

## Role of Systematic Steroids in Sepsis and Septic Shock Treatment Outcome: A Systematic Review

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### ABSTRACT

**Introduction:** The use of restorative corticosteroids in very ill patients with sepsis is disputable. This study aiming at evaluation of evidence supporting use of corticosteroids therapy for prevention of septic shock in patients with severe sepsis. **Methods:** The electronic search was conducted in Medline and Embase databases using specific search terms. The search resulted in 106 relevant articles. The primary screening for relevance of this articles lead to exclude of 101 titles and only 5 studies were finally included in this review. **Results:** The review included 5 double-blind randomized clinical trials, 4 of them were prospective, and one retrospective study. Overall sample size (n= 1157 patients) in the prospective studies and (n=328 patients) in the retrospective study. Mean age ranged from (50 to 65 years) in the prospective studies and it was 65 years in the retrospective study.

**Conclusions:** This review could not support the evidence of using corticosteroids in the management of patients of sepsis especially those at risk for development of septic shock.

**Keywords:** Steroids, Sepsis, Septic Shock, Management.

### INTRODUCTION

The corticosteroid therapy role in the management of septic shock has been argued for more than fifty years. As septic shock stays a common condition resulted in substantial morbidity, mortality, and economic cost, there is proceeded with enthusiasm for recognizing novel operators or new uses of existing medications that may enhance result of therapy<sup>(1)</sup>. In spite of the many demonstrated mitigating properties of corticosteroids, the abundance of good investigations using different non-human models of septic shock, and numerous episodic positive reports in clinical sepsis, multicenter clinical trials have not succeeded to help this type of treatment. Clinical trials again raise the likelihood that corticosteroids may enhance results from severe sepsis<sup>(2)</sup>. These new investigations, may contrast past methods, since relative low doses of corticosteroids are used over long time<sup>(3)</sup>.

The use of restorative corticosteroids in very ill patients with sepsis is disputable. Tow essential inquiries still exist in this type of patients. First, is there a very ill patients group who have inadequate corticosteroids, and if this is the case, how to managed them<sup>(3)</sup>? Second, do all very ill patients benefit from steroids? These inquiries have been researched fundamentally in those patients with septic shock, also, adequate investigations have been directed to permit numerous Meta -analyses<sup>(4-6)</sup>, counting the late Cochrane review<sup>(4)</sup>. However, not all corticosteroids are similar. Even at dose equivalency, some of them (e.g., dexamethasone),

have more immunosuppressive effects, and some (e.g., hydrocortisone), have more mineralocorticoid and vasoactive effects. This, tied with the proof that endogenous glucocorticoids are emitted in a pulsatile way in health, major surgery and critical illness justified further investigation of the impacts of the individual medications and the doses utilized<sup>(7)</sup>.

The “low-dose” hydrocortisone (200-300 mg/d) used in the treatment of patients with very severe sepsis and septic shock not evident. The updated guidelines for the use of hydrocortisone based on 14 randomized clinical trials (RCTs)<sup>(8)</sup>. In the study by **Annane et al.**<sup>(9)</sup> in patients with relative adrenal insufficiency hydrocortisone decline mortality and increase reversal of septic shock. In the CORTICUS study<sup>(10)</sup>, septic shock was managed in a lesser period of time but survival rate was not improved. The elevated risk of death and septic shock degree in the study by **Annane et al.**<sup>(8)</sup> brought about more prohibitive suggestions for hydrocortisone utilize just in patients with insufficient reaction to fluid and vasopressor resuscitation. However, septic shock reversal in the CORTICUS study was accounted for to be fundamentally quickened by the organization of hydrocortisone regardless of the adrenal reaction to corticotropin. A global accord articulation suggested changing the terminology relative or absolute adrenal insufficiency, which mean only adrenal cortisol secretion, by the critical illness-related corticosteroid deficiency (CIRCI) concept<sup>(11)</sup>. This study aiming at

evaluation of evidence supporting use of corticosteroids therapy for prevention of septic shock in patients with severe sepsis.

**METHODS**

The electronic search was conducted in Medline and Embase data bases using search terms demonstrated in figure 1. The search resulted in 106 relevant articles. The primary screening for relevance of this articles lead to exclude of 101 titles and only 5 studies were finally included in this review. The data collected from included studies using data extraction forms and summarized in table 2.

**The study was done after approval of ethical board of Umm Al-Qura university.**

**RESULTS**

The search of the literature, after exclusion of irrelevant, duplicated and review studies, revealed 5 studies met the inclusion criteria. Included studies aimed to assess the effect of systematic steroids in the treatment of severe sepsis and septic shock in adults.

The review included 5 double-blind randomized clinical trials, 4 of them were prospective <sup>(12-15)</sup>, and one retrospective study of Schumer <sup>(15)</sup>. Overall sample size (n= 1157 patients) in the prospective studies and (n=328 patients) in the retrospective study. Mean age ranged from (50 to 65 years) in the prospective studies and it was 65 years in the retrospective study.

Three of the prospective studies <sup>(12, 13, 15)</sup> as well as the retrospective study <sup>(15)</sup> used low dose of steroids (30 mg/kg), while one prospective study <sup>(14)</sup> used high dose of steroids (200 mg/kg) in the continuous infusion.

Development of septic shock was reported in 3 prospective studies. The rate of septic shock development in sepsis patients was ranged from 13.6% to 46% in steroids group, while the range was 11.6% - 37% in the placebo group. **Keh et al.** <sup>(14)</sup> reported a rate of shock development within 14 days was 21.2% in the hydrocortisone

group compared to 22.9% in the placebo group. **Bone et al.** <sup>(12)</sup> reported that 72% of septic shock occurred within 24 hours. They found that septic shock occurred in 46% of the corticosteroids group and in 37% of the placebo group. In a study veterans group <sup>(13)</sup> the rate of septic shock was 13.6% of the glucocorticoid group, and 11.6% of the placebo group; and they did not report the time of onset for septic shock.

Regarding the mortality in the intensive care unit or the hospital, 14 days mortality was reported in 2 prospective studies. It varied from 21% to 34% in the corticosteroids group, while it was 22% to 25% in the placebo group <sup>(12, 13)</sup>. Another prospective study reported 28 days mortality rate of 8.8% in the hydrocortisone group and 8.2% in the placebo group <sup>(14)</sup>. Other study <sup>(15)</sup> assessed the mortality rates without reporting the time of septic shock onset. In the prospective study, the findings showed 11.8% mortality rate in steroids group compared to 47.8% in the control group <sup>(15)</sup>. The mortality rate was 20.0% in steroids group compared to 49.6% in control group were found in the retrospective study of Schumer <sup>(15)</sup>. Survival up to 180 days was reported only in one prospective study, as it was 26.8% in the hydrocortisone group in comparison to 22.2% in the placebo group <sup>(14)</sup>. Three prospective studies reported secondary infection rate, it was ranged from 14.5% to 21.5% of the hydrocortisone group in comparison to a range of 16.9% -21.1% in the placebo group <sup>(12-14)</sup>.

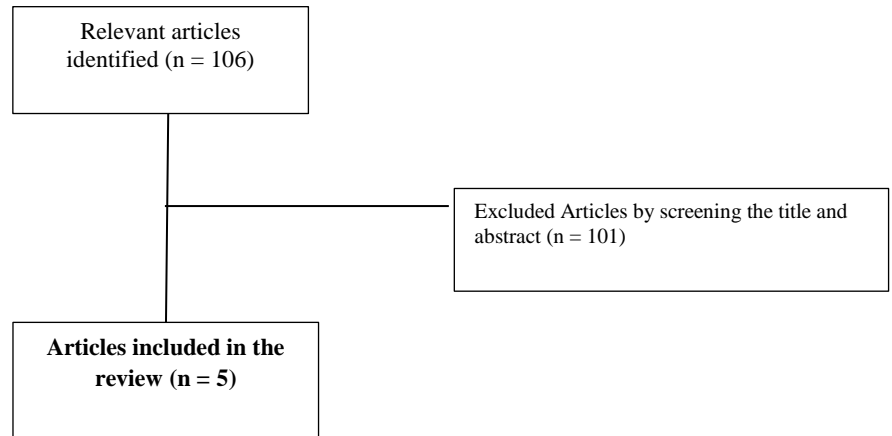
Only two prospective studies reported a higher incidence of hyperglycemia in the steroids group in comparison to control group (blood glucose level >150 mg/dl) <sup>(13, 14)</sup>. All the included studies reported presence of other outcomes that include: weaning failure, muscle weakness, elevated serum creatinine, gastrointestinal infection, pulmonary insufficiency, gastrointestinal bleeding, electrolyte imbalance, non-ketotic hyperosmolar diabetes and psychosis.

**Table (1): Search term and search strategy**

Search strategy	Databases	Number of eligible articles
(sepsis OR septic shock OR bacteremia) AND (steroids OR corticosteroids OR betamethasone OR cortisone OR dexamethasone OR hydrocortisone OR methylprednisolone OR prednisolone OR triamcinolone OR prednisone OR rayos) AND (death OR mortality OR infection OR gastrointestinal bleeding OR hyperglycemia)	Medline and Embase	106

**Table (2): Summary of the results of the included studies**

Study	Sample size	Age of patients	Dose of corticosteroids	Development of septic shock	Time until septic shock	Mortality in the intensive care unit or hospital,	Secondary infections	Hyperglycemia	Other important outcomes	Effect on outcome
<b>Keh et al.</b> <sup>(14)</sup>	380 adult patients. 64.9% males 35.1% females	Mean age = 65 years.	200 mg (low dose)	Septic shock occurred in 21.2% in the hydrocortisone group and 22.9% in the placebo group	14 days	8.8% of patients in the hydrocortisone group & 8.2% of patients in the placebo group	21.5% in the hydrocortisone group & 16.9% in the placebo group.	90.9% in the hydrocortisone group & 81.5% in the placebo group	8.6% & 8.5% had weaning failure. 30.7% & 23.8% had muscle weakness in the hydrocortisone group & placebo group respectively	Among adults with severe sepsis not in septic shock, use of hydrocortisone compared with placebo did not reduce the risk of septic shock within 14 days.
<b>Bone et al.</b> <sup>(12)</sup>	382 patients Males = 235 Females: 147	Mean age = 53.6	high-dose corticosteroids (30 mg per kilogram of body weight)	46% of corticosteroids group & 37% of placebo group	24 hours [72% of septic shock]	34% corticosteroids group, & 25% placebo group. (14 days mortality)	19% of corticosteroids group & 20% of placebo group.	Not reported	Elevated serum creatinine level more than 2 mg/dl occur in 42% of corticosteroids group, & 3% of placebo group	Use of high-dose corticosteroids provides no benefit in the treatment of severe sepsis and septic shock.
<b>VASSCS Group</b> <sup>(13)</sup>	223 patients 12 received glucocorticoid and 111 placebo)	Mean age: 60.9 Glucocorticoid group, & 60.6 placebo group	30 mg/kg [High dose]	13.6% of Glucocorticoid group & 11.6% Placebo group	Not reported	21% in Glucocorticoid group, & 22% in placebo group (14 days mortality)	14.5% of Glucocorticoid group & 21.1% of placebo group	20% in Glucocorticoid group & 15.2% in placebo group	Pulmonary insufficiency and Gastrointestinal bleeding	High-dose glucocorticoid therapy does not reduce mortality significantly in patients with systemic sepsis
<b>Schumer et al.</b> <sup>(15)</sup> <b>con-current controls</b>	172 patients Males: 167 Females: 5	Mean age: 50 years	30 mg/kg [High dose]	Not reported	Not reported	11.8% of corticosteroids group & 47.8% in Control group	Not reported	Not reported	Gastrointestinal bleeding, non-ketotic, hyperosmolar diabetes, and psychosis	Significant improvement in survival rates
<b>Schumer et al.</b> <sup>(15)</sup> <b>historical controls</b>	328 patients Males: 301 Females: 27	Mean age: 56 years	30 mg/kg (High dose)	Not reported	Not reported	20.0% in corticosteroids group & 49.6% in control group	Not reported	Not reported	Gastrointestinal bleeding, non-ketotic, hyperosmolar diabetes, and psychosis	Significant improvement in survival rates



**Figure (1): Flow diagram of the included studies in the review**

**DISCUSSION**

According to the literature, about 40% of severe sepsis develops septic shock <sup>(16)</sup>. Severe sepsis and septic shock are associated with high fatality rate, which can be attributed to the increased antibiotic resistance of microorganism, increased number of immunocompromised patients, and elevated number of elderly who associated with higher mortality rate from sepsis or septic shock <sup>(17)</sup>. The general guidelines of the Surviving Sepsis Campaign recommended administration of hydrocortisone in septic shock with vasopressor-dependency <sup>(8)</sup>.

The findings of this review, evaluated the evidence supporting use of corticosteroids in patients with severe sepsis. The included studies showed that use of low dose hydrocortisone compared with placebo did not reduce the risk of septic shock development in patients with sepsis. In addition, the majority of included studies demonstrated that use of high-dose corticosteroids had no significant effect on mortality rates related to septic shock. Only two included studies reported that use of high dose corticosteroids reduced mortality rates and improved survival rates of patients with septic shock <sup>(15)</sup>. These unclear findings could be attributed partially to the variation in the definition of sepsis and septic shock, in addition to various denominators used in the calculations of mortality rates <sup>(18)</sup>. The pituitary-adrenal mechanisms of adults are different from that of children. Thus, studies that conducted among children were excluded of this review to reduce the heterogeneity in the findings of eligible studies <sup>(13)</sup>.

The majority of included studies used hydrocortisone to prevent development of septic shock and reduce mortality. However, all corticosteroids have a positive effect in immunity,

metabolic balance, individual variations between the effect of each drugs have been reported <sup>(19)</sup>. The effect of corticosteroids is mediated by two types of receptors, mineralocorticoids receptors in health situation and glucocorticoid receptors in the critical conditions <sup>(20)</sup>. Intermittent activation of both receptors is important to achieve the required regulatory effect of corticosteroids. In the critical situation such as sepsis or septic shock, the glucocorticoid receptors remain continually activated and administration of hydrocortisone may not achieve the benefits gained in the normal situations <sup>(21)</sup>. However, two included studies <sup>(13,14)</sup> reported development of hyperglycemia associated with hydrocortisone administration, which may exacerbate the status of the critically ill patients.

The strengths of this review include the homogeneity in the study populations and intervention group. In addition, a wide spectrum of outcomes was assessed from reduction in septic rate within 24 hours to improvement in the survival rate over 180 days. The weaknesses include the lack of quality evaluation and risk of bias assessment of the included studies.

**CONCLUSION**

This review could not support the evidence of using corticosteroids in the management of patients of sepsis especially those at risk for development of septic shock.

**CONFLICT OF INTERESTS**

The authors declared no conflict of interests.

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