septic shock who should receive hydrocortisone (grade 2B).
3. We suggest that clinicians taper the treated patient from steroid therapy when vasopressors are no longer required (grade 2D)" 63.

Summary

Sepsis and septic shock are common in critically ill patients, and they are one of the most common causes of death in the intensive care unit. Absolute or relative adrenal insufficiency are common in septic critically ill patients. The ACTH test has failed to identify patients who will respond to corticosteroids. Thus, it is recommended not to use the ACTH stimulation test to identify the subset of patients with septic shock who should receive hydrocortisone and who should not.

High dose corticosteroids have been extensively investigated and there is no evidence for a survival benefit with a possible harmful effect in septic patients. Several meta-analysis confirmed that high dose corticosteroids do not improve mortality or survival rate, and suggested that their use might be harmful and tend to increase mortality from secondary infection. It is therefore generally accepted that high dose steroid should not be given to septic patients. On the other hand, the administration of a low dose of hydrocortisone (200 to 300 mg/day i.v.) for longer durations in patients with septic shock requiring vasopressors was associated with improved systemic vascular resistance and increased the speed of shock reversal. However, the available data does not confirm whether there is an improvement in morality rate with the administration of

low dose corticosteroid to vasopressor-dependent septic shock patients or not. Hyperglycemia, Critical illness polymyoneuropathy and secondary infection from are major adverse effects of cortisol therapy that might increase mortality and prolong ICU admition. Thus, it is therefore, low dose corticosteroid should only be given to patients with refractory septic shock who did not respond to both fluid and inotropic treatment.

References

1. Angus, D.C., Linde-Zwirble, W.T and Lidicker, J. et al (2001) Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. **Crit Care Med**; 29:1303–1310.
2. Martin, G.S., Mannino, D.M. and Eaton, S. et al (2003) The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med; 348:1546–1554.
3. Annane, D., bellissant, E. and Cavaillan, J.M (2005) Septic shock. **Lancet,** 365(9453):63-78
4. Bone RC, Balk RA, Cerra FB, et al. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med*.1992;20(6):864-874.
5. . Levy MM, Fink MP, Marshall JC, et al; International Sepsis Definitions Conference. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Intensive Care Med*. 2003;29(4):530-538.
6. Singer, M., Deutschman, C.S. and Seymour, C. W. et al. The Third International Consensus Definitionsfor Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801-810.
7. Hinds, C.J. and Watson, D. (2008) **Intensive care A concise Textbook.** Third edition. London: Saunders.
8. Patel, G.P. and Balk, R.A. (2012) Systemic steroid in severe sepsis and septic shock concise clinical review. **AM J Respir Crit Care Med,** 185(2):133-139
9. Mesotten, D. Vanhorebeck, I. and Van den Berghe, G. (2008) The altered adrenal axis treatment with glucocorticoid during critical illness. **Nat Clin Pract Endocrine Metab,** 4:496-505
10. Michie, H.R., Manogue, K.R. and Spriggs, D.R. et al (1988a) detection of circulating tumor necrosis factor after endotoxine administration. **New England journal of medicine, 318:1482-1486**
11. Bone, R.C. (1996) Immunologic dissonance: A continuing evolution in our understanding of the systemic inflammatory response syndrome (SIRS) and the multiple organ dysfunction syndrome (MODS). **Annual of internal medicine,** 125:680-687
12. Singer, M. And Grant, I. (1999) **ABC of Intensive Care.** First edition. London: BMJ.
13. Knotzer, H., Pajk, W. And Martin, W. et al (2006) Regional microvascular function and vascular reactivity in patients with difference degrees of multiple organ dysfunction syndrome. **Critical care and trauma,** 102:1187-93
14. Kaufman, D.A. and Mancebo, J. (2013) Corticosteroid therapy in septic shock
15. Cooper, M.S. and Stewart, P.M (2003) corticosteroid insufficiency in acutely ill patients. **N Engl J Med,** 348:727-734
16. Shenker, Y. and Skatrud, J.B. (2001) Adrenal insufficiency in critically ill patients. **Am J Respir Crit Care Med,** 163:1520.
17. Annane, D. Sébille, V. and Troché, G. et al (2000) A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. **J A M A,** 283:1038.
18. Bornstein, S.R. (2009) Predisposing factors for adrenal insufficiency. **N Engl J Med,** 360:2328

19. Marik, PE, Pastores, S.M. and Annane, D. et al (2008) Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. **Crit Care Med,** 36:1937
20. Hinshaw, L.B., Beller, B.K. and chang, A.C. et al (1985) Corticosteroid/antibiotic treatment of adrenalectomized dogs challenged with lethal E.coli. **Circ shock,** 16:265-277
21. Venkatesh, B., Mortimer, R.H. and Couchman, et al (2005) Evaluation of random plasma cortisol and the low dose corticotropin test as indicators of adrenal secretory capacity in critically ill patients: a prospective study. **Anaesth Intensive Care,** 33:201
22. Malerba, G., Romano-Girard, F. and Cravoisy, A. et al (2005) Risk factors of relative adrenocortical deficiency in intensive care patients needing mechanical ventilation. **Intensive Care Med,** 31:388
23. Cuthbertson, B.H., Sprung, C.L. and Annane, D. et al (2009) The effects of etomidate on adrenal responsiveness and mortality in patients with septic shock. **Intensive Care Med,** 35:1868
24. Watt, I. and Ledingham, I.M. (1984) Mortality amongst multiple trauma patients admitted to an intensive therapy unit. **Anaesthesia,** 39:973-981
25. Ledingham, I.M. and Watt, I. (1983) Influence of sedation mortality in critically ill multiple trauma patient. **Lancet,** 1:1270
26. Annane, D., Seblle, V. and Charpentier, C. et al (2002) Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. **J AM A,** 288:862-870
27. Jabre, P., Combes, X. and Lapostolle, F. et al (2009) Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial. **Lancet,** 374:293.
28. Mohammed, Z., Afessa, B. and Finkielmen, J.D. (2006) the incidence of relative adrenal insufficiency in patients with septic shock after the administration of etomidate. **Crit Care,** 10:R150
29. Marik, P. and Zaloga, G. (2000) Prognostic value of cortisol response in septic shock. **JAMA,** 284:308.
30. Jurney, T.H., Cockrell, J.L. and Lindberg, J.S. et al (1987) Spectrum of serum cortisol response to ACTH in ICU patients. Correlation with degree of illness and mortality. **Chest,** 92:292
31. Jarek, M.J., Legare, E.J. and McDermott, M.T. et al (1993) Endocrine profiles for outcome prediction from the intensive care unit. **Crit Care Med,** 21:543
32. Ho J.T., Al-Musalhi H. and Chapman M.J. et al (2006) Septic shock and sepsis: a comparison of total and free plasma cortisol levels. **J Clin Endocrinol Metab,** 91:105
33. Hamrahian A.H. Oseni T.S. and Arafah B.M. (2004) Measurements of serum free cortisol in critically ill patients. **N Engl J Med,** 350:1629
34. Vassiliadi D.A., Ilias I. and Tzanela M. et al (2013) Interstitial cortisol obtained by microdialysis in mechanically ventilated septic patients: correlations with total and free serum cortisol. **J Crit Care,** 28:158

35. Lipiner-Friedman D., Sprung C.L. and Laterre P.F. et al (2007) Adrenal function in sepsis: the retrospective CORTICUS cohort study. **Crit Care Med,** 35:1012
36. Marik P.E. and Zaloga G.P. (2003) Adrenal insufficiency during septic shock. **Crit Care Med**, 31:141
37. Loisa P., Uusaro A. and Ruokonen E. (2005) A single adrenocorticotropic hormone stimulation test does not reveal adrenal insufficiency in septic shock. **Anesth Analg,** 101:1792
38. Venkatesh B., Mortimer R.H. and Couchman B. et al (2005) Evaluation of random plasma cortisol and the low dose corticotropin test as indicators of adrenal secretory capacity in critically ill patients: a prospective study. **Anaesth Intensive Care,** 33:201
39. Briegel J., Sprung C.L. and Annane D. et al (2009) Multicenter comparison of cortisol as measured by different methods in samples of patients with septic shock. **Intensive Care Med,** 35:2151
40. Schumer W. (1976) Steroid in the treatment of clinical septic shock. **Ann Surg,** 184:333-339
41. Bone R.C., Fisher C.J. Jr. and Clemmer T.P. et al (1987) A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. **N Engl J Med,** 317: 653–658
42. Veterans Administration Systemic Sepsis Cooperative Study Group. (1987) Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis. **N Engl J Med,** 317:659–665.
43. Sprung C.L., Caralis P.V. and Marcial E.H. (1984) Pierce M, Gelbard MA, Long WM, Duncan RC, Tendler MD, Karpf M. The effects of high-dose corticosteroids in patients with septic shock: a prospective, controlled study. **N Engl J Med,** 311:1137–1143
44. Minneci, P.C., Deans, K.J. and Bank, S.M. et al (2004) Meta-analysis: the effect of steriod on survival and shock during sepsis depend on the dose. **Ann intern med,** 141:47-56
45. Cronin L., Cook D.J. and Carlet, J. et al (1995) Corticosteroid treatment for sepsis: a critical and meta-analysis of the literature. **Crit Care Med,** 23(8):1430
46. Annane, D. (2001) Corticosteroid for septic shock, **Crit care Med,** 29(7):517-520
47. Bollaert P.E., Charpentier C. and Levy B. et al (1998) Reversal of late septic shock with supraphysiologic doses of hydrocortisone. **Crit Care Med,** 26:645
48. Briegel J., Forst H. and Haller M. et al (1999) Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. Crit Care Med, 27:723
49. Yildiz O., Doganay M. and Aygen B. et al (2002) Physiological-dose steroid therapy in sepsis [ISRCTN36253388]. **Crit Care,** 6:251
50. Russell J.A., Walley K.R. and Gordon A.C. et al (2009) Interaction of vasopressin infusion, corticosteroid treatment, and mortality of septic shock. **Crit Care Med,** 37:811–818.
51. Dellinger R.P., Carlet J.M. and Masur H. et al (2004) Surviving sepsis campaign guidelines for severe sepsis and septic shock. **Crit Care Med,** ;32:858–873
52. Sprung C.L., Annane D. and Keh D. et al (2008) Hydrocortisone therapy for patients with septic shock. **N Engl J Med,** 358:111

53. Keh D., Trips E. and Marx G. et al (2016) Effect of Hydrocortisone on Development of Shock Among Patient With Severe Sepsis: The HYPRESS Randomized Trial. JAMA. 1:316(17):1775-1785
54. Annane D., Bellissant E. Bollaert P.E. et al (2009) Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. **JAMA,** 301:2362
55. Minneci P.C., Deans K.J. Eichacker P.Q. et al (2009) The effects of steroids during sepsis depend on dose and severity of illness: an updated meta-analysis. **Clin Microbiol Infect,** 15:308
56. Sligl W.I., Milner D.A. Jr. and Sundar S. et al (2009) Safety and efficacy of corticosteroids for the treatment of septic shock: A systematic review and meta-analysis. **Clin Infect Dis,** 49:93
57. New network Meta-analysis
58. Finney, S.J., Zekveld, C. and Elia, A. et al (2003) Glucose Control and Mortality in Critically Ill Patients, **Journal American medical association,** 290(15): 2041-2047
59. Mark, E.P. and Raghavan, M. (2004) Stress hyperglycemia insulin and immunomodulation in sepsis. **Intensive care medicine,** 30: 748-756
60. Van den Berghe, G., Wouters, P. and Weekers, F. et al (2001) Intensive insulin therapy in the critically ill patients. **N Engl J Med,** 345:1359–1367
61. Weber-Carstens S., Deja M. and Bercker S. et al (2007) Impact of bolus application of low-dose hydrocortisone on glycemic control in septic shock patients. **Intensive Care Med;** 33:730-733
62. COIITSS Study Investigators, Annane D., Cariou A. and Maxime V. et al (2010) Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. **JAMA;** 303:341
63. Dellinger R.P., Levy M. and Rhodes A. et al (2013) Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012**. Intensive Care Med,** 39:165–228
64. Casserly B. Gerlach H. and Phillips G.S. et al (2012) Low-dose steroids in adult septic shock: results of the Surviving Sepsis Campaign. **Intensive Care Med,** 38:1946
65. Rhodes A., Evan L.E and Alhazzani W. et al (2017) Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2016**. Intensive Care Med,** DOI 10.1007/s00134-017-4683-6
66. Marik P.E., Khangoora V. and Rivera R. et al (2017) Hydrocortisone, Vitamin C, and Thiamine for the treatment of severe sepsis and septic shock. A Retrospective Before-After Study. Chest: 151(6): 1229-1238