American Journal of Emergency Medicine 37 (2019) 1353–1361

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Review

The controversial role of corticosteroids in septic shock

Ali Pourmand, MD, MPH, RDMS [a,*], Tess Whiteside, BS [a], David Yamane, MD [a], Amir Rashed, BS [a], Maryann Mazer-Amirshahi, PharmD, MD, MPH [b,c]

[a] Department of Emergency Medicine, George Washington University School of Medicine and Health Sciences, Washington, DC, United States
[b] Department of Emergency Medicine, MedStar Washington Hospital Center, Washington, DC, United States
[c] Georgetown University School of Medicine, Washington, DC, United States

ARTICLE INFO

Article history:
Received 3 December 2018
Received in revised form 13 April 2019
Accepted 25 April 2019

Keywords:
Corticosteroid
Hydrocortisone
Septic shock
Therapeutic use
Drug therapy
Pharmacology

ABSTRACT

Background: Several clinical trials and literature reviews have been conducted to evaluate the impact of corticosteroids on the physiological markers and clinical outcomes of patients in septic shock. While the findings have been somewhat contradictory, there is evidence of moderate benefit from the administration of low-dose corticosteroids to patients in septic shock. In this review, we discuss recent studies evaluating the impact of corticosteroids on morbidity and mortality in septic shock and explore future directions to fully elucidate when and how the administration of corticosteroid therapies can be beneficial.

Methods: A literature review was performed using the Mesh database of PubMed with the term "septic shock" and subheadings "therapeutic use", "drug therapy", "pharmacology", and "therapy" followed by the addition of "steroid". Filters were added to restrict the search to 18+ age, English and human studies, and articles published within the last 10 years. One hundred sixty-five articles were examined and twenty-five were deemed relevant to this review.

Results: The twenty-five articles reviewed here provide conflicting evidence as to the usefulness of corticosteroid treatments during septic shock. Several showed improved physiological outcomes, including rates of organ failure, need for life supporting interventions, adverse effects, inflammatory markers, and perfusion during the course of septic shock, as well as decreased mortality for a statistically significant number of patients.

Conclusions: There remains a need for improved therapy for patients in septic shock. Corticosteroids have shown some potential in improving mortality rates and clinical markers. Additional studies are needed to determine the optimal role of corticosteroids in septic shock.

1. Introduction

Sepsis is the dysregulated host response to systemic infection that results in organ dysfunction due to serious cellular, circulatory, and metabolic damage [1]. In the clinical setting, patients who advance to septic shock can be identified by a need for vasopressor therapy to maintain a mean arterial pressure ≥ 65 mmHg and by a serum lactate level > 2 mmol/L in the absence of hypovolemia [1]. Sepsis remains a leading cause of mortality in the United States and the primary cause of death in intensive care units (ICUs) [2] [3]. Septic shock (sepsis with hypotension or hyperlactemia) has high mortality burden with a short-term mortality of 45–50% and 50% of survivors suffering from long-term cognitive damage [2] [4]. The strongest predictor of death in septic shock is cumulative organ failure defined by the number of organs affected and the degree of failure as defined by Sequential Organ Failure Assessment (SOFA) score [5]. Aside from early hemodynamic stabilization, respiratory resuscitation procedures, and appropriate anti-infective therapy, there are no approved adjuvant therapies for use once septic shock has occurred [3]. The role of pro-inflammatory pathways suggests a potential use for corticosteroids as an adjuvant therapy in the treatment of sepsis and septic shock.

Dysregulated inflammation is the basis for septic shock and the progression to organ failure. Corticosteroids have the potential to decrease inflammation and improve tissue perfusion to restore organ function and reverse shock [6]. Corticosteroids (specifically glucocorticoids) are the synthetic analogue of cortisol, the naturally occurring hormone produced by the adrenal glands [7]. The normal body state maintains homeostatic cortisol levels within a narrow range. The sympathetic nervous system releases catecholamines in response to stress, which in turn activate the hypothalamic-pituitary-adrenal (HPA) axis [8]. Hypoxemia and hypotension are detected by the hypothalamus, increasing the secretion of corticotropin releasing hormone (CRH) [8]. CRH stimulates the release of adreno-corticotropin (ACTH) from the anterior

* Corresponding author at: Department of Emergency Medicine, George Washington University School of Medicine and Health Sciences, 2120 L St., Washington, DC 20037, United States.
E-mail address: pourmand@gwu.edu (A. Pourmand).

https://doi.org/10.1016/j.ajem.2019.04.045
0735-6757/

pituitary, which circulates to the adrenal cortex and stimulates release of cortisol [8]. Glucocorticoids are immune-modulators and have anti-inflammatory properties that work through both genomic and non-genomic methods. They bind to the C-terminal end of cytoplasmic glucocorticoid receptor (GR), which induces a conformational change to expose nuclear localization signals [9]. The GR-corticosteroid complex dimerizes and binds DNA at glucocorticoid response elements in the 5′-upstream promotor region of steroid-responsive genes to alter transcription [9]. Corticosteroids decrease the synthesis of inflammatory mediators (prostaglandins, cytokines, interleukins) via transrepression. DNA-bound transcription factors (NF-kB and activator protein-1) recruit the GR-corticosteroid complex to chromatin via protein-protein interactions where it inhibits transcription [7]. Additionally, corticosteroids induce more immediate, non-genomic effects by binding and activating GR, which in turn activates accessory proteins to participate in secondary cascades [7]. However, it is important to consider that not all corticosteroids have the same therapeutic properties. For example dexamethasone has immunosuppressive properties and hydrocortisone has more vasoactive properties [10].

During the early 2000's relative adrenal insufficiency was shown in conjunction with sepsis and glucocorticoids were given to patients in septic shock [11]. In 2002, Annane et al. enrolled 300 adult patients in a placebo-controlled, randomized, double-blind, parallel-group trial to give hydrocortisone (50 mg IV bolus every 6 h) and fludrocortisone (50 μg tablet once daily) or a placebo for 7 days. Vasopressor therapy was terminated within 28 days in 65 patients (57%) in the corticosteroid group and in 46 patients (40%) in the placebo group ($p = 0.001$). Overall, low dose steroid therapy (LDST) was demonstrated to reduce time to shock reversal and improve mortality rates with no difference in the rate of adverse events (including gastrointestinal bleed, infection, psychiatric disorder, dysrhythmia, myocardial infarction, and ischemia) [12]. This lead to widespread acceptance of LDST as appropriate adjunctive treatment for septic shock. However, these results were not corroborated by the Corticosteroid Therapy of Septic Shock (CORTICUS) study in 2008, which failed to identify any significant effect of low-dose hydrocortisone on 28-day mortality or shock reversal [13]. In 2017, the Society of Critical Care Medicine published a recommendation based on low-quality evidence that long course, low dose corticosteroids (e.g. IV hydrocortisone <400 mg/day for 3 or more days) be administered to patients in septic shock who are not responsive to fluid or vasopressor therapy [14]. Thus, the utility of corticosteroids in the treatment of septic shock remains unresolved and requires further investigation, with particular attention to areas of controversy that include age of population, time to administration, use with fludrocortisone, and adverse effects. In this review, we examine recent clinical trials and reviews of corticosteroid therapy to best direct the informed management of septic shock patients from the emergency department to the intensive care unit.

2. Methods

This narrative review was compiled through PubMed and MEDLINE database searches with the terms “septic shock” and subheadings “therapeutic use”, “drug therapy”, “pharmacology”, and “therapy” followed by the addition of “steroid” to yield 37,897 articles. Additional filters were added to restrict the search to studies involving patients 18+ years of age, English language, human studies, full texts, and articles published within the last 10 years. Boolean operators and medical subject headings (MeSH) terms were used to combine search terms. Two authors independently assessed the results and reviewed the articles for relevance to septic shock while a third individual reviewed for potential conflicts. In total, one hundred and sixty-five articles were examined. Of those, twenty-five were relevant to clinical outcomes of patients in septic shock who were administered corticosteroid therapy and thus included in this review.

3. Results

3.1. Studies demonstrating improved hemodynamic outcomes

Several studies and reviews found that while corticosteroid use in septic shock did not improve mortality rates, it was associated with improved hemodynamic outcomes and decreased adverse events (see Table 1). Venkatesh et al. conducted a randomized controlled trial with 3800 patients in septic shock who received a continuous infusion of hydrocortisone (200 mg per day) or placebo for one week. In the treatment group versus the placebo group, shock resolved faster (3 days vs 4 days; $p < 0.001$), mechanical ventilation was discontinued sooner (6 days vs 7 days; $p < 0.001$), and fewer blood transfusions were required (37% of patients vs 41.4% of patients; $p = 0.004$). However, there was no significant difference in 28-day or 90-day mortality, recurrence of shock, days alive out of the ICU or hospital, rate of renal-replacement therapy, or incidence of secondary infection. This study did not collect data regarding all possible secondary infections which limits the inferences that can be drawn regarding adverse events. Overall, Venkatatesh et al. did not find a difference in mortality but did see some positive hemodynamic effects from the hydrocortisone [15]. Moreno et al. conducted an 11-day study in which 251 patients received 50 mg IV hydrocortisone and 248 received placebo every 6 h for days 1–5, every 12 h for days 6–8, and every 24 h for days 9–11. SOFA scores were used to quantify organ dysfunction/failure. No difference was observed in 28-day mortality between the two groups (34.3% in the treatment group vs 31.5% in the placebo group). However, organ failure rate improved by 75% in the treatment group compared to placebo group as measured by a decrease in SOFA score from day 0 to day 7 ($p = 0.0027$), primarily due to improvement in cardiovascular failure ($p = 0.0005$) and liver failure ($p < 0.0001$). Limitations of this study were that it was underpowered, had slow recruitment, and while commonly used, organ parameters used by the SOFA score may not be wholly indicative of all of that organ's function [16]. Tongyoo et al. conducted a 4-year randomized controlled trial to determine the effect of low-dose steroid therapy on 28-day mortality. Within 12-h of meeting ARDS criteria, patients with severe sepsis or septic shock were randomized to receive 50 mg hydrocortisone or placebo every 6 h for 7 days. The treatment group had significantly improved pulmonary status, with improved ratios of partial pressure of oxygen to fraction of inspired oxygen and lung injury score ($p = 0.01$). However, the decrease in 28-day mortality was not statistically significant (65.3% in the treatment group vs 55.6% in the placebo group; $p = 0.19$). The rates of adverse events were similar except hyperglycemia was higher in the treatment group (80.6% vs 67.7%; $p = 0.04$) though it did not affect patient outcomes. Limitations of this study were that it was underpowered due to recruitment of patients with less severe illness, which included severe sepsis and ARDS [17].

Gordon et al. demonstrated potential for adjuvant hydrocortisone to shorten duration of vasopressin therapy in septic shock patients. Thirty-one patients were given vasopressin and hydrocortisone and 30 patients were given vasopressin and placebo. Plasma vasopressin levels were the same in both groups at various time points. The hydrocortisone group required a shorter time course and lower total dose of vasopressin compared to the placebo group. The results showed no difference in mortality rates or organ failure rates between the two groups, however this may have been due to limitations of the small sample size to detect differences in clinical outcome measures [18]. Similar results were obtained through a literature review by Wang et al. that was conducted to determine whether hydrocortisone could reduce time to shock reversal at 7 and 28 days and reduce 28 day mortality. Shock reversal was defined as stable systolic blood pressure > 90 mmHg for >24 h without vasopressors or blood transfusion. They found that although low-dose hydrocortisone therapy (daily dose ± 300 mg) improved the time to shock reversal at 7 days ($p < 0.0001$) and 28 days ($p = 0.006$), it did not reduce 28 day mortality. Additional studies

Table 1
Studies demonstrating improved hemodynamic outcomes.

Study	Design	Population	Intervention/control	Outcomes	Adverse effects
Venkatesh et al. (2018) [15]	Randomized	Septic shock patients on mechanical ventilation n = 3800	Hydrocortisone 200 mg/day or placebo for 1 week	Primary outcome was all-cause mortality within 90 days.	33 adverse events reported; 1.1% in the hydrocortisone group vs 0.3% in the placebo group, p = 0.009)
Moreno et al. (2011) [16]	Prospective, randomized, double-blind, placebo-controlled	Patients with septic shock for <72 h n = 499	Subjects were randomized into two groups, one received 11-day hydrocortisone treatment and the other received placebo.	SOFA score was used to quantify organ dysfunction.	No significant difference for adverse events between hydrocortisone and placebo groups- stroke (3 vs 1), myocardial infarction (14 vs 13), or limb ischemia (0 vs 1) respectively. No bowel infarcts occurred.
Tongyoo et al. (2016) [17]	Double-blind, single-center, randomized, placebo-controlled	Included patients who experienced severe sepsis or septic shock within 12 h of ARDS onset n = 197	Subjects were randomized to receive either hydrocortisone 50 mg every 6 h or placebo.	Hydrocortisone group had significant improvement in pulmonary function-ratio of partial pressure of arterial oxygen to fraction inspired oxygen and lung injury score (p = 0.01).	Adverse events were similar between the two groups, except hyperglycemia was higher in the hydrocortisone group (80.6% vs 67.7%, p = 0.04).
Gordon et al. (2014) [18]	Prospective, open-label randomized- controlled pilot trial	Patients with septic shock (2/4 systemic inflammatory response criteria) who required vasopressors despite IV fluid resuscitation n = 61	Septic shock patients were randomized to vasopressin+hydrocortisone or to vasopressin+placebo treatment groups.	Hydrocortisone group had 47% lower total dose and 3.1 day shorter duration vasopressin therapy vs the placebo group.	No difference in adverse events between the two groups.14 total events reported with 6 potentially related to treatment: one extension of preexisting cerebral infarct, three episodes of cool/mottled peripheries, one increased serum lactate, and one increased troponin.
Wang et al. (2014) [19]	Meta-analysis	8 RCTs of low dose hydrocortisone therapy in septic shock were included.		Low-dose hydrocortisone therapy improved effects of septic shock at 7- and 28-days but did not reduce 28-day mortality.	Low-dose hydrocortisone increased blood glucose levels in patients (p < 0.0001), had a statistically insignificant trend toward increased GI bleeding (p = 0.057), and was not associated with increased risk of superinfection (p = 0.507).

with larger sample sizes are required to explain this lack of improvement [19].

3.2. Studies demonstrating decreased mortality and improved hemodynamic outcomes

Several retrospective studies showed improved morbidity and mortality rates with adjuvant corticosteroid administration (see Table 2). Bauer et al. conducted a retrospective case study and determined that there was no significant difference in median time to vasopressor withdrawal between the corticosteroid and non-corticosteroid groups (65 h vs 20 h; $p = 0.09$). However, patients who received corticosteroids were significantly more likely survive without the use of vasopressors at day 7 compared to patients who received only the vasopressor regimen (80.9% vs 47.6%, $p = 0.02$). This study was limited by the retrospective nature and small sample size, which may have prevented underpowered outcomes from showing a significant difference [20]. In a similarly underpowered retrospective study, Torgersen et al. observed the effect of arginine-vasopressin (AVP) and hydrocortisone therapy on mortality in septic shock patients. The use of both AVP and hydrocortisone resulted in lower ICU ($p = 0.08$) and 28-day ($p = 0.11$) mortality. The probability of survival at 28 days was significantly higher in patients treated with both AVP and hydrocortisone as compared to those receiving only AVP ($p = 0.001$) [21]. In a prospective longitudinal study, Katsenos et al. investigated the effect of timely doses of hydrocortisone on cytokine release and clinical outcomes in septic shock. Forty-six patients received early initiation of hydrocortisone (<9 h. after vasopressors) and 124 patients received late initiation of hydrocortisone (>9 h. after vasopressors). Patients receiving the early hydrocortisone had lower production of tumor necrosis factor alpha (a cytokine involved in cell survival, proliferation, and death) and showed improved survival compared to the late initiation group (52.2% vs 30.6%; $p = 0.012$) [22]. Median time to discontinuation for vasopressors was 4 days for the early initiation group versus 15 days for the late initiation group ($p < 0.0001$). This study was limited by the fact that it was not randomized and because it lacked an untreated arm for comparison [23].

The results found in the retrospective and prospective studies above were corroborated by several randomized trials. Cicarelli et al. found that patients treated with dexamethasone required less vasopressor therapy over the 7day period than the placebo group (71.9 ± 28.2 h vs 91.1 ± 18.6 h; $p = 0.043$). Early treatment with dexamethasone significantly decreased the 7day mortality rate among septic shock patients (21% vs 67%) and indicated a reduction of 28-day mortality. The primary limitation of this study was the small sample size of 29 patients [24]. Annane et al. evaluated the use of corticosteroids in 117 patients with septic shock and early acute respiratory distress syndrome (ARDS). The patients underwent corticotropin testing and were considered to be nonresponders if cortisol increase was <9 μg/dL. There were 129 nonresponders (67 received placebo, 62 received corticosteroids) and 48 responders (25 received placebo, 23 received corticosteroids). In nonresponders, there was 75% mortality in the placebo group and 53% in the corticosteroid group ($p = 0.013$). The average days off mechanical ventilation was 2.6 in the placebo group and 5.7 in the corticosteroid group ($p = 0.006$). Adverse event rates were similar across the two groups. Overall, the 7day treatment with low dose corticosteroids was associated with better outcomes in septic shock-associated early ARDS nonresponders. However, these results did not translate to corticotropin responders, patients not in septic shock, or to patients without ARDS. This study was limited by the retrospective nature and by the small number of patients without ARDS because it is unclear whether the benefit from corticosteroids in the septic shock-associated ARDS group is related to the ARDS treatment rather than treatment of the septic shock directly [25]. Russell et al. also conducted a study to assess whether corticosteroids increased the effectiveness of vasopressin and norepinephrine. Patients who received corticosteroids had decreased mortality with vasopressin compared to norepinephrine (35.9% vs

Table 2
Studies demonstrating decreased mortality and improved hemodynamic outcomes.

Study	Design	Population	Intervention/control	Outcomes	Adverse effects
Annane et al. (2018) [4]	Multicenter, double-blind, randomized	Patients in severe septic shock, as defined by high Simplified Acute Physiology Score II, high lactate, and vasopressor dependency. n = 1241	Patients were randomized to receive hydrocortisone (50 mg IV every 6 h)-plus-fludrocortisone (50microg tablet/day) vs those who received placebo.	90- day all-cause mortality was lower in patients who received the corticosteroids vs those who received placebo (43% vs 49.1%).	53.1% (326/614) of patients in the hydrocortisone-plus-fludrocortisone group and 58.0% (363/626) of patients in the placebo group had at least one serious adverse event by day 180 (p = 0.08)
Bauer et al. (2008) [20]	Retrospective, case-control	Enrolled patients met the following criteria at AVP initiation: systolic blood pressure ≤ 90 mmHg or MAP ±70 mmHg within 1 h before AVP initiation, positive fluid balance, 2+ SIRS criteria (including mechanical ventilation) n = 42	Patients in septic shock received vasopressin with or without concomitant corticosteroids. There were 21 patients in each group.	Patients treated with corticosteroids showed no significant difference in time to vasopressor withdrawal (median 65 h vs 20 h, p = 0.09) but were significantly more likely to be alive without vasopressors at 1 week than patients who received vasopressin alone (80.9% vs 47.6%, p = 0.02).	Not reported.
Torgersen et al. (2011) [21]	Retrospective	Enrolled patients were in septic shock (defined by the 1992 ACCP/SCCM consensus conference) and had been treated with supplementary AVP. n = 159	76 patients were administered low dose (200–300 mg) hydrocortisone in addition to AVP versus control group treated with AVP alone.	Concomitant AVP (arginine-vasopressin) and hydrocortisone therapy was associated with lower 28-day mortality compared with AVP alone (p = 0.001), with no mortality difference between patients who had hydrocortisone therapy started before or after AVP.	Not reported.
Katsenos et al. (2014) [23]	Prospective longitudinal study	Inclusion criteria was presence of septic shock treated with norepinephrine ≥ 0.5 μg/kg/min and low dose hydrocortisone (50 mg q6h for 7 days) n = 170	170 septic shock patients were treated with low dose hydrocortisone.	Time to d/c vasopressors was faster and TNF-alpha was lower in the early initiation group.	Not reported.
Cicarelli et al. (2007) [24]	Prospective, randomized, double-blind, single-center	Patients diagnosed with septic shock after admission to the ICU. n = 29	Patients were randomized into a treatment group (dexamethasone 0.2 mg/kg) or placebo group, with their respective treatments administered three times at over 36 h. Patients were monitored over one week via SOFA score.	Patients who received dexamethasone required less vasopressor therapy compared to the placebo group (p = 0.043).	No adverse effects observed. The study concluded the use of corticosteroids at "physiological" doses will not cause adverse effects (ex. gastrointestinal bleed or secondary infections)
Annane et al. (2006) [25]	Retrospective, placebo-controlled, randomized, double blind	300 septic shock patients were enrolled.	177 patients with septic shock and ARDS underwent corticotropin testing and were determined to be responders vs nonresponders if cortisol increase was <9 μg/dL.	For non-responders with ARDS, 7-day treatment with dexamethasone was associated with better outcomes.	No significant difference between treatment groups for rates of adverse events (superinfection, gastrointestinal bleeding, or psychiatric disorders) in septic shock patients both with and without ARDS.
Russell et al. (2009) [26]	Post-hoc sub study of multicenter blinded RCT	Enrolled patients had septic shock with hypotension requiring at least 5 μg/min of norepinephrine for 6 h. n = 779	Hypotensive patients in septic shock who required at least 5 microg/min of norepinephrine for 6 h were included and randomized to receive additional 0.01–0.03 units/min vasopressin or 5–15 μg/min norepinephrine.	There was a statistically significant interaction between vasopressin infusion and corticosteroid treatment (p = 0.008). Patients treated with corticosteroids and vasopressin had significantly decreased mortality vs norepinephrine (35.9% vs 44.7%, p = 0.03).	Rates of serious adverse events were similar in the two treatment groups. The rate of cardiac arrests was significantly in norepinephrine patients treated with corticosteroids (2.4% vs 0.3%, p = 0.04).
Annane, et al. (2015) [27]	Systematic review	Included were RCTs of corticosteroids vs placebo in septic patients	Review of 33 randomized controlled trials: corticosteroids compared to supportive treatment in sepsis.	Corticosteroids reduced 28 day mortality in 27 trials (p = 0.05). Decreased organ failure in 8 trials	81/1219 in the treatment group and 62/1163 in the control group had an episode of GI bleeding. (p = 0.15) 219/1307 in the treatment group and 203/1260 in the control group had a nosocomial infection.(p = 0.81)

44.7%; $p = 0.03$). Patients who did not receive corticosteroids had increased mortality with vasopressin compared to norepinephrine (33.7% vs 21.3%; $p = 0.06$). In patients who received vasopressin, the use of corticosteroids significantly raised plasma vasopressin levels by 33% at 6 h ($p = 0.006$) to 67% at 24 h ($p = 0.025$). Results showed that the combination of low-dose vasopressin with corticosteroids decreased mortality and organ dysfunction versus norepinephrine with corticosteroids. Limitations of this study included the use of relatively low-dose vasopressin and that the administration of corticosteroids was not randomized, controlled, or blinded [26]. Recently, Annane et al. conducted a randomized trial analyzing outcome differences in septic patients who received hydrocortisone-plus-fludrocortisone versus placebo for one week. The test group's 90-day mortality was 43.0% vs 49.1% for the placebo group ($p = 0.03$) and 180-day mortality rates were 46.6% vs 52.5% respectively ($p = 0.04$). The number of vasopressor-free days was greater in the test group versus the placebo group (17 vs 15; $p < 0.001$) as were the organ failure free days (14 vs 12; $p = 0.003$). The ventilator free days were similar (11 days) but the test group did have increased hyperglycemia ($p = 0.002$). Fifty-three percent of the test group and 58% of the placebo group had at least one serious adverse event by day 180 ($p = 0.08$) There was no significant association between corticosteroid and risk of gastroduodenal bleeding ($p = 0.56$) or superinfection ($p = 0.30$). Overall, Annane et al. did see a lower 90-day mortality rate and positive hemodynamic effects from the hydrocortisone and fludrocortisone. A potential limitation of this study was that it was originally designed and powered to have drotrecogin alfa as a component of the intervention arm before it was taken off the market [4].

In a comprehensive review of 33 randomized controlled trials, Annane et al. assessed the use of adjuvant corticosteroids versus standard supportive treatment for septic patients. Corticosteroids reduced 28-day mortality in 27 trials ($p = 0.05$) and reduced ICU mortality in 13 trials ($p = 0.04$). This trend was also seen in 17 in-hospital trials ($p = 0.03$). The lower the dose (<400 mg/day) and the longer the duration of treatment (3 or more days), the better the outcome depending on the severity of the illness. After a week, corticosteroids seemed to increase the chances of recovery in 12 trials ($p = 0.0001$) and by day 28 in 7 trials ($p = 0.01$). A decrease in organ failure was seen in 8 trials. The duration of ICU stay was decreased by >2 days in 10 trials. There was no increase in gastrointestinal bleeding or superinfection in 19 trials and no increase in neuromuscular weakness in 3 trials. However, there was an increased risk of hyperglycemia noted in 13 trials ($p = 0.00001$) and hypernatremia in 3 trials ($p = 0.0001$). Annane et al. concluded that low-quality evidence suggests corticosteroids reduce mortality in septic patients and that moderate-quality evidence shows that a long course of low-dose corticosteroids could improve mortality rates but also increase metabolic disorders [27].

3.3. Studies demonstrating increased adverse events

Two studies showed that corticosteroids were associated with increased adverse events and had minimal effect on in-hospital mortality rates (see Table 3). Nazer et al. conducted a retrospective study of 96 adult oncology patients with septic shock who were given hydrocortisone (200 mg/day) compared to a control group of 62 patients who did not receive hydrocortisone. In the treatment group, shock reversal was demonstrated in 46 patients (47.9%), ICU mortality was 64.6% (vs 32.3% in the control group; $p > 0.0001$), and 28-day mortality was 65.6% (vs 38.7% in the control group; $p = 0.0009$). A higher incidence of superinfection was shown is those receiving corticosteroids compared to the control group (44.8% vs 27.4%; $p = 0.028$). Overall, Nazer et al. determined that about half of the patients who received hydrocortisone achieved shock reversal but that there was an association with increased secondary infections. Weaknesses of this study include its retrospective nature, lack of comparison arm, and limited generalizability because it was performed at a single center and included oncology patients with septic shock. [28] Arabi et al. studied the effect of corticosteroid replacement on mortality for septic patients with liver cirrhosis. Patients received 50 mg of intravenous hydrocortisone or placebo every six hours until hemodynamic stability was achieved. The hydrocortisone group had a significant reduction in vasopressor doses and higher rates of shock reversal ($p = 0.05$). However, hydrocortisone administration did not result in a reduction in 28-day mortality ($p = 0.19$) and was associated with an increase in shock relapse ($p = 0.03$) and gastrointestinal bleeding ($p = 0.02$). In addition to limited generalizability as a single-center study, another potential limitation is that 33% of patients received etomidate, which may cause adrenal suppression. However,

Table 3
Studies demonstrating increased adverse events.

Study	Design	Population	Intervention/control	Outcomes	Adverse effects
Nazer et al. (2015) [28]	Retrospective case-control	Adult cancer patients identified through ICU sepsis database n = 96	Treatment group were patients with septic shock who had been given IV hydrocortisone (50 mg IV push every 6 h) for a MAP <65 mmHg despite IV fluid resuscitation and high doses of vasopressor therapy (norepinephrine 20 μg/min or equivalent dose).	Effectiveness was assessed by time to reversal of septic shock and mortality. Reversal was reported in 46 (47.9%) patients after median of 1.9 days. ICU mortality was reported in 62 (65.26%) patients and 28-day mortality in 64 (66.7%) patients.	Incidence of secondary infections was higher in the treatment group compared to placebo group, (44.8% vs 27.4%, p = 0.028)
Arabi et al. (2010) [29]	Randomized double-blind placebo-controlled	Patients with cirrhosis and septic shock n = 75	Enrolled patients were randomized to receive 50 mg IV hydrocortisone (n = 39) or placebo (n = 36) q 6 h until hemodynamically stable.	Trial stopped after interim analysis due to futility. Primary outcome was all-cause 28-day mortality. Compared with placebo group, the hydrocortisone group had significantly reduced vasopressor doses and increased rate of shock reversal (p = 0.05), no reduction in 28-day mortality (p = 0.19), and increased rates of both shock relapse (p = 0.03).	Hydrocortisone group had higher rates of gastrointestinal bleeding (p = 0.02) and hyperglycemia (0.06).
Casserly et al. (2012) [30]	Retrospective	Patients with septic shock (identified from the Surviving Sepsis Campaign database). N = 17,847	Septic shock patients had required vasopressors despite fluid resuscitation. 8992 of these patients had received low-dose corticosteroids (defined as 50 mg IV qds or 100 mg IV tds).	Hospital mortality was significantly higher for the patients who received corticosteroids vs those who did not (p < 0.001).	Not reported.

the authors found no association with 28-day mortality between the assigned treatment and etomidate use [29].

Of the studies assessed, only one exhibited increased mortality rates with LDST. Casserly et al. analyzed the Surviving Sepsis Campaign (SSC) database to determine how the administration of low dose corticosteroids affected the outcomes of nearly 9000 adults in septic shock from 2005 to 2010. The hospital mortality was significantly higher in patients who received low-dose steroids compared to those who did not (41% vs 35%; $p < 0.001$). This may reflect the study's limitation as an observational design, as it is possible that only the most severely ill patients in septic shock received steroid therapy[30].

3.4. Studies demonstrating no association with mortality or morbidity outcomes

There were a number of randomized studies that suggested no association between corticosteroids and mortality rates or patient outcomes (see Table 4). Hyvernat et al. performed a randomized study to determine the difference between low dose (200 mg) and high dose (300 mg) hydrocortisone. Fifty-nine patients in the 200 mg group were given a 50 mg IV bolus every 6 h for 7 days and 63 patients in the 300 mg group were given a 100 mg initial bolus followed by continuous infusion of 300mg daily for 5 days. There was no significant difference between the 200 mg and 300 mg group on 28-day mortality (52.5% vs 44.4%; $p = 0.47$). There was also no difference in refractory shock incidence, delay from shock to vasopressor cessation, shock relapse, or adverse events between the groups. With the exception of the higher occurrence of permanent shock with lower dose hydrocortisone, Hyvernat et al. found little difference in results between the two doses. Main weaknesses of this study were the lack of a control group and the comparison between two therapeutic protocols that differed at several points (including dosage, timing, and course length) [11]. Lv et al. designed a randomized controlled trial to determine the significance of early initiation low dose hydrocortisone in septic shock. Fifty-eight patients received continuous IV hydrocortisone with saline and 60 received only normal saline, both simultaneously with vasopressors. There was no significant difference in the 28-day mortality ($p = 0.369$), length of stay in the ICU ($p = 0.799$), length of stay in the hospital ($p = 0.771$), or shock reversal ($p = 0.602$) between the two groups. Limitations of this study include lack of generalizability due to small sample size and single-center design. Additionally, the study was most likely underpowered by recruitment of patients with lower mortality because the control 28-day mortality was only 31.7% when the original sample size calculation was based on a control mortality of 60% (based on the largest prior study) [31]. Povoa et al. conducted a sub-study of the PROWESS-Shock trial in which 436 patients received drotrecogin alfa (DrotAA) with corticosteroids, 414 received DrotAA without corticosteroids, 403 received placebo with corticosteroids, and 442 received placebo without corticosteroids. There was little difference in the 28 day ($p = 0.38$) and 90-day mortality ($p = 0.27$) between all groups. Additionally, vasopressor use and cardiovascular SOFA scores were not influenced by corticosteroid therapy. The limitations of this study were largely based on incomplete data from the PROWESS-Shock database, which did not report steroid-related complications or the type, dose, or duration of steroid therapy [32]. Huh et al. studied the effect of receiving hydrocortisone for 3 or 7 days in a randomized study of 130 septic shock patients. After 28 days, mortality did not differ between the 3 and 7 day treatment groups (33.8% vs 36.9%, $p = 0.629$). Withdrawal of vasopressor therapy was achieved in a median of 5 days in the 3 day treatment group and 6.4 days in the 7 day treatment group ($p = 0.102$). This single-center study with a small sample size may have underestimated the statistical significance of the clinical outcomes and thus requires follow-up with a large multi-center randomized controlled trial (RCT). Other limitations of this study were that the randomization was not blinded and that the study was prematurely terminated due to low enrollment rate. [33]

Yu et al. conducted a study to compare the effects of hydrocortisone and methylprednisolone on sepsis. The corticosteroid therapy was 7 days of IV hydrocortisone (50 mg every 6 h) but switched to methylprednisolone (20 mg every 12 h) because hydrocortisone could no longer be prescribed at the study hospital. There was no significant difference in mortality or shock reversal time between the 2 patients given hydrocortisone and 19 patients given methylprednisolone. For the hydrocortisone group vs methylprednisolone group, median time to shock reversal was 7 days vs 5 days and median survival was 25 days vs 7 days. However, Kaplan-Meier curves and Cox regression analysis showed no significant effect of hydrocortisone or methylprednisolone for these outcomes. It was concluded that the two drugs have similar effects on time to shock reversal and mortality. Limitations of this study were that it was potentially underpowered due to the small sample size of only 40 ICU patients [34]. Gibbison et al. compared the data from 22 randomized controlled trials to analyze the effects of giving hydrocortisone, dexamethasone, methylprednisolone, or prednisolone to patients in septic shock. There is weak evidence that dexamethasone boluses decrease in-hospital mortality compared to placebo (OR 0.47, 95% CI 0.15–1.46) and increase risk of superinfections compared to placebo (OR 2.78, 95% CI 0.73–10.6). Hydrocortisone boluses (OR 0.37, 95% CI 0.19–0.72) and infusions (OR 0.24, 95% CI 0.07–0.81) were more likely than methylprednisolone boluses and placebo to increase the likelihood of shock reversal. There was no substantial evidence that any particular corticosteroid drug or treatment regimen is more likely to be effective in reducing mortality, gastrointestinal bleeding, or further infection during septic shock. Limitations of this study were that there were only two comparisons of treatment regimens with all the others being intervention vs placebo. Additionally, a source of bias is that data was used from the last 50 years, during which time the ICU patient population has changed in terms of patient condition, age, and treated comorbidities. [10] Raurich et al. performed a retrospective study of 203 patients with septic shock to determine the effect of low dose corticosteroids on clinical outcomes. Corticosteroids were administered to 124 patients with 79 other patients making up the control group. The in-hospital mortality was 62% in the corticosteroid group and 52% in the control group ($p = 0.84$). Overall, the treatment with low-dose corticosteroid therapy did not yield a significant reduction in time to shock reversal or mortality. This study was limited by its retrospective, non-randomized design. [35] In a prospective study, Ferrer et al. analyzed 995 septic shock patients to whom low-dose corticosteroids were administered due to lactate >36 mg/dL and/or for persistent hypotension despite fluid resuscitation. There was no association between LDST and mortality rate. This study's major limitation was its observational design. [36]

4. Discussion

The administration of corticosteroids during septic shock has long been a contentious point of debate. The continuance of poor outcomes for nearly half of sepsis cases demonstrates the need for improved therapies. Evidence shows that sepsis affects the functioning of the hypothalamic-pituitary-adrenal axis. Sepsis may cause resistance of body tissues to corticosteroids due to decreased corticosteroid receptors and reduced binding capacity of the remaining receptors from the effects of increased nitric oxide. This inhibitory mechanism causes poor adrenal activity in about half of septic patients [27]. These hypotheses provide a potential explanation for some beneficial responses seen in these trials and demonstrate a the need for further exploration in the use of adjuvant corticosteroid therapies during septic shock.

Two recent studies address the possible mechanisms by which corticosteroids function in septic shock patients (see Table 5). Wu et al. studied LDST in relation to cytokine response from peripheral blood nuclear cells (PMBCs) and HLA-DR expression with 29 septic patients and 30 healthy controls. Regression analysis showed the LDST to be independently and negatively associated with IL-12 response. There was

Table 4
Studies demonstrating no significant associations.

Study	Design	Population	Intervention/Control	Outcomes	Adverse Effects
Gibbison et al. (2017) [10]	Network meta-analysis	Included complete data from 22 studies and partial data from 1 study.	Analysis was done to determine any differences between the multiple corticosteroids and treatment regimens that have been used for septic shock.	The analysis showed no specific evidence that any intervention or treatment is better than any other for any outcome except shock reversal. Hydrocortisone treatment was more likely to result in shock reversal than methylprednisolone or placebo.	There is weak evidence that dexamethasone boluses decrease in-hospital mortality compared to placebo (OR 0.47, 95% CI 0.15–1.46) and increase risk of superinfections compared to placebo (OR 2.78, 95% CI 0.73–10.6).
Hyvernat et al. (2016) [11]	Multicenter, prospective, randomized, double-blind pilot study	Patients with septic shock with persistent hypoperfusion despite adequate fluid resuscitation and norepinephrine. n = 122	Patients in septic shock were randomized to receive one of two hydrocortisone regiments: 50 mg IV bolus q6hrs for 7 days or 100 mg bolus followed by 300 mg/day continuous infusion for 5 days.	No significant difference for 28-day mortality (p = 0.47), for incidence of refractory shock, delay to vasopressor therapy cessation, or adverse events.	No difference in incidence of hemorrhage (6.8% in the 200-mg group vs 12.7% in the 300-mg group, p = 0.42) or superinfections (15.3% in the 200-mg group vs 28.5% in the 300-mg group, p = 0.12).
Lv et al. (2017) [31]	Placebo-controlled, randomized	Patients who had developed septic shock within 6 h of admission n = 118	Patients with septic shock were randomized to receive vasopressor therapy with either hydrocortisone or normal saline.	No significant differences in shock reversal (p = 0.602), in 28-day mortality, or in length of ICU/hospital stay between the two groups.	Not reported.
Povoa et al. (2015) [32]	Randomized sub-study of the PROWESS-Shock trial	Septic shock patients who received fluids and vasopressor for at least 4 h. n = 1695	Septic shock patients who received fluids and vasopressors above a predefined threshold for >4 h were randomized to receive DrotAA or placebo for 96 h.	49.5% of enrolled patients received corticosteroids for treatment of septic shock.	Vasopressor use, secondary infection, and cardiovascular SOFA scores were not affected by corticosteroid therapy.
Huh et al. (2011) [33]	Prospective, randomized	n = 130	Patients with septic shock who required vasopressor support after fluid resuscitation were included in the study. They were randomized to receive 50 mg hydrocortisone q6hrs for either 3 or 7 days.	28-day mortality was not significantly different between the groups- 33.8% in the 3-day group vs 36.9% in the 7-day group (p = 0.629)	Not reported.
Yu et al. (2009) [34]	Randomized	Patients admitted to the ICU with low-dose steroid therapy due to septic shock. n = 40	40 ICU patients in septic shock were included- 21 patients were given 50 mg hydrocortisone q6hrs x 7 days and 19 patients were given 20 mg methylprednisolone q12hrs x 7 days because hydrocortisone could not be prescribed due to change in hospital policy.	The hydrocortisone group had higher survival rate than the methylprednisolone group, but the difference was not significant. No significant difference for time to shock reversal between groups.	Adverse events in the hydrocortisone group vs methylprednisolone group: GI bleed 3 vs 5 (p = 0.139), arrhythmia 5 vs 2 (p = 0.488), acute renal failure 11 vs 8 (p = 0.456), jaundice 5 vs 2 (p = 0.816), thrombocytopenia 13 vs 1 (p = 0.402).
Raurich et al. (2007) [35]	Retrospective	Patients selected from a database with septic shock who had high-dose corticotropin stimulation tests performed. n = 203	A corticotropin test had been performed in all enrolled ICU patients within 72 h of septic shock onset.	The corticosteroid group had higher Simplified Acute Physiology Score II and higher maximum SOFA scores.	Not reported.
Ferrer et al. (2009) [36]	Prospective observational	Patients in severe sepsis or with septic shock from 77 ICUs. n = 2796	Patients were assessed for four therapeutic goals (CVP, central venous oxygen saturation, blood glucose, and inspiratory plateau pressure for mechanically ventilated patients) and four treatments (early broad-spectrum antibiotics, fluid challenge, low-dose corticosteroids for septic shock, and activated drotrecogin alfa for multiorgan failure).	41.6% of enrolled patients died before hospital discharge. Low-dose corticosteroids showed no benefits.	Not reported.

Table 5
Hypothesized mechanisms of corticosteroids in septic patients.

Study	Design	Population	Intervention/control	Outcomes	Adverse effects
Büchele et al. [10]	Prospective, open-label	Patients in the first 12 h of septic shock, n = 20	Hemodynamic measurements and orthogonal polarization spectral images for sublingual microcirculation (Cytoscan ARII, Cytometrics) were taken before first hydrocortisone dose (50 mg/6 h) and at 1, 2, 4, and 24 h later.	Hemodynamics were similar at all study time points. Sublingual microcirculation improved by one hour from start, average perfused vessel density increased from 5.7 to 7.2n/mm, $p < 0.01$ and average proportion of perfused vessels increased from 82.1 to 89.2%, $p < 0.01$.	Not reported.
Wu et al. [37]	Post-hoc analysis	Patients admitted to the ICU for severe sepsis and septic shock n = 29	29 patients with severe sepsis were enrolled and of these 18 were given low-dose steroids (7 days of 50 mg hydrocortisone q6hrs).	Patients who received low-dose steroids had lower IL-12 responses on days 1 and 7. IL-12 responses in patients who did not receive steroids increased significantly from day 7 to day 1.	Rates of gastrointestinal bleed, acute renal failure, thrombocytopenia, bacteremia, and mortality were similar between the two groups.

no difference in monocyte HLA-DR expression between the two groups [37]. Büchele et al. demonstrated improved microcirculatory indicators in septic shock at 1 h after the start of hydrocortisone administration. Specifically, perfused vessel density increased from 5.7 to 7.2 n/mm due to combined increases in small vessel density and in the proportion of perfused vessels ($p < 0.01$). It was determined that giving moderate doses of hydrocortisone in septic shock results in a modest but consistent improvement in capillary perfusion, which underlies the development of organ ischemia and failure in septic shock. The pathway by which this effect is achieved needs to be further investigated [38]. One potential explanation is that corticosteroids may improve cardiovascular function by restoring blood volume through increased mineralocorticoid activity and by increasing systemic vascular resistance via activity of endothelial glucocorticoid receptors [10].

This review demonstrates the conflicting findings regarding the use of corticosteroids in septic shock patients. Twenty-five articles were reviewed in total. Five of the studies demonstrated improved hemodynamic stability but no change in mortality. Two of the studies showed decreased hemodynamic stability and one showed increased mortality. Eight of the articles reported both decreased mortality and improved hemodynamic stability. Eight of the articles described no association between corticosteroid administration and morbidity or mortality in patients with septic shock. One article showed vasopressin to be associated with fewer adverse events and faster hemodynamic stability than hydrocortisone.

Randomized controlled trials by Venkatesh et al. (n = 3800) and Moreno et al. (n = 499), as well as a meta-analysis of 8 RCTs by Wang et al., showed faster time to shock reversal but no difference in mortality associated with adjuvant corticosteroids. Arabi et al. (n = 75) demonstrated faster time to shock reversal with corticosteroids but also increased relapse and GI bleeding. Tongyoo et al. (n = 197) showed improved pulmonary function but no change in mortality. In a large retrospective analysis, Casserly et al. assessed data from the Surviving Sepsis Campaign database (n = 17,847) and found corticosteroids were associated with increased mortality and therefore not appropriate for septic shock therapy. A large proportion of reviewed studies showed no significant associations and thus no support for the use of corticosteroids in septic shock. Hyvernat et al. (n = 122), Lv et al. (n = 118), and Huh et al. (n = 130) showed no change in mortality or in shock reversal/SOFA score. Raurich et al. (n = 203) and Ferrer et al. (n = 2796) concluded that low-dose corticosteroids had no association with mortality rate and was of no benefit to septic shock patients. Gibbison et al. conducted a meta-analysis of 22 studies that showed the only benefit of hydrocortisone to be improved time to shock reversal for patients with vasopressor-dependent septic shock.

The majority of studies reviewed here point to limited therapeutic benefit for the use of corticosteroids in septic shock, with the one potential improvement being time to shock reversal. These modest potential benefits support the current Surviving Sepsis Campaign guidelines that recommend against routine use of corticosteroids in patients responsive to fluids and vasopressors, but suggest low dose corticosteroids (200 mg per day of hydrocortisone) for nonresponders [39].

4.1. Limitations

The relatively small number of studies containing information on adverse effects, such as secondary infections, similarities and differences between patients, long-term outcomes of enrolled patients, and cost benefit analyses limits this review. Additional limitations include the retrospective nature of certain studies, the differences in dose and duration of corticosteroid treatment, and the small sample sizes of several included studies.

5. Conclusion

These 23 trials and 2 reviews have provided conflicting evidence as to the usefulness of corticosteroid treatments during septic shock. Overall, most have demonstrated minimally improved physiological outcomes during the course of septic shock for a statistically significant number of patients. Based on our review, we do not advocate for the routine administration of steroids for septic shock, but may consider them in patients' refractory to other therapies and in patients with adrenal insufficiency. The optimal dose, timing, duration, and specific patient populations have yet to be elucidated. More research is needed to expand upon previous results, particularly for scenarios where corticosteroids are administered early in the course of septic shock and in those cases with healthier patients in less severe forms of sepsis/septic shock. Additionally, the possible benefits of adding mineralocorticoids (fludrocortisone) to corticosteroid treatment has shown promising results with improved mortality and should be investigated further [4].

Conflict of interest

The authors do NOT have a financial interest or relationship to disclose regarding this research project.

Financial support

This is a non-funded study with no compensation or honoraria for conducting the study.

References

[1] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315(8):801 Feb 23.
[2] Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med 2013;369(9):840–51 Aug 29.

[3] Boyer A, Chadda K, Salah A, Annane D. Glucocorticoid treatment in patients with septic shock: effects on vasopressor use and mortality. Int J Clin Pharmacol Ther 2006;44(7):309–18 Jul.
[4] Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot J-P, Siami S, et al. Hydrocortisone plus fludrocortisone for adults with septic shock. N Engl J Med 2018; 378(9):809–18 Mar.
[5] Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. Virulence 2014;5(1): 4–11 Jan 1.
[6] Annane D. Corticosteroids for severe sepsis: an evidence-based guide for physicians. Ann Intensive Care 2011;1(1):7.
[7] Ramamoorthy S, Cidlowski JA. Corticosteroids. Rheum Dis Clin North Am 2016; 42(1):15–31 Feb.
[8] Varvarousi G, Stefaniotou A, Varvaroussis D, Xanthos T. Glucocorticoids as an emerging pharmacologic agent for cardiopulmonary resuscitation. Cardiovasc Drugs Ther 2014;28(5):477–88 Oct.
[9] Barnes PJ. Molecular mechanisms of corticosteroids in allergic diseases. Allergy 2001;56(10):928–36 Oct.
[10] Gibbison B, López-López JA, Higgins JPT, Miller T, Angelini GD, Lightman SL, et al. Corticosteroids in septic shock: a systematic review and network meta-analysis. Crit Care 2017 Dec;21(1) Internet. cited 2018 Jul 31. Available from http://ccforum.biomedcentral.com/articles/10.1186/s13054-017-1659-4.
[11] Hyvernat H, Barel R, Gentilhomme A, Césari-Giordani JF, Freche A, Kaidomar M, et al. Effects of increasing hydrocortisone to 300 mg per day in the treatment of septic shock: a pilot study. SHOCK 2016;46(5):498–505 Nov.
[12] Annane D, Sébille V, Charpentier C, Bollaert P-E, François B, Korach J-M, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002;288(7):862–71 Aug 21.
[13] Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008;358(2):111–24 Jan 10.
[14] Annane D, Pastores S, Rochwerg B, Arlt W, Balk R, Beishuizen A, et al. Guidelines for the diagnosis and management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in critically ill patients (part I). Crit Care Med 2017;45(12):2078–88 Dec 1.
[15] Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, et al. Adjunctive glucocorticoid therapy in patients with septic shock. N Engl J Med 2018;378(9): 797–808 Mar.
[16] Moreno R, Sprung CL, Annane D, Chevret S, Briegel J, Keh D, et al. Time course of organ failure in patients with septic shock treated with hydrocortisone: results of the Corticus study. Intensive Care Med 2011;37(11):1765–72 Nov.
[17] Tongyoo S, Permpikul C, Mongkolpun W, Vattanavanit V, Udompanturak S, Kocak M, et al. Hydrocortisone treatment in early sepsis-associated acute respiratory distress syndrome: results of a randomized controlled trial. Crit Care 2016;20(1) Dec [cited 2018 Jul 31]. Available from: http://ccforum.biomedcentral.com/articles/10.1186/s13054-016-1511-2.
[18] Gordon AC, Mason AJ, Perkins GD, Stotz M, Terblanche M, Ashby D, et al. The interaction of vasopressin and corticosteroids in septic shock: a pilot randomized controlled trial. Crit Care Med 2014;42(6):1325–33 Jun.
[19] Wang C, Sun J, Zheng J, Guo L, Ma H, Zhang Y, et al. Low-dose hydrocortisone therapy attenuates septic shock in adult patients but does not reduce 28-day mortality: a meta-analysis of randomized controlled trials. Anesth Analg 2014;118(2):346–57 Feb.
[20] Bauer SR, Lam SW, Cha SS, Oyen LJ. Effect of corticosteroids on arginine vasopressin-containing vasopressor therapy for septic shock: a case control study. J Crit Care 2008;23(4):500–6 Dec.
[21] Torgersen C, Luckner G, Schröder DCH, Schmittinger CA, Rex C, Ulmer H, et al. Concomitant arginine-vasopressin and hydrocortisone therapy in severe septic shock: association with mortality. Intensive Care Med 2011;37(9):1432–7 Sep.
[22] WANG X, LIN Y. Tumor necrosis factor and cancer, buddies or foes? Acta Pharmacol Sin 2008;29(11):1275–88 Nov.
[23] Katsenos CS, Antonopoulou AN, Apostolidou EN, Ioakeimidou A, Kalpakou GT, Papanikolaou MN, et al. Early administration of hydrocortisone replacement after the advent of septic shock: impact on survival and immune response*. Crit Care Med 2014;42(7):1651–7 Jul.
[24] Cicarelli DD, Vieira JE, Benseñor FEM. Early dexamethasone treatment for septic shock patients: a prospective randomized clinical trial. Sao Paulo Med J 2007 Jul 5; 125(4):237–41.
[25] Annane D, Sébille V, Bellissant E, Ger-Inf-05 Study Group. Effect of low doses of corticosteroids in septic shock patients with or without early acute respiratory distress syndrome. Crit Care Med 2006;34(1):22–30 Jan.
[26] Russell JA, Walley KR, Gordon AC, Cooper DJ, Hébert PC, Singer J, et al. Interaction of vasopressin infusion, corticosteroid treatment, and mortality of septic shock. Crit Care Med 2009 Mar;37(3):811–8.
[27] Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for treating sepsis. Cochrane anaesthesia, critical and emergency care group, editor. Cochrane Database Syst Rev 2015 Dec 3. https://doi.org/10.1002/14651858.CD002243.pub3 [cited 2018 Jul 31]; Available from.
[28] Nazer L, AlNajjar T, Al-Shaer M, Rimawi D, Hawari F. Evaluating the effectiveness and safety of hydrocortisone therapy in cancer patients with septic shock. J Oncol Pharm Pract 2015;21(4):274–9 Aug.
[29] Arabi YM, Aljumah A, Dabbagh O, Tamim HM, Rishu AH, Al-Abdulkareem A, et al. Low-dose hydrocortisone in patients with cirrhosis and septic shock: a randomized controlled trial. Can Med Assoc J 2010;182(18):1971–7 Dec 14.
[30] Casserly B, Gerlach H, Phillips GS, Lemeshow S, Marshall JC, Osborn TM, et al. Low-dose steroids in adult septic shock: results of the surviving sepsis campaign. Intensive Care Med 2012;38(12):1946–54 Dec.
[31] Lv Q-Q, Gu X-H, Chen Q-H, Yu J-Q, Zheng R-Q. Early initiation of low-dose hydrocortisone treatment for septic shock in adults: a randomized clinical trial. Am J Emerg Med 2017;35(12):1810–4 Dec.
[32] Póvoa P, Salluh JI, Martinez ML, Guillamat-Prats R, Gallup D, Al-Khalidi HR, et al. Clinical impact of stress dose steroids in patients with septic shock: insights from the PROWESS-shock trial. Crit Care 2015;19:193. https://doi.org/10.1186/s13054-015-0921-x.
[33] Huh JW, Choi H-S, Lim C-M, Koh Y, Oh YM, Shim TS, et al. Low-dose hydrocortisone treatment for patients with septic shock: a pilot study comparing 3 days with 7 days: corticosteroid therapy in septic shock. Respirology 2011;16(7):1088–95 Oct.
[34] Yu T-J, Liu Y-C, Yu C-C, Tseng J-C, Hua C-C, Wu H-P. Comparing hydrocortisone and methylprednisolone in patients with septic shock. Adv Ther 2009;26(7):728–35 Jul.
[35] Raurich JM, Llompart-Pou JA, Ibáñez J, Frontera G, Pérez O, García L, et al. Low-dose steroid therapy does not affect hemodynamic response in septic shock patients. J Crit Care 2007;22(4):324–9 Dec.
[36] Ferrer R, Artigas A, Suarez D, Palencia E, Levy MM, Arenzana A, et al. Effectiveness of treatments for severe sepsis: a prospective, multicenter, observational study. Am J Respir Crit Care Med 2009;180(9):861–6 Nov.
[37] Wu H-P, Shih C-C, Chuang D-Y, Chen T-H. Low-dose steroid therapy is associated with decreased IL-12 production in PBMCs of severe septic patients. Mediators Inflamm 2016;2016:1–8.
[38] Büchele GL, Silva E, Ospina-Tascón GA, Vincent J-L, De Backer D. Effects of hydrocortisone on microcirculatory alterations in patients with septic shock. Crit Care Med 2009;37(4):1341–7 Apr.
[39] Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 2017;43(3):304–77 Mar.