THE IMPACT OF CORTICOSTEROIDS ON MORTALITY IN ADULT PATIENTS WITH SEPTIC SHOCK

by

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A Major Paper Submitted in Partial Fulfillment

of the Requirements for the Degree of

Master of Science in Nursing

in

The School of Nursing

Rhode Island College

2019

Abstract

Septic shock is a complication that affects thousands of patients leading to high mortality rates and increased healthcare costs. One treatment in the attempt to decrease poor outcomes is corticosteroids. A systematic review was conducted to evaluate the impact of corticosteroids on mortality in adult patients with septic shock. Databases searched were CINAHL, PubMed, OVID, and Cochrane Library. A literature review was performed and pertinent data from each article was recorded in data collection tables. A total of six articles were critically analyzed. The Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and flow diagram were used to guide this systematic review. The Critical Appraisal Skills Programme (CASP) checklist assisted in assessing the quality of the articles selected. Cross study analysis was performed via the data collection tables developed by this author. This analysis revealed five of the six trials did not detect a decrease in mortality using corticosteroids in adult patients with septic shock; the sixth study did document a reduction in mortality rate. Four studies were underpowered which may affect the generalizability of their outcomes. Two studies were adequately powered with one demonstrating positive outcomes. Possible benefits were seen in the secondary outcomes such as faster resolution of shock and decreased vasopressor use. Advanced practice nurses are having an increased prominent role in patient care within healthcare. This role provides an opportunity for high quality evidence-based results to be applied to improve patient care. Results of this systematic review provide information to guide decision making by the advanced practice nurse as well as suggestions for further study.

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Background/Statement of the Problem

In the United States (US), more than 1.5 million people develop sepsis each year, with about 250,000 ultimately dying from the disease process (Center for Disease Control [CDC)], 2017). In addition, sepsis is the most expensive condition in hospitals, accounting for $20.3 billion in the US in 2011 (Pfuntner, Weir, & Steiner, 2013). Singer et al. (2016) indicated that even with advanced medical technologies such as vaccines, antibiotics, and acute care, sepsis is the leading cause of death from infection. Sepsis can progress into its most severe form, septic shock, defined as a "dysregulation of the host response to infection, with circulatory, cellular, and metabolic abnormalities" (Annane et al., 2018, p. 809).

The typical treatment regimen of septic shock includes intravenous fluids, antibiotics, and vasopressors. This regimen has remained largely unchanged over the last several years. The Surviving Sepsis Campaign first introduced guidelines in 2004, with the goal of decreasing mortality from sepsis by 25% in five years. Although the initial goal was not met, there were improvements in mortality rates, with some hospitals experiencing a 20% decrease in mortality (Melville, Ranjan, & Morgan, 2015). Since the first set of guidelines, three revisions have been made as new research is published. In addition to fluids, antibiotics, and vasopressors, the organization makes recommendations on adjunctive treatment options such as albumin, immunoglobulins, blood products, and corticosteroids (Rhodes et al., 2017).

Corticosteroids are typically used as adjunctive in the treatment of septic shock. The theory behind administering corticosteroids is that patients experience adrenal insufficiency when critically ill and therefore, will benefit from an exogenous source

such as intravenous steroids (Gupta & Ba, 2008). Despite this theory, there have been conflicting results involving their use in septic shock. Lv, Gu, Chen, Yu, and Zeng (2017) affirmed that controversies on the association between corticosteroids and mortality in patients with septic shock exist. Studies may exhibit considerable variability in mortality due to the time frame between the onset of septic shock and the initiation of corticosteroid therapy (Lv et al.). Furthermore, the Surviving Sepsis Campaign suggested a daily dose of 200mg IV hydrocortisone if adequate fluid resuscitation and vasopressor therapy are not able to restore hemodynamic stability, although it must be noted that this is a weak recommendation with a low quality of evidence (Rhodes et al.). The Surviving Sepsis Campaign stated the low quality of evidence stems from contradictory results from prior studies, in which some have exhibited a reduction in mortality rates while others have demonstrated no difference in mortality (Rhodes et al.).

Since the latest publication of the Surviving Sepsis Campaign in 2016, recent studies, including randomized control trials, have been published that may provide new evidence on the effects of corticosteroids on mortality in adult patients with septic shock. Therefore, the purpose of this paper is to conduct a systematic review to examine whether the use of corticosteroids in septic shock impacts overall mortality in adult patients.

A review of the literature will be presented in the next section.

Literature Review

The databases searched include PubMed, CINAHL, and OVID. Articles from 2000 to 2018 were included in the search. The keywords used to find relevant literature included corticosteroids, steroids, sepsis, septic shock, hypothalamic-pituitary-adrenal axis, and mortality.

Sepsis

Sepsis is a very common diagnosis in hospitals, and if undertreated or mistreated, can cause multi-organ failure and possibly death. Healthcare providers encounter sepsis frequently and recognition of sepsis and initiating treatment in a timely manner are necessary to provide the best chance for survival (László, Trásy, Molnár, & Fazakas, 2015). An understanding of the pathophysiology of sepsis should be achieved to better treat this disease process.

Definition and Pathophysiology. The most recent definition of sepsis by the Third International Consensus Definitions Task Force (Sepsis-3) is defined as a "life-threatening organ dysfunction caused by a dysregulated host response to infection" (Singer et al., 2016, p. 2). Sepsis begins when the body's localized defenses can no longer defend itself from an external insult. Normally, the human body experiences a myriad of attacks on its immune system daily and can fight its way back to a normal state even when its primary defenses have been penetrated. László et al. (2015) stated that these processes are well regulated and maintain an even balance that keep the inflammatory response localized. When an attack overwhelms the body's localized defenses, the body reacts with a systemic inflammatory response to fight the infection.

This dysregulated and unbalanced response affects the entire body and starts impairing the function of vital organs (László et al.).

Sepsis may develop from an infectious or non-infectious process. The infectious process could be caused by a bacterial, viral, or fungal source, whereas the non-infectious process can occur from the inflammatory response of ischemia or muscle damage caused by severe trauma, surgery, myocardial infarction, burns, or acute pancreatitis (Steen, 2009).

Diagnosis. Unlike many other diseases and conditions, there is no single diagnostic test to diagnose sepsis. Sepsis requires the recognition of several factors to be properly diagnosed. In intensive care units, the Task Force, assembled by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine, recommended using the Sequential Organ Failure Assessment (SOFA) instrument to identify patients with organ dysfunction (Singer et al., 2016). The Sequential Organ Failure Assessment measures mortality risk although it can be used to clinically characterize a septic patient (Singer et al.). This instrument examines assessment data such as creatine, bilirubin, platelet levels, $Pa0_2$ and $Fi0_2$ ratios, mean arterial pressure (MAP), and the Glasgow Coma Scale with a score ≥ 2 indicating organ dysfunction. A new measure, called the quick SOFA (qSOFA) uses assessment data of mentation, systolic blood pressure, and respiratory rate and is a simpler instrument to identify patients with suspected infection who are likely to have poor outcomes (Singer et al.). A positive qSOFA is an indicator for healthcare providers to investigate for organ dysfunction, begin therapy, and consider a higher level of care with more frequent monitoring (Singer et al.).

Shock

The first classification system of shock was devised by the surgeon Alfred Blalock in 1934 in which he categorized shock into four types: hypovolemic, cardiogenic, neurogenic, and vasogenic (septic shock). As research evolved, a new classification system, based on cardiovascular characteristics, was created by Hinshaw and Cox in 1972 that deemed septic shock as a form of distributive shock (Funk, Parrillo, & Kumar, 2018).

Shock is defined as "a life-threatening condition categorized by inadequate delivery of oxygen and nutrients to vital organs relative to their metabolic demand" (Strehlow, 2010, p. 57). The body is in a state in which there is insufficient energy to keep up with its requirements to function properly. There are different types of shock, which include hypovolemic, cardiogenic, anaphylactic, neurogenic, and septic shock. Many of these types of shock are characterized by common symptoms. The early signs typically include tachypnea, tachycardia, weak or bounding peripheral pulses, delayed capillary refill, pale or cool skin, oliguria, and lactic acidosis (Stehlow). Late signs of shock consist of central cyanosis, decreased mental status, weak or absent central pulses, hypotension, and bradycardia (Stehlow). Each type of shock has other, more defining signs and symptoms that may help clinicians identify and treat the type of shock appropriately.

Septic Shock

Septic shock is the most severe form of sepsis. Singer et al. (2016) defined septic shock as "a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality" (p. 9). The clinical criteria used to identify septic shock are: (1) sepsis; (2) vasopressor therapy

needed to elevate MAP ≥65 mmHg; and (3) lactate >2mmol/L (18mg/dL) despite adequate fluid resuscitation (Singer et al.). The key variables in septic shock are the need for vasopressors and fluid resuscitation to maintain an adequate blood pressure and maintain lactate levels less than 2mmol/L. Failure to recognize septic shock and treat it effectively can cause organ damage and death (Singer et al.).

Effects of Sepsis on the Hypothalamic-Pituitary-Adrenal Axis

The human body has defense mechanisms that protect itself from threats occurring both inside and outside the body. The hypothalamic-pituitary-adrenal axis (HPA) is comprised of the hypothalamus, pituitary gland, and adrenal glands. These organs interact with each other to create a system that regulates many bodily functions such as digestion, the immune system, mood and emotions. Although all these are important functions, the most essential purpose of the HPA axis may be in controlling the body's reaction to stress (Schroeder et al., 2001).

When a stressful event occurs, the HPA axis is activated to respond and protect the body from its potential harmful effects. A cascade of actions occurs in this stress response. Corticotrophin-releasing hormone (CRH) is released from the hypothalamus and acts on the anterior pituitary to release adrenocorticotrophic hormone (ACTH), which stimulates cortisol production and release from the adrenal glands (Gupta & Bhatia, 2008). Cortisol is the hormone that is important in fighting stressful events such as sepsis. The adrenal glands are incapable of generating enough cortisol in inflammatory states caused by serious diseases (Williams, 2018). This impairment in HPA axis cortisol production in the setting of sepsis may contribute to the body's difficulty in returning to a homeostatic state.

In a study by Schroeder et al. (2001), the functional integrity of the HPA axis in patients with severe sepsis was investigated by simulating the axis through a CRH test. The pituitary-adrenal response was examined after the administration of CRH within 24 hours after diagnosis of severe sepsis and before discharge when patients were without signs of sepsis. The CRH test involved injecting 100 μg of human CRH intravenously, once between 8:00am and 9:00am. Plasma ACTH and cortisol levels were drawn 15 minutes before the administration of CRH, at the time of administration, then 15, 30, 45, and 60 minutes after administration. Results demonstrated impaired plasma cortisol response to a CRH test as well as lower plasma cortisol concentrations in non-survivors compared with survivors of severe sepsis. Schroeder et al. concluded that dysfunction of the endocrine system in severe sepsis may be evident through the reduced response to CRH stimulation in this sample of patients. The deficiency in the HPA axis caused by sepsis may contribute to mortality in this population.

Corticosteroids

Corticosteroids are a class of hormones that play an integral part in the body's daily functions. Corticosteroids have the ability to treat allergic and inflammatory disorders and suppress unwanted immune system actions (Williams, 2018). There are two types of corticosteroids, glucocorticoids and mineralocorticoids. Mineralocorticoids refer to hormones, such as aldosterone, and are involved in regulating electrolyte and water balance in the kidney. In the clinical setting, the term corticosteroid refers to agents with glucocorticoid activity (Williams). This class contains the endogenous cortisol, which as described prior, have immunosuppressive and anti-inflammatory effects. Among others, different types of corticosteroids are used to mimic cortisol

including hydrocortisone, dexamethasone, and prednisolone. Each have their own unique onset, peak and duration of action although they all are intended to mimic cortisol's properties of suppressing or preventing undesirable allergic reactions or inflammation (Williams).

Corticosteroids affect several stages in the inflammatory pathway by diffusing across cell membranes and binding to glucocorticoid receptors causing changes in the receptor (Williams, 2018). These changes include decreasing the production of T lymphocytes, decreasing activity of natural killer cells, reversing macrophage activity, and suppressing synthesis, secretion, and action of chemical mediators in the inflammatory and immune response. These chemical mediators include interleukins, prostaglandins, leukotrienes, bradykinin, serotonin, and histamine. Other mechanisms inhibited are those involved in the production of cyclooxygenase-2, nitric oxide synthase, and pro-inflammatory cytokines like tumor necrosis factor alpha and various interleukins (Williams).

Corticosteroids are utilized in many areas of medicine. One such use is in the management of asthma. Inhaled corticosteroids (ICS) are the most effective therapy in maintaining asthma control through its anti-inflammatory effects on the airway (Williams, 2018). Corticosteroid use has been shown to decrease mortality in this population (Raissy, Kelly, Harkins, & Szefler, 2013). Corticosteroids are also used in the management of irritable bowel syndrome (IBS). The role of corticosteroids in IBS is to rapidly control symptoms and the acute phase of the disease with their anti-inflammatory and immunosuppressive properties (Hall, 2011).

The utilization of corticosteroids in conditions that effect different systems of the body creates the possibility of a beneficial use in septic shock. Williams (2018) stressed the acute use of corticosteroids should not be delayed in life-threatening conditions. Success in reducing mortality in the management of asthma exacerbations possibly supports the potential of corticosteroids in effecting mortality rates in septic shock.

Septic Shock Treatment and Management Strategies

Septic shock, a form of distributive shock, is defined as being "caused by a loss of vasomotor control resulting in arteriolar and venular dilation, and after resuscitation with fluids, characterized by increased cardiac output and decreased systemic capsular resistance" (Funk et al., 2018, p. 96). The cardiovascular component, along with the presence of an infection, forms the basis of treatment and management of septic shock.

The treatment of septic shock has remained largely unchanged over the last few years despite the latest research and improvements in medicine. Singer et al. (2016) asserted that even with advanced medical technologies such as vaccines, antibiotics, and acute care, sepsis leads as the primary cause of death from infection. The typical treatment regimen for septic shock has included antibiotics, fluid resuscitation, and vasopressors.

The most current guidelines in managing septic shock by the Surviving Sepsis Campaign include a long list of recommendations that may be used throughout the course of septic shock. The initial guidelines in managing septic shock include:

1. Application of fluid challenge technique and continued fluid administrations as long as hemodynamic factors continue to improve. Crystalloids are the preferred fluid or initial resuscitation and subsequent fluid replacement.

2. Administration of IV antimicrobials initiated as soon as possible after recognition and within one hour for both sepsis and septic shock.

3. Norepinephrine is the first vasopressor recommended followed by vasopressin and epinephrine. In some cases, dopamine and dobutamine may be used (Rhodes et al., 2017).

Fluid Resuscitation. Fluid resuscitation is the first-line therapy in patients who are experiencing septic shock. Hypotension and increased serum lactate levels are signs of tissue hypoperfusion and are indicators for the initiation of fluid therapy. At least 30 ml/kg of IV crystalloid fluid should be given within the first three hours and additional fluids given thereafter to maintain hemodynamic status (Rhodes et al., 2017). Providing this therapy aids in decreasing the chances of organ dysfunction that could lead to further deterioration in patients.

Antibiotics. The initial management strategies are key to survival when a patient is presumed to be experiencing septic shock. The suspected infection needs to be addressed by obtaining cultures from body fluids (blood, urine, peritoneal, and other sources), beginning broad-spectrum antibiotics, and initiating infectious source control. Identifying the source of infection is crucial as without this action treatment would not be effective. Removing the source of infection may consist of removing a device such as a peripherally inserted central catheter (PICC), draining an infected fluid such as an abscess, or debriding infected tissue as seen in necrotizing pancreatitis. The broad-spectrum intravenous antibiotics will provide the necessary treatment against the most likely pathogens until exactly identified from obtained cultures (Seymour & Rosengart, 2015).

Vasopressors. In conjunction with fluid therapy, vasopressors provide additional assistance in maintaining adequate tissue perfusion. Vasopressors are initiated when fluid therapy alone is not enough in providing hemodynamic stability. There are different types of vasopressors that have an effect on different parts of the cardiovascular system, with the intended action of raising blood pressure to an adequate level. Norepinephrine has been the typical vasopressor of choice and recommended by various guidelines and expert opinions (Seymour & Rosengart, 2015). In addition, vasopressin at a fixed rate (0.03-0.04 U/min) in patients with increased norepinephrine requirement is suggested as a supplementary medication therapy (Seymour & Rosengart). These medications, along with fluid resuscitation, are important in the treatment and management of septic shock.

Adjunctive Treatments. There are multiple adjunctive therapies that can be used to treat septic shock. In fluid therapy, colloids such as albumin have been used to assist with blood pressure control. Hydroxyethyl starch, another colloid, had previously been used as well, although this has been shown to increase rates of renal replacement therapy (Seymour & Rosengart, 2015). Recently, vitamin C has been researched in treating sepsis and septic shock. The anti-oxidant and enzyme cofactor properties of vitamin C is thought to reverse sepsis induced organ dysfunction (Marik, 2018); however, the use of vitamin C requires more research to be considered part of the septic shock treatment regimen. A more widely used adjuvant is corticosteroids. The rationale for their use is patients experience adrenal insufficiency during sepsis and would benefit from an exogenous source such as intravenous steroids.

Use of Corticosteroids in Septic Shock

Corticosteroids have been used in different areas of medicine for many years. Their use in sepsis and septic shock was started soon after an observation by Sir William Osler, in the 1900s, who postulated that many suffering from a severe infection were more inclined to die from the body's inflammatory response to the infection rather than the infection itself (Salluh & Póvoa, 2017). This observation, coupled with the fact that a patient's HPA axis is suppressed when critically ill, led medical professionals to utilize corticosteroids in septic patients. Salluh and Póvoa (2017) believe the ability to manage the inflammatory response caused by an infection would clinically stabilize patients and increase survival rates.

Many types of studies ranging from as far back to the 1980s were used to support the recommendations made by the Surviving Sepsis Campaign. It is important to note that in the 1980s steroids were used more often instead of adequate fluid therapy, early initiation of antibiotics, early collection of blood cultures, and lactate monitoring (Salluh & Póvoa, 2017). The use of corticosteroids in septic patients became standard after the Surviving Sepsis Campaign released the first guidelines in 2004 (Salluh & Póvoa). The organization's latest guidelines note that the recommendation related to corticosteroids is weak with a low quality of evidence. Their efficacy in reducing mortality in this specific population has been debated. The Surviving Sepsis Campaign stated their designation of low quality of evidence comes from contradictory results from prior studies with some exhibiting a reduction of mortality rate while others show no difference in mortality (Rhodes et al., 2017). Lv et al. (2017) supported this and noted controversies on the association between corticosteroids and mortality in patients with septic shock exist. The authors mention the possibility of substantial variability in mortality due to the time

frame between the start of septic shock and the initiation of corticosteroid therapy (Lv et al.).

In a prospective observational study conducted by Ferrer et al. (2009), researchers analyzed the effectiveness of four treatments including early broad-spectrum antibiotics, fluid challenge, low-dose steroids, and drotrecogin alfa. This later drug, drotrecogin alfa, was a recombinant form of human activated protein C that exhibited anti-inflammatory effects but has since been withdrawn from the market due to its failure to demonstrate survival benefit. Two thousand seven hundred ninety-six adult patients from 77 intensive care units were observed and the primary outcome measured was mortality. Ferrer et al.'s findings indicated there was no association between the administration of low-dose steroids in septic shock and mortality. The effectiveness of each treatment was measured using propensity scores: early-broad spectrum antibiotics (odds ratio, 0.67; 95% confidence interval (CI), 0.50-0.90, P = 0.008), drotrecogin alfa (odds ratio, 0.59; 95% CI, 0.41-0.84, P = 0.004), fluid challenge (odds ratio, 1.01; 95% CI, 0.73-1.39, P = 0.966), and low-dose steroids (odds ratio, 1.04; 95% CI, 0.85-1.28, P = 0.688). No risk or benefit was found with use of low-dose steroids, but it is important to note that the observational design may have limited the results of the study. The authors revealed the possibility of the results being influenced by different patient presentations among the intensive care units examined and current trends in septic shock management (Ferrer et al.).

Duane et al. (2014) evaluated the benefit of early low-dose corticosteroid in patients with septic shock. The study included 6,663 patients of whom 1,838 were administered a low-dose corticosteroid intravenously within 48 hours of being diagnosed

with septic shock and were compared to patients who did not receive low-dose corticosteroids. The primary outcome of 30-day mortality was assessed. Results showed the group that received the corticosteroid therapy was associated with a similar 30-day mortality when compared with the group who did not receive corticosteroid therapy (35.5% vs 34.9%). Duane et al. determined early-administration of corticosteroids does not decrease mortality in septic shock patients.

Recent studies, including randomized control trials, have been published since the latest recommendations that may provide new evidence on the effects of corticosteroids on mortality in adult patients with septic shock. In addition, the standard of care should have been modified since the release of the Surviving Sepsis Campaign's initial guidelines in 2004. Randomized control trials published after this date may offer different evidence than those conducted before release of the guidelines. These randomized control trials will be included in the systematic review.

Next, the framework that will be used to guide this research will be presented.

Theoretical Framework

The theoretical framework utilized to guide this systematic review will be the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The aim of PRISMA is to assist authors in generating a clear and comprehensive reporting of systematic reviews and meta-analyses. Systematic reviews and meta-analyses are important research in healthcare as they are high level quality studies and can assist clinicians in creating evidence based clinical practice guidelines (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009). The focus of PRISMA is on randomized control trials, but it can also be used in reporting systematic reviews of other types of research. PRISMA consists of a 27-item checklist (Appendix A) and a four-phase flow diagram (Appendix B).

The PRISMA checklist pertains to the content of a systematic review and assists the researcher in structuring the report in an organized manner. It summarizes results from multiple studies into a single succinct document. The checklist contains seven major headings such as title, abstract, introduction, methods, results, funding and lastly includes several sub-headings (Moher et al., 2009).

The four-phase flow diagram depicts the course of studies through the different stages of the systematic review process. It guides the researcher in the identification and selection of studies. The diagram's four phases are identification, screening, eligibility, and inclusion (Moher et al., 2009). Identification involves discovering studies or records within databases and other sources. Through use of the databases, the researcher combines search terms in different combinations and applies limits such as a specific population, years of search, and English language only. This results in a specific number

of studies. The screening phase is comprised of eliminating duplicate studies, including screening the articles for ones that are pertinent to the research question. The eligibility phase entails omitting studies that may not meet specific inclusion and exclusion criteria. Finally, the inclusion phase is the final number of studies that will be used in the systematic review.

To assess the quality of articles selected, the Critical Appraisal Skills Programme, (CASP) will be used. The Critical Appraisal Skills Programme enables the researcher to systematically assess the trustworthiness, relevance, and results of studies (CASP, 2018). This program contains eight critical appraisal tools that can be used in systematic reviews, randomized control trials, cohort studies, and others. The checklist used in this research project was the CASP Randomized Control Trial Checklist (Appendix F). This checklist is comprised of 11 questions divided into three sections. The sections cover broad issues such as what the results are, whether they are valid, and if the results will help locally (CASP). Through utilization of this checklist randomized control trials can be successfully appraised to create a valid systematic review.

Next, the methods that will be used to guide the research will be discussed.

Method

Purpose

The purpose of this systematic review was to examine whether the use of corticosteroids, in septic shock, impacts overall mortality in adult patients. Outcomes examined included corticosteroid administration compared to no corticosteroid administration in the management of septic shock on mortality rates. The research question examined was: Does the administration of corticosteroids in septic shock decrease mortality in adult patients?

Inclusion/Exclusion Criteria

Inclusion criteria included randomized control trails published from 2008 to 2018. Studies must have included participants 18 years of age or older and experiencing septic shock. Studies must have been peer reviewed and written in the English language. Lastly, studies must have compared the administration of corticosteroids to no corticosteroids for the treatment of septic shock and impact on mortality rates. Exclusion criteria were articles published prior to 2008, participants less than 18 years old, non-English language articles, and articles that were not randomized control trials.

Search Strategy

A comprehensive search was conducted using the CINAHL, PubMed, OVID, and Cochrane Library databases. Keywords used included sepsis, septic shock, corticosteroids, steroids, and mortality.

Using the PRISMA four-phase diagram, studies were identified, screened for duplicates, and assessed for eligibility, which resulted in a select number of studies to be

used in the systematic review. This provided transparency and ensured a careful selection of studies necessary to conduct the systematic review (Moher et al., 2009).

Data Collection

Two data collection tables, created by the author of this paper, was used to collect and organize information extracted from the selected studies. Data collected in Table 1 included the studies' purpose, design, sample, mortality endpoint, and corticosteroid used and dose. Table 2 included any identified placebo (no corticosteroid), mortality rate, key findings, and limitations. Organizing data into these tables ensured a clear means of assessing and examining significant information from each study.

Table 1.

Data Collection Tool 1

Study:				
Purpose	Study Design	Sample Demographics	Mortality Endpoint	Corticosteroid

Table 2.

Data Collection Tool 2

Study:				
Identified Placebo	Mortality Rate		Key Findings	Limitations
	Corticosteroid	Placebo (No corticosteroid)		

Critical Appraisal

The quality of the studies was assessed using the Critical Appraisal Skills Programme (CASP) Randomized Control Trial Checklist. As described in the theoretical framework section, this 11-question tool validates the results of each trial, assesses the preciseness of treatment results, and considers clinically important outcomes (CASP, 2018). This checklist guarantees the selected studies are of the highest quality. Each study was appraised and their results reported.

Cross Analysis

Once the studies have been critically appraised, a cross-study analysis was conducted. The information was recorded in a table created by the author to evaluate the similarities and differences regarding the impact of corticosteroids on mortality in patients' experiencing septic shock (Table 3).

Table 3.

Cross Analysis

Author, Year	Mortality Rate at Day 28	Resolution of Shock	Vasopressor Usage	Length of Stay (LOS)	
				ICU	Hospital

Next, the results of the systematic review will be discussed.

Results

The PRISMA flowchart (Appendix B) and the inclusion/exclusion criteria were used to select articles that were applicable for this systematic review. The breakdown of the search strategy is depicted in Appendix C. The original search terms ceded 237 results. After eliminating duplicate articles, there were 165 remaining for review. The titles and abstracts were evaluated to determine appropriateness looking specifically for inclusion and exclusion criteria. This yielded 18 articles. The full-text of these articles were read and again, inclusion and exclusion criteria used, to decide if they could be applied for this review. A total of six articles remained and were used in this systematic review. Key information was extracted and inputted onto the data collection tables in Appendices D and E. After analyzing the obtained articles' data, each study was summarized as shown in the following section. The studies are presented in chronological order. In addition, the studies were critically appraised using the CASP checklist (Appendix F).

The randomized control trial conducted by Sprung et al. (2008) (Appendices D1 & E1) evaluated the efficacy and safety of low-dose hydrocortisone in patients with septic shock. Patients were enrolled from March 2002 to November 2005 at 52 ICUs in nine countries. Enrollees needed to be 18 years or older, have clinical evidence of infection and a systemic response to the infection, an onset of shock within the previous 72 hours, and hypoperfusion or organ dysfunction related to sepsis. Excluded were those who had an underlying disease with a poor prognosis, a life expectancy of less than 24 hours, immunosuppression, and treatment with long-term corticosteroids within the past six months or short-term corticosteroids within the last four weeks. Of the 500 patients enrolled, one withdrew consent. The rest were divided into two groups: the

hydrocortisone group and placebo group. The 251 participants in the hydrocortisone group had a mean age of 63 ± 14 years with a mean SOFA score of 10.6 ± 3.4. The group was 66% male. The 248 participants in the placebo group had a mean ago of 63 ± 15 with a mean SOFA score of 10.6 ± 3.2 consisting of 67% male gender. The study's main endpoint was death at 28 days in patients who did not have a response to corticotropin. Other endpoints were death at 28 days in patients with a corticotropin response, mortality rate in the hospital, ICU, and overall. Also, the rate of shock reversal, and length of stay (LOS) in the ICU and hospital were assessed. The study drug, hydrocortisone, was given intravenously as a 50 mg bolus every 6 hours for 5 days, then every 12 hours for days 6 to 8, every 24 hours for days 9 to 11, and then stopped. Vials containing placebo were given in the same manner.

The study revealed (Appendix E1) there was no significant difference between the two groups in the rate of death at 28 days among overall patients and those with and without a response to corticotropin (P=0.51). Overall, 34.3% of the hydrocortisone group died while 31.5% of the placebo group died. In those with no corticotropic response, 39.2% of the hydrocortisone group and 36.1% of the placebo group died whereas 28.8% of the hydrocortisone group and 28.7% of the placebo group died in those with a corticotropin response. The hospital and ICU discharge 28-day mortality were similar in both groups. The reversal of shock was similar among both groups as well. In terms of median time until reversal of shock, the hydrocortisone group experienced a shorter time of 3.3 days while the placebo group required 5.28 days. The LOS was similar in both groups for both in hospital and in ICU. Lastly, the hydrocortisone group experienced

more adverse events such as an increased rate of superinfections, hyperglycemia, and hypernatremia.

Critical analysis of the Sprung et al. (2008) study using the CASP checklist (Appendix F1) revealed a less precise treatment effect due to a sample size of 500 instead of the 800 patients needed the achieve a statistical power of 80%. Also, one patient was not accounted for at the end of the trial due to withdrawal of consent after randomization. Some patients did openly receive corticosteroids after enrollment due to allergic reactions, laryngeal edema, bronchospasm, brain edema, replacement of long-term corticosteroid therapy whose history was unknown at enrollment, acute respiratory distress syndrome, and septic shock. This rate was similar among the hydrocortisone and placebo group at 4.4% and 4.0%, respectively.

The study conducted by Arabi et al. (2010) (Appendices D2 & E2) examined the effect of low-dose hydrocortisone in patients with cirrhosis who presented with septic shock. The study was a randomized double-blind placebo-controlled trial conducted at a 900-bed tertiary care academic hospital on a 21-bed medical-surgical ICU. Patients enrolled required to be aged 18 years or older with liver cirrhosis who presented with septic shock within 72 hours of the onset of hypotension. Patients were excluded if there was evidence of hemorrhagic shock, known adrenal insufficiency, any prior systemic steroid usage, contraindications for systemic steroids, post-cardiac arrest, and do-not-resuscitate status. Of the 140 patients that were screened, 75 were enrolled and randomly allocated into two groups. The hydrocortisone group was 44% female with a mean age of 60.6 ± 12.6 and mean SOFA score of 14.6 ± 3.7. The placebo group was also 44% female with a mean age of 59.3 ± 12.2 and mean SOFA score of 14.3 ± 3.7. The primary

endpoint of this study was 28-day all-cause mortality and secondary outcomes included ICU and hospital mortality at 28 days, shock reversal, and vasopressor-free days. Patients received intravenous bolus injections every six hours of either 5mL of 50 mg of hydrocortisone or placebo. This was given until shock resolved which was defined as a stable blood pressure (MAP>65) without a vasopressor for 24 hours. At this point, the dose was reduced by 1 mL every 2 days until discontinued.

Results of this study (Appendix E2) demonstrated no significant difference between the hydrocortisone and placebo groups in 28-day mortality (P=0.19). Deaths in the hydrocortisone group accounted for 85% of the patients while the placebo group encountered 72% deaths. The ICU (P=0.86) and hospital LOS (P=0.90) were similar in both groups. Mortality was also similar in both groups in the ICU and hospital (P=0.64 and P=0.82, respectively). ICU mortality was 62% and 67% in the hydrocortisone and placebo group, respectively. Hospital mortality was 87% in those receiving hydrocortisone and 89% in those receiving placebo. The hydrocortisone group did show some improvement in hemodynamic parameters. There were more patients in the hydrocortisone group who experienced shock reversal (62%, P=0.05) and more vasopressor-fee days (6.8 days, P=0.54) than the placebo group (39% and 5.6 days). When looking at adverse events, severe hyperglycemia and gastrointestinal bleeding was more prevalent in patients receiving hydrocortisone. There existed some limitations in this study such as the single center setting that could affect generalizability. Others included the long length of randomization of 72 hours and the use of etomidate in some patients that has been proven to cause adrenal suppression.

Upon critical appraisal of the Arabi et al. (2010) study (Appendix F2), the CASP checklist revealed that the groups were not treated equally. There were five patients in the placebo group that ended up receiving corticosteroid therapy due to life-threatening hypotension. Because of this, they were moved to the other study arm and considered crossovers. Also, blinding was opened for one patient at the primary physician's request, but the therapy was continued as planned. Despite these factors, the trial did clearly address the focused issue, groups were similar at the start of the trial, and all the patients were accounted for at the trial's conclusion. Although 150 patients were required, allocation of patients was stopped at 75 after a planned interim analysis revealed it was unlikely that a treatment benefit would be evident if it were completed to the targeted sample size.

In the study by Gordon et al. (2014) (Appendices D3 & E3), researchers tested for an interaction between vasopressin and corticosteroids in septic shock. The study was a prospective open-labeled randomized controlled trial conducted between October 2009 and March 2012 at four adult ICUs in London teaching hospitals. Inclusion criteria consisted of adult patients greater than 16 years old who had sepsis requiring vasopressors despite intravenous fluid administration. There were many exclusion criteria as described in the appendix that included patients who received a previous continuous infusion of vasopressors during the current hospitalization, had an ongoing requirement for systemic steroids, death anticipated within 24 hours, or enrollment in another trial that may interact with study drugs. Sixty-one patients were assigned to one of two groups: hydrocortisone or placebo. All patients received vasopressin and either hydrocortisone or placebo once the vasopressin was titrated to 0.06 U/min. The

hydrocortisone group comprised of 58% males with a mean age of 61 and APACHE II score of 19 while the placebo group was 60% male with a mean age of 60 and APACHE II score of 20. The primary outcome of this study was the difference in plasma vasopressin concentration between the two groups. Secondary outcomes included difference in vasopressin requirements and 28-day, ICU, and hospital mortality. Hydrocortisone was given as a 50 mg IV bolus every 6 hours for 5 days, every 12 hours for 3 days, and then once daily for 3 days. The placebo (0.9% saline) was given in the same way as the study drug.

The primary outcome of plasma vasopressin levels was found to be no different between the two groups (64 pmol/L difference at 6 to 12-hour time point, 95% CI, -32 to 160 pmol/L) (Appendix E3). There was also no difference in mortality rates. The 28-day mortality was 23% in the hydrocortisone group and 23% in the placebo group (-0.01; -0.22, 0.20). ICU mortality in the hydrocortisone group was also 23% while 27% of the placebo group died (-0.04; -0.26, 0.18). Hospital mortality was 26% in the hydrocortisone group and 30% in the placebo group (-0.04; -0.27, 0.18). The value in parentheses is the difference in proportions (vasopressin and hydrocortisone minus vasopressin and placebo) and 95% CI. In terms of vasopressin requirements, the hydrocortisone group was weaned off of the vasopressor more quickly, having a 3.1 days shorter duration and halving the total dose requirement than the placebo group (P=0.001). Limitations to this study included the small number of participants which has limited power to detect differences in clinical outcomes. The trial was powered to detect a difference in plasma vasopressin levels after reaching a maximum rate of vasopressin and corticosteroid administration. Some patients received norepinephrine first as suggested

by the Surviving Sepsis Campaign guidelines. These patients were weaned off this vasopressor and started on vasopressin although not all patients reached the maximum rate which reduced the sample size and potential power.

Critical appraisal of the Gordon et al. (2014) study (Appendix F3) showed similar group demographics and randomization of patients to the two groups. There were two factors that prevented the two groups from being treated equally. First, due to emergent situations not all patients received vasopressin as the initial vasopressor. This accounted for 30% of the study participants who were transitioned over to vasopressin to be included in the trial. Second, 11 patients did not reach the maximum vasopressin requirements so did not receive the study drug. In addition, there were five crossovers from the placebo group to the hydrocortisone group due to refractory shock although researchers claim the results remained unchanged.

The Lv, Q., Gu, X., Chen, Q., Yu J., & Zheng, R. study (2017) (Appendices D4 & E4) examined 118 patients with septic shock. The study took place from September 2015 to September 2016 on a 35-bed ICU of the Subei People's Hospital. The aim was to assess the importance of early initiation of low dose hydrocortisone. The inclusion criteria consisted of having an age of 18 years or older and the onset of septic shock beginning within six hours. Exclusion criteria was receiving corticosteroid therapy within the last three months, high-dose steroid therapy, presence of immunosuppression, and refusal of the attending staff or patients' family. Patient demographics comprised of a 70/48 male-to-female ratio. Study participants were divided into two groups: the hydrocortisone group and the placebo group. The hydrocortisone group had a mean age of 68.8 $\pm$ 12.6 years and the placebo group was 64.8 $\pm$ 16.7 years. The mean SOFA

score for the hydrocortisone group was 11.9 ± 3.3 and the placebo group was 9.9 ± 3.0. The intervention comprised of administering 200 mg/dl of hydrocortisone as a continuous infusion for six days and then tapering it off. Once all vasopressors were discontinued, the taper protocol was initiated: half dose for five days, then quarter dose for three days, then stopped. The placebo was normal saline which was administered in the same manner as the hydrocortisone.

The results of this study (Appendix E4) showed that there were no significant differences in 28-day or hospital all-cause mortality, length of stay (LOS) in the intensive care unit (ICU), or hospital between patients treated with hydrocortisone or placebo. Both the 28-day and hospital all-cause mortality was 39.7% in the hydrocortisone group and 31.7% in the placebo group. There was a significance level of P=0.365 in both categories. LOS in the ICU was 10.9 ± 17.5 days in the hydrocortisone group while the placebo group experienced 10.2 ± 13.1 days with a significance level of P=0.799. LOS in the hospital was 23.7 ± 36.8 days for the hydrocortisone group and 21.7 ± 21.7 days for the placebo group with a P=0.711 significance level. Early administration of hydrocortisone enabled earlier titration off vasopressor therapy. Here, the hydrocortisone group experienced 2.5 ± 2.4 days of vasopressor while the placebo group had 2.8 ± 4 days (P=0.639). In conclusion, the study demonstrated no decrease in the risk of mortality or the length of stay in the ICU or hospital with early administration of low-dose hydrocortisone in adults with septic shock. The findings do not support the use of hydrocortisone in this population.

The critical appraisal of this study (Appendix F4) shows the two groups were not similar at the start of the trial. The hydrocortisone group started off with a statistically

significant (P<0.001) SOFA score that was higher than the placebo group. Also, the study recruited a small number of patients. The authors pointed out the study was likely to be underpowered to detect a significant difference by the recruitment of patients with lower mortality. Despite this, the placebo-controlled, randomized design of the trial contributes to the validity of the study.

In the Venkatesh et al. (2018) (Appendices D5 & E5) study, the authors examined whether hydrocortisone reduces mortality among patients with septic shock. This study recruited a total of 3,800 patients from March 2013 through April 2017. The patients underwent randomization at 69 med-surg ICUs. The authors compared intravenous infusions of hydrocortisone with placebo in patients with septic shock who were undergoing mechanical ventilation in the ICUs. Inclusion criteria required patients to be older than 18 years of age, on mechanical ventilation, a documented suspicion of infection, met >2 criteria of the systemic inflammatory response syndrome, and treatment with vasopressors or inotropic agents for a minimum of 4 hours up to the time of randomization. The criteria excluding patients from this study were those who were likely to receive steroids for an indication other than septic shock, had received etomidate, were considered to likely die from a pre-existing condition within 90 days, had treatment limitations in place, or had met all the inclusion criteria for more than 24 hours. Of the 3,800 patients randomized, 3,658 were included in the study and were split into two groups: 1,823 in the hydrocortisone group and 1,826 in the placebo group. The mean age of the hydrocortisone group was 62.3 $\pm$ 14.9 years and the placebo group 62.7 $\pm$ 15.2 years. There were 60.4% males in the hydrocortisone group and 61.3% in the placebo group. The median APACHE II score was 24.0 in the hydrocortisone group

while the placebo group had a score of 23.0. The primary outcome of the study was death from any cause at 90 days. A secondary outcome was death from any cause at 28 days. The intervention group received 200mg of hydrocortisone per day via a continuous intravenous infusion over a period of 24 hours for a maximum of seven days or until discharge from the ICU. The control group received placebo in the same manner as described.

The results of this study (Appendix E5) demonstrated that septic shock patients undergoing mechanical ventilation with a continuous hydrocortisone infusion did not experience a lower 90-day mortality than placebo. The hydrocortisone group had a 27.9% mortality rate while the placebo group was 28.8% (P=0.50). The mortality rate at 28 days did not differ as well between the hydrocortisone and placebo group with rates of 22.3% and 24.3%, respectively (P=0.13). In terms of resolution of shock, it took the hydrocortisone group 3 days and the placebo group 4 days to resolve shock (P<0.001). Patients receiving hydrocortisone had a shorter time to ICU discharge needing 10 days whereas the placebo group required 12 days (P<0.001). The authors noted some limitations to the trial including the inability to decide on the appropriateness of prescribed antibiotic therapy and the inability to arbitrate the judgement of the treating clinicians on adverse effects related to the study. Lastly, data on all possible secondary infections were not collected.

The critical appraisal (Appendix F5) of the Venkatesh et al. (2018) study revealed not all patients were accounted for at the end of the trial. This was due to 114 patients withdrawing or not having informed consent. Also, 28 patients were lost to follow-up. Regardless of this, the large number of patients provided the study with validity. The

3,800 originally recruited provided the trial with 90% to detect an absolute difference of 5% in 90-day all-cause mortality.

Annane et al. (2018) (Appendices D6 & E6) conducted a randomized control trial involving 1,241 patients experiencing septic shock to evaluate the effect of hydrocortisone and fludrocortisone versus placebo. The trial was conducted from September 2008 to June 2015 at 34 hospitals. Participants were required to have septic shock for less than 24 hours. Those excluded from the study had septic shock for at least 24 hours, a high risk of bleeding, pregnancy or lactation, underlying conditions that could affect long-term survival, or previous treatment with corticosteroids. Participants were divided into two groups. The hydrocortisone/fludrocortisone group was 65.5 % male with a mean age of 66 $\pm$ 14 and a SOFA score of 12 $\pm$ 3. The placebo group was 67.7% male with a mean age of 66 $\pm$ 15, and a SOFA score of 11 $\pm$ 3. The study's primary outcome was 90-day all-cause mortality. Secondary outcomes included all-cause mortality at ICU discharge, hospital discharge, and day 28, and vasopressor free days by day 28. The method entailed administering a 50mg bolus of hydrocortisone intravenously every 6 hours and 50µg of fludrocortisone via a nasogastric tube once daily every morning. This was given for seven days without tapering. The respective placebos were given in the same manner.

The main results of the study revealed a 0.88 relative risk of death (95% CI, 0.78 to 0.99) in support of the hydrocortisone/fludrocortisone group. The 90-day all-cause mortality rate was 43% for this group while the placebo group saw a rate of 49.1% (P=0.03). In terms of 28-day mortality, there was a 33.7% rate in the intervention group while the placebo group saw a 38.9% rate P=0.06). Mortality was also significantly

lower in the hydrocortisone and fludrocortisone group compared to placebo group at ICU discharge, 35.4% vs 41% (P=0.04), and hospital discharge, 39% vs 45.3% (P=0.02). Also, the intervention group witnessed 17 $\pm$ 11 vasopressor-free days by day 28 while the placebo group had 15 $\pm$ 11 days (P<0.001). A key finding that surfaced from the study was the increased incidence of hyperglycemia in the hydrocortisone and fludrocortisone group although the risk of secondary infection, GI bleeding, and neurological events were similar in both groups. The authors did not declare any limitations in this study.

Critical analysis of the Annane et al. (2018) study using CASP (Appendix F6) found the study met all criteria. The trial had a precise estimate of the treatment effect. Researchers determined 320 patients were needed in each group to detect an absolute difference of 10% in 90-day mortality. The study was able to recruit a total of 1,241 patients or about 620 patients in each group.

Cross Analysis

The randomized control trials described were compared and analyzed using the data collection tables in Appendices D1-6 and E1-6. The tables tracked important data such as mortality rates, the primary objective of this paper, as well as other common data like resolution of shock, vasopressor-free days, and LOS in the ICU and hospital. These results were recorded in Appendix G for cross analysis. Adverse events that occurred in the studies will also be analyzed.

Participants in all six studies had similar mean ages, gender percentage, and illness severity using the Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE II) scores. Mean ages ranged between 59.3 and 68.8 years and the male gender represented 56-67% of study

participants among all the studies. Sequential Organ Failure Assessment scores ranged from 9.0 to 14.6 in the Sprung et al. (2008), Arabi et al. (2010), Lv et al. (2017), and Annane et al. (2018) studies and APACHE II scores ranged from 19 to 24 in the Gordon et al. (2014) and Venkatesh et al. (2018) studies which all indicate a high mortality prediction. The Arabi et al. (2010) study used only patients with liver cirrhosis. This may have led to the high mortality rate among all the studies. Despite this, there was still no significant difference in 28-day mortality between the two study groups, with the hydrocortisone group having an 85% rate and the placebo group a 72% rate (P=0.19.) The Venkatesh et al. (2018) study included only mechanically ventilated patients within their participants whereas the other studies did not exclude non-ventilated participants. This study also specifically excluded patients who had received etomidate as it was noted the drug has adrenal-suppressant properties. All other studies did not exclude patients who received this drug. In the end, mortality rates remained similar, with the hydrocortisone group exhibiting a 22.3% rate and placebo group a 24.3% rate (P=0.13).

Five of the six randomized control trials, Sprung et al. (2008), Arabi et al. (2010), Gordon et al. (2014), Lv et al. (2017), and Venkatesh et al. (2018), showed there was no significant difference between corticosteroid and placebo groups in 28-day mortality (Appendix G). Only one randomized control trial, the Annane et al. (2018) study, showed a decrease in mortality at day 28 in the corticosteroid group compared to the placebo group. Here, the mortality at day 28 was 33.7% for the corticosteroid group and 38.9% for the placebo group (P=0.06).

There were some variances among the studies in terms of the secondary endpoints. In terms of resolution of shock, there was faster shock reversal in the

corticosteroid group in the Arabi et al. (2010) and Venkatesh et al. (2018) studies. Arabi et al. (2010) showed 62% of patients in the corticosteroid group demonstrated resolution of shock compared to 39% in the placebo group (P=0.05). In the Venkatesh et al. (2018) study, shock resolved one day earlier in the corticosteroid group (P=<0.001). There were no differences in reversal of shock the Sprung et al. (2008) study (79.7% vs 74.2%) and in the Lv et al. (2017) study (65.6% vs 70.0%, P=0.602). However, the median time until reversal of shock was shorter in the corticosteroid group in the Sprung et al (2008) study: 3.3 days in the corticosteroid group compared to 5.28 days in the placebo group. The other studies did not report this endpoint.

Four studies, Arabi et al. (2010), Gordon et al. (2014), Lv et al. (2017), and Annane et al. (2018), exhibited more vasopressor-free days or less days on a vasopressor in the hydrocortisone group than the placebo group. The most significant result was in the Gordon et al. (2014) study in which the corticosteroid group demonstrated a 3.1day shorter duration of vasopressor therapy than the placebo group (P=0.001). The Lv et al. (2017) study had the corticosteroid group on 2.5 $\pm$ 2.4 days of vasopressor whereas the placebo group was 2.8 $\pm$ 4 days (P=0.639). Arabi et al. (2010) reported 6.8 vasopressor-free days in the corticosteroid group versus 5.6 days in the placebo group (P=0.54). The study by Annane et al. (2018) reported that the corticosteroid group had 17 $\pm$ 11 vasopressor-free days compared to 15 $\pm$ 11 days in the placebo group (P<0.001). The remaining two studies did not report this secondary endpoint.

There was no difference in LOS in the ICU or hospital in the Sprung et al. (2008), Arabi et al. (2010), and Lv et al. (2017) studies. Venkatesh et al. (2018) reported a

shorter time to ICU discharge in the hydrocortisone group (P<0.001). This secondary endpoint was not reported by Gordon et al. (2014) or Annane et al. (2018).

The most common adverse event attributed to the use of corticosteroids was hyperglycemia. This was documented in the randomized control trials by Sprung et al. (2008), Arabi et al. (2010), Venkatesh et al. (2018), and Annane et al. (2018). Other more prominent adverse events included superinfection and hypernatremia in Sprung et al. (2008) as well as gastrointestinal bleeding in Arabi et al. (2010). The Lv et al. (2017) study did not report adverse events and the study by Gordon et al. (2016) could not attribute the adverse events as a result of corticosteroid use.

There existed differences among the studies that may have influenced the end results. There were some differences in type of corticosteroid and administration method. Although five studies, Sprung et al. (2008), Arabi et al. (2010), Gordon et al. (2014), Lv et al. (2017), and Venkatesh et al. (2018), used the same corticosteroid, hydrocortisone, the dosages and timing of administration may have varied. Sprung et al. (2008) and Gordan et al. (2014) used 50 mg dosage boluses and the same administration method and the drug was tapered after five days. Arabi et al. (2010) used the same dosage, although tapering only occurred once shock was resolved. Lv et al. (2017) and Venkatesh et al. (2018) used the same dosage of 200 mg/d as a continuous infusion. Lv et al. (2017) tapered the drug once vasopressors were discontinued whereas Venkatesh et al. (2018) discontinued it after seven days or at ICU discharge. The study conducted by Annane et al. (2018) used fludrocortisone in addition to hydrocortisone. The hydrocortisone was administered as a 50 mg intravenous bolus every 6 hours and fludrocortisone was given

as a 50 μg tablet through a nasogastric tube once daily in the morning. These were administered for seven days without tapering.

The study by Gordon et al. (2016) had a key difference in treatment method that could have impacted end results. The Gordon et al. (2016) study was the only study that did not use norepinephrine as the primary vasopressor. Here, vasopressin was used as the primary vasopressor instead of norepinephrine. Although vasopressin is not recommended as the initial vasopressor in septic shock, one of the primary objectives in this study was to test the interaction between vasopressin and corticosteroids. All other treatment was based on the Surviving Sepsis Campaign Guidelines at the time the study was conducted.

Next, summary and conclusions will be addressed.

Summary and Conclusions

Sepsis is a major concern in hospitals that results in a high mortality (Center for Disease Control [CDC)], 2017) and increased health care costs (Pfuntner, Weir, & Steiner, 2013). Its most severe form, septic shock, has been the focus of groups such as the Surviving Sepsis Campaign. A widely used adjunctive in the treatment of septic shock is corticosteroids. The use of intravenous corticosteroids has been thought to improve the insufficient adrenal function of critically ill patients experiencing septic shock (Gupta & Ba, 2008). There have been disagreements on the efficacy of corticosteroids in decreasing mortality in septic shock patients (Lv et al., 2017). The Surviving Sepsis Campaign has cited corticosteroid use as a weak recommendation due to contradictory results of prior studies showing either reduction or no difference in mortality rates (Rhodes et al., 2017). Since the latest recommendation in 2016, studies have been published that may provide new evidence on the effects of corticosteroids on mortality in adult patients with septic shock. Furthermore, the widespread use of the guidelines by medical care providers in hospitals has decreased variances in treatment methods that may have existed in past randomized control trials.

The purpose of this systematic review was to examine whether the use of corticosteroids in septic shock impacts overall mortality in adult patients. The CINAHL, PubMed, OVID, and Cochrane Library databases were used to conduct a comprehensive search on this topic. The PRISMA 27-item checklist and four-phase diagram (Moher et al., 2009) were utilized in the search process to ensure a thorough selection of studies. This search strategy ultimately resulted in six randomized control trials to be used in this systematic review. Pertinent data was extracted and organized using two data collection tables produced by this author (Appendices D1-6 and E1-6). The quality of each study

was assessed using the Critical Appraisal Skills Programme (CASP) Randomized Control Trial Checklist (Appendix F). Cross analysis of the studies was conducted utilizing the chart depicted in Appendix G. This chart recorded the primary objective of mortality rate at day 28 as well as the secondary endpoints of resolution of shock, vasopressor usage, and length of stay in the ICU and hospital.

The randomized control trials conducted by Sprung et al. (2008), Arabi et al. (2010), Gordon et al. (2014), Lv et al. (2017), and Venkatesh et al. (2018) showed corticosteroids did not have an effect on mortality in adult patients with septic shock. There was no significant difference between corticosteroid and placebo groups in 28-day mortality (Appendix G). The Annane et al. (2018) study was the only one of the six studies that demonstrated a decrease in mortality at day 28 in the corticosteroid group compared to the placebo group. The most significant difference between these two conflicting results was that the Annane et al. (2018) study utilized fludrocortisone in addition to hydrocortisone. The other studies used only hydrocortisone as the drug of choice. It is important to note there existed some variations among the studies: Arabi et al. (2010) used only patients with cirrhosis; Gordon et al. (2014) used vasopressin instead of norepinephrine as the primary vasopressor; and Venkatesh et al. (2018) used only patients who were ventilated and did not receive etomidate. Even with these differences among studies, each study's intervention and control groups were alike regarding patient characteristics and both groups received the same treatment method.

There was faster shock reversal in patients receiving corticosteroids in the Arabi et al. (2010) and Venkatesh et al. (2018) studies. Sprung et al. (2008) and Lv et al. (2017) did not find a significant difference in the two groups, although Sprung et al.

(2008) did report a shorter median time until reversal of shock in the corticosteroid group. The remaining studies did not report this endpoint. Results of four studies by Arabi et al. (2010), Gordon et al. (2014), Lv et al. (2017), and Annane et al. (2018) displayed more vasopressor-free days or less days on a vasopressor in the hydrocortisone group than the placebo group. The other two studies did not investigate this endpoint. In terms of LOS in the ICU or hospital, the Sprung et al. (2008), Arabi et al. (2010), and Lv et al. (2017) studies did not find any difference among the two study groups. The only significant finding was attained by Venkatesh et al. (2018); these authors reported a shorter time to ICU discharge in the hydrocortisone group. This secondary endpoint was not studied in the Gordon et al. (2014) or Annane et al. (2018) trials. The action of corticosteroids on patient's suppressed HPA axis could explain the quicker resolution of shock and decreased vasopressor usage in the corticosteroid groups of the studies. Their anti-inflammatory properties may assist in reducing shock time. Also, corticosteroids' effects of increasing the body's sensitivity to catecholamines, like norepinephrine, may decrease time and amount of vasopressor usage.

The most common adverse event attributed to the use of corticosteroids was hyperglycemia. This was documented in the randomized control trials by Sprung et al. (2008), Arabi et al. (2010), Venkatesh et al. (2018), and Annane et al. (2018). Other more prominent adverse events included superinfection and hypernatremia in Sprung et al. (2008) as well as gastrointestinal bleeding in Arabi et al. (2010). The Lv et al. (2017) study did not report adverse events and the study by Gordon et al. (2016) could not attribute the adverse events as a result of corticosteroid use. These adverse events could possibly have occurred in patients with high risk conditions. A patient with a history of

uncontrolled diabetes or with multiple gastrointestinal bleedings may have a higher propensity of these adverse events occurring when receiving corticosteroids. The studies did not provide information on whether these events occurred in such patients.

There existed some limitations in this systematic review. First, there were only six studies that met the inclusion and exclusion criteria, which may affect generalizability. Second, although the primary aim of researching mortality was achieved, not all studies reported the same secondary endpoints. There also existed limitations among the six studies in this systematic review. Some studies (Arabi et al., 2010; Lv et al., 2017) reported a single center setting which may affect generalizability. Three studies (Sprung et al., 2008; Gordon et al., 2014; Lv et al., 2017) reported a small sample size resulting in a limited power to detect differences in the measured clinical outcomes. All the studies reported power except Lv et al. 2017. Here, the authors believed the study to be underpowered based on the recruitment of patients with lower mortality (original sample size calculation based on control mortality of 60%, but their study's control 28-day mortality was almost half). The Arabi et al. (2010) study did not achieve their intended sample size, although they did not report this as a limitation. The limited power in these studies may affect generalizability as well. This means these trials demonstrated no significant difference between the groups being studied or they failed to detect a difference due to the lack of power. The Sprung et al. (2008) and Gordon et al. (2014) studies stated there were crossovers from the placebo group to the hydrocortisone group, meaning these patients received open-label corticosteroids. The authors stated that this was unlikely to have an effect on the outcomes.

Despite the limitations mentioned, this systematic review provided sufficient evidence to draw a conclusion. The majority of studies in the systematic review did not show an impact on overall mortality between the use of corticosteroids and placebo in adult patients with septic shock. The limitations previously mentioned must be taken into consideration. The four studies that were under-powered could have failed to detect a difference between the corticosteroid and placebo groups. Also, two studies used a single center setting to conduct their trial. The generalizability should be applied with caution considering these two factors. Further studies that are adequately powered using multiple centers are required in order to provide more statistically significant data and clinical importance. Future studies with a power of 80% would be sufficient considering any rise in power could be difficult since it would require increased sample sizes and study costs. Additional studies using fludrocortisone should be conducted as well. The study by Annane et al. (2018) was the only study that used this corticosteroid in addition to hydrocortisone and the only study demonstrating a decrease in mortality rates. In spite of these results, fludrocortisone cannot be singly attributed to decreased mortality rates. More studies using this corticosteroid, while also using adequate power and multiple centers, would provide supplemental data on the impact of corticosteroids on mortality in adult patients experiencing septic shock.

The achievement of the primary aim in this systematic review in combination with the comparison of the secondary endpoints results in recommendations and implications that can be made for the advanced practice nurse in the clinical setting. Recommendations and implications for advanced practice will be discussed in the next section.

Recommendations and Implications for Advanced Nursing Practice

Septic shock is a condition with a high mortality rate and high cost for healthcare institutions. Advanced practice nurses (APNs) are increasingly becoming an integral part of healthcare teams. It should be an expectation for all APNs to stay informed on the most current evidence-based results and incorporate them into their practice. This review was able to contribute to evidence-based knowledge and provided an opportunity to guide APNs in making more informed decisions.

The results of this systematic review demonstrate that the use of corticosteroids in patients with septic shock cannot be strongly recommended. Five of the six studies in the review showed no improvement in mortality in this population; only one study by Annane et al. (2018) showed a decrease in mortality. It is important to note that mortality did not increase in any study and therefore the use of corticosteroids should not be disregarded as an option when managing care for a patient with septic shock. Advanced practice nurses should take this into consideration when contemplating using corticosteroids in patients with septic shock.

This systematic review generated valuable information and evidence on whether the use of corticosteroids in septic shock impacts overall mortality in adult patients. The review shed light on the latest results of randomized control trials on this topic. Current practice leaves it up to the discretion of the provider to use corticosteroids in this patient population. It is sometimes used as a last-ditch effort to save the patient when hemodynamic parameters fail to improve with other interventions. The information from this systematic review can be utilized to potentially improve the care that APNs provide as well as to teach student and novice nurse practitioners. The APN should be aware of the limitations of this systematic review and the research studies, as mentioned

previously, that affect generalizability. Nevertheless, the use of the latest research should guide the APN in making informed decisions and should be the standard in which care is provided.

The secondary outcomes also need to be considered. Advanced practice nurses need to be cognizant of the adverse events that could occur with corticosteroid administration. Patients with past medical histories of brittle diabetes, gastrointestinal bleeding or hypernatremia likely would potentially suffer from worse outcomes if given corticosteroids. One must be mindful of these unique patient characteristics so that the appropriate care can be optimized. Caution should be taken in such patients as administration of corticosteroids would require closer monitoring and may necessitate additional resources. For example, when using corticosteroids, an insulin drip may be required for labile glucoses in patients with diabetes. Being able to recognize these differences and applying research results when suitable is the critical thinking that should be expected of APNs.

The resolution of shock and decreased vasopressor use could be an incentive in using corticosteroids. Furthermore, the possibility of decreased length of stay in the intensive care unit and hospital are other benefits. Venkatesh et al. (2018) mention the overall cost-effectiveness of hydrocortisone in patients with septic shock should be assessed. This would align with healthcare's recent approaches in providing better care at a lower cost. More research needs to be conducted to provide additional data regarding this topic.

Advanced practice nurses are in prime position to be a part of research teams to investigate further the effect of corticosteroids on mortality in septic shock patients. The

limitations described earlier identify areas in which future studies can be improved: larger sample sizes with adequate power and more centers used. The limitations also provide an area requiring further investigation which is the effect of fludrocortisone on mortality in this selected patient population. Other areas of research include focusing on the relationship between corticosteroid use and shock reversal, vasopressor use, or ICU and hospital length of stay. Qualitative research questions could also be explored, such as differences in patient and family satisfaction with hospitalization after corticosteroid use or patient's perception of quality of life. Septic shock guideline adherence by providers is another area of qualitative research that could be investigated. The APN can be involved in conducting such research that could deliver key data resulting in changes in clinical practice.

The information from this systematic review also has implications for education and training. The education and training of future APNs should embrace the most current research available. Informing students of results such as those presented in this review will deliver fundamental information that shapes practice.

Results of this review should also be discussed with staff nurses and other members of the interdisciplinary team. Staff nurses spend more time at the patient's bedside than any other provider. Staff nurses who are aware of the potential risk of adverse events can provide more vigilance during corticosteroid administration and thereby alert the medical team to minimize the effects of adverse events or prevent them from occurring.

Current guidelines recommend corticosteroids in septic shock patients only if hemodynamics stability is not achieved with fluid resuscitation or vasopressors. The

review of the most recent randomized control trials included in this systematic review does not suggest changes be made to this recommendation. These results should be used as a supplemental resource to assist the APN in clinical decision making. Advance practice nurses should also be attentive to the factors the lead to septic shock. This attention to clinical prevention has the potential to greatly reduce the number of patients who develop this deadly condition. Policies regarding central line-associated blood stream infections, catheter-associated blood stream infections, and surgical site infections should be carefully followed. Adhering to guidelines on the management of conditions such as pneumonia, burns, and acute pancreatitis can also prevent development of septic shock. It is important to prevent infections in patients with weakened immune systems such as those receiving long-term steroid treatment and chemotherapy as well as patients with long-term health conditions like diabetes and cirrhosis. Being aware of these patient populations and providing appropriate teaching can prevent sepsis that could eventually lead to septic shock.

Septic shock is a condition that has detrimental effects on patients and healthcare overall. Measures must be taken to prevent mortality and any negative consequences that may result. Awareness of the latest research on the impact of corticosteroids on mortality in adult patients with septic shock contributes to the knowledge APNs require to improve and deliver the best care for their patients.

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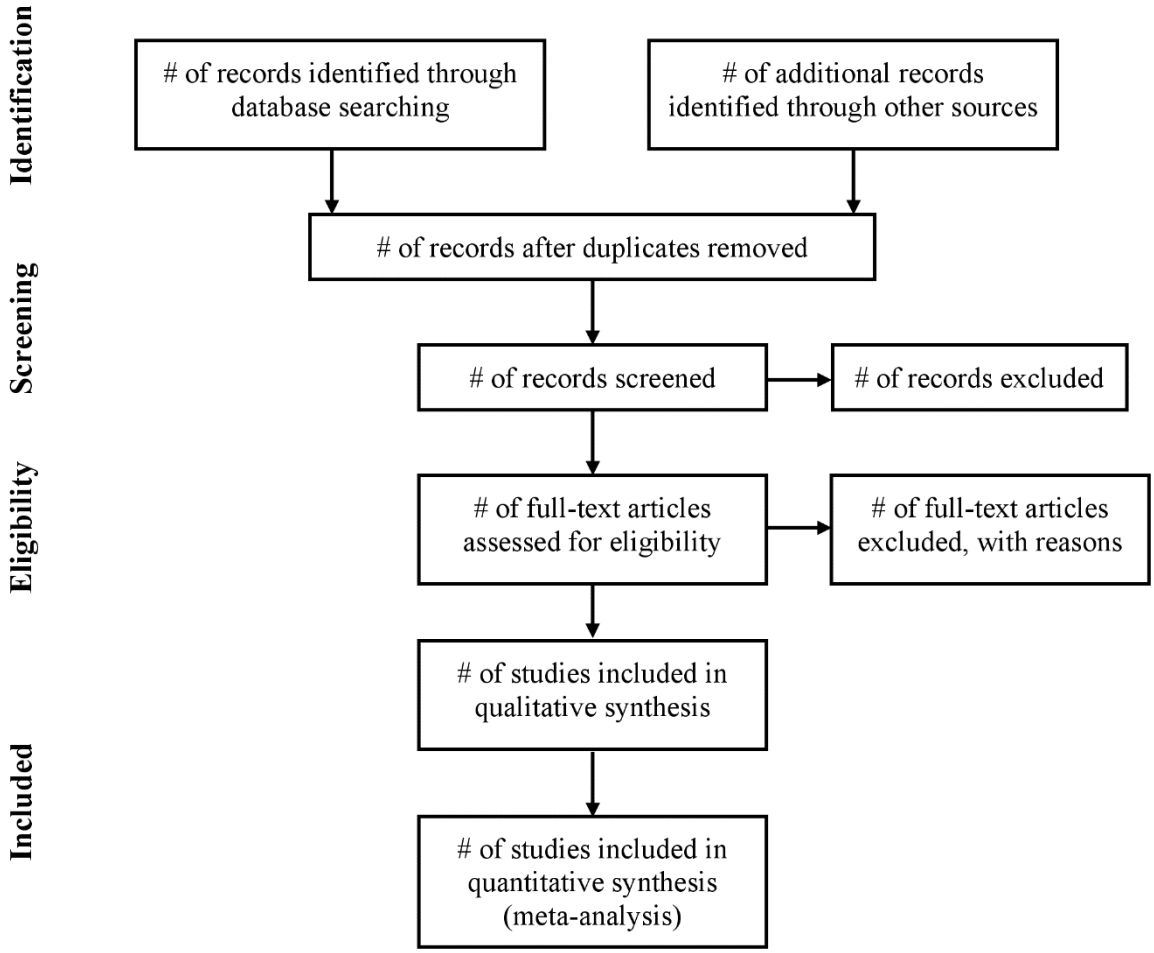
Appendix A

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

doi:10.1371/journal.pmed.1000097.t001

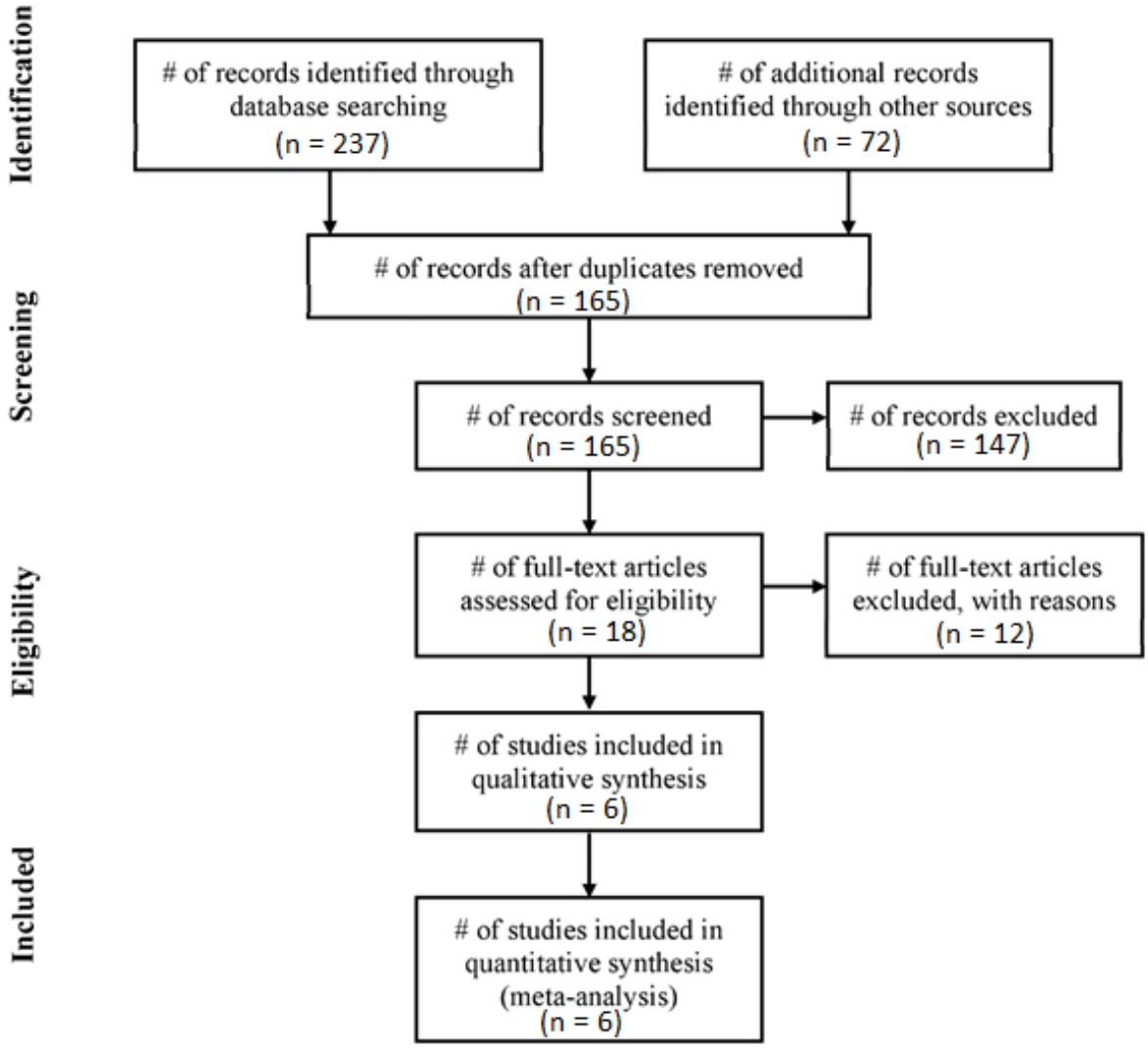
Check List for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Moher et al., 2009)

Appendix B



Flow diagram for preferred reporting items for systematic reviews and meta-analyses (Moher et al., 2009)

Appendix C



Flow diagram for preferred reporting items for systematic reviews and meta-analyses (Moher et al., 2009)

Appendix D

D1: Data Collection Tool 1

Sprung, C. L., Annane, D., Keh, D., Moreno, R., Singer, M., Freivogel, K., … Briegel, J. (2008). Hydrocortisone therapy for patients with septic shock. *The England Journal of Medicine, 358*(2), 111-124.				
Purpose	Study Design	Sample Demographics	Mortality Endpoint	Corticosteroid
To evaluate the efficacy and safety of low-dose hydrocortisone in patients with septic shock – in particular, patients who had a response to a corticotropin test.	Multicenter, randomized, double-blind, placebo-controlled study. Patients were enrolled from March 2002 to November 2005 at 52 ICUs in 9 countries. Inclusion criteria: 18 years or older, clinical evidence of infection, evidence of a systemic response to infection, the onset of shock within the previous 72 hours, and hypoperfusion or organ dysfunction attributable to sepsis. Exclusion criteria: underlying disease with a poor prognosis, a life expectancy of less than 24	500 patients enrolled, although 1 withdrew consent. Divided into 2 groups: hydrocortisone group (251 patients) and placebo group (248 patients). Mean age: hydrocortisone group = 63 $\pm$ 14, placebo group = 63 $\pm$ 15. Male gender: hydrocortisone group = 166 (66%), placebo group = 166 (67%). SOFA score: hydrocortisone group = 10.6 $\pm$ 3.4, placebo group = 10.6 $\pm$ 3.2.	The primary endpoint was death at 28 days in patients who did not have a response to corticotropin. Secondary endpoints included rates of death at 28 days in patients who had a response to corticotropin and overall, in the ICU, in the hospital, the rate of shock reversal, and LOS in the ICU and hospital.	Hydrocortisone was given as a 50 mg bolus intravenously every 6 hours for 5 days, then tapered to 50 mg every 12 hours for days 6 to 8, 50 mg every 24 hours for days 9 to 11, and then stopped.

Purpose	Study Design	Sample Demographics	Mortality Endpoint	Corticosteroid
	hours, immunosuppression, and treatment with long-term corticosteroids within the past 6 months or short-term corticosteroids within the last 4 weeks.			

D2: Data Collection Tool 1

Arabi Y. M., Aljumah A., Dabbagh O., Tamim H. M., Rishu A. H., Al-Abdulkareem, A., … Cherfan A. (2010). Low-dose hydrocortisone in patients with cirrhosis and septic shock: A randomized controlled trial. *Canadian Medical Association Journal, 182*(18), 1971-7. doi: 10.1503/cmaj.090707				
Purpose	Study Design	Sample Demographics	Mortality Endpoint	Corticosteroid
Examine the effect of low-dose hydrocortisone in patients with cirrhosis who presented with septic shock.	Randomized double-blind placebo-controlled trial. 900-bed tertiary care academic hospital on a 21-bed medical-surgical ICU. Inclusion criteria: patients aged 18 years or older with liver cirrhosis who presented with septic shock within 72 hours of the onset of hypotension. Exclusion criteria: hemorrhagic shock, known adrenal insufficiency, any prior systemic steroid usage, contraindications for systemic steroids, post-cardiac arrest, and do-not-resuscitate status. Full dose of study drug was continued until shock	140 patients screened, 75 enrolled and randomly allocated. 60 patients were enrolled within 24 hours after the onset of shock and 71 within 48 hours. Mean age: hydrocortisone group = 60.6 $\pm$ 12.6, placebo group = 59.3 $\pm$ 12.2 Female(%): hydrocortisone group = 17(44%), placebo group = 16(44%) Mean SOFA score: hydrocortisone group = 14.6 $\pm$ 3.7, placebo group = 14.3 $\pm$ 3.7	The primary outcome was 28-day all-cause mortality. Secondary outcomes included ICU-specific and hospital-specific mortality, shock reversal, and vasopressor-free days.	Participants received intravenous bolus injections every six hours of 5 mL of normal saline containing 50 mg of hydrocortisone Once shock resolved, the dose was reduced by 1 mL every 2 days until discontinuation.

Purpose	Study Design	Sample Demographics	Mortality Endpoint	Corticosteroid
	resolution, which was defined as blood pressure stability (MAP>65) without vasopressors for 24 hours.			

D3: Data Collection Tool 1

Study: Gordon, A. C., Mason, A. J., Perkins, G. D., Stotz, M., Terblanche, M., Ashby, D., & Brett, S. J. (2014). The interaction of vasopressin and corticosteroids in septic shock: a pilot randomized controlled trial. *Critical Care Medicine 42*(6), 1325-1333.				
Purpose	Study Design	Sample Demographics	Mortality Endpoint	Corticosteroid
To test for an interaction between vasopressin and corticosteroids in septic shock.	Prospective open-label randomized controlled pilot trial. Conducted between October 2010 and March 2012 at four adult ICUs in London teaching hospitals. Inclusion criteria: adult patients (>16 yrs) who had septic shock requiring vasopressors despite adequate IV fluid resuscitation. Exclusion criteria: patients who received a previous continuous infusion of vasopressors during current hospitalization, an ongoing requirement for systemic steroids, end-stage renal failure, known mesenteric ischemia, Raynaud's phenomenon, systemic sclerosis	61 adult patients who had septic shock. Male gender: hydrocortisone group = 58%, placebo group = 60%. Mean age: hydrocortisone group = 61, placebo group = 60. Mean APACHE II score: hydrocortisone group = 19, placebo group = 20.	The primary outcome was the difference in plasma vasopressin concentration between the two groups. Secondary outcomes included 28-day, ICU, and hospital mortality.	Hydrocortisone phosphate was given as a 50mg IV bolus every 6 hours for 5 days, every 12 hours for 3 days, and then once daily for 3 days.

Purpose	Study Design	Sample Demographics	Mortality Endpoint	Corticosteroid
	or other vasospastic disease, ongoing treatment for an acute coronary syndrome, death anticipated within 24 hours, known pregnancy, hypersensitivity to any study drugs, or enrollment in another trial that may interact with study drugs. Patients were assigned to one of two groups: vasopressin and hydrocortisone or vasopressin and placebo. All patients were planned to receive vasopressin (titrated to 0.06U/min as the initial vasopressor. Once max infusion rate reached, patients received either hydrocortisone or placebo.			

D4: Data Collection Tool 1

Lv, Q., Gu, X., Chen, Q., Yu J., & Zheng, R. (2017). Early initiation of low-dose hydrocortisone treatment for septic shock in adults: A randomized clinical trial. *American Journal of Emergency Medicine, 35*(12), 1810-1814. doi: 10.1016/j.ajem.2017.06.004				
Purpose	Study Design	Sample Demographics	Mortality Endpoint	Corticosteroid
To assess the importance of early initiation of low dose hydrocortisone.	A placebo-controlled, randomized clinical trial. From Sept 2015 to Sept 2016, 118 patients admitted to the 35-bed ICU of the Subei People's Hospital were recruited. Inclusion criteria: age 18 yrs or older, onset of septic shock within 6 hours. Exclusion criteria: systemic corticosteroid therapy within the last 3 months, high-dose steroid therapy, immunosuppression, refusal of the attending staff or patient family.	118 patients Gender: male/female = 70/48 Age (mean $\pm$ SD): hydrocortisone group = 68.8 $\pm$ 12.6, placebo group = 64.8 $\pm$ 16.7 SOFA score (mean $\pm$ SD): hydrocortisone group = 11.9 $\pm$ 3.3, placebo group = 9.9 $\pm$ 3.0	28-day mortality	Hydrocortisone administered 200 mg/d as a continuous infusion for 6 days, then tapered off. Once all vasopressors discontinued, the taper protocol was initiated (half dose for 5 days, then quarter dose for 3 days, then stopped)

D5: Data Collection Tool 1

Venkatesh, B., Finfer, S., Cohen, J., Rajbhandari, D., Arabi, Y., Bellomo, R., … Myburgh, J. (2018). Adjunctive glucocorticoid therapy in patients with septic shock. *The New England Journal of Medicine, 379*(9), 797-808.				
Purpose	Study Design	Sample Demographics	Mortality Endpoint	Corticosteroid
To determine whether hydrocortisone reduces mortality among patients with septic shock.	Investigator-initiated, international, pragmatic, double-blind, parallel-group, randomized controlled trial. From March 2013 through April 2017, a total of 3,800 patients underwent randomization at 69 med-surg ICUs. Compared intravenous infusions of hydrocortisone with matched placebo in patients with septic shock who were undergoing mechanical ventilation in an ICU. Inclusion criteria: Adults (≥18 years), undergoing mechanical ventilation, documented suspicion of infection, met ≥2 criteria of the systemic	3,658 enrolled patients: 1,832 in hydrocortisone group, 1,826 in placebo group. Age (mean ± SD): hydrocortisone group = 62.3 ± 14.9, placebo group = 62.7 ± 15.2 Male gender: hydrocortisone group = 60.4%, placebo group = 61.3% APACHE II median score: hydrocortisone group = 24.0, placebo group = 23.0	Primary outcome was death from any cause at 90 days. Death from any cause at 28 days was a secondary outcome.	Hydrocortisone at a dose of 200mg per day administered by means of continuous intravenous infusion over a period of 24 hours for a maximum of 7 days or until ICU discharge. Masked vial reconstituted to produce a concentration of 1mg per milliliter.

Purpose	Study Design	Sample Demographics	Mortality Endpoint	Corticosteroid
	inflammatory response syndrome, and who had been treated with vasopressors or inotropic agents for a minimum of 4 hours up to and at the time of randomization. Exclusion criteria: If patients were likely to receive glucocorticoids for an indication other than septic shock, had received etomidate, were considered to be likely to die from a pre-existing disease within 90 days, had treatment limitations in place, or had met all the inclusion criteria for more than 24 hours.			

D6: Data Collection Tool 1

Annane, D., Renault, A., Brun-Buisson, C., Megarbane, B., Quenot, J. P., Siami, S., … Bellissant, E. (2018). Hydrocortisone plus fludrocortisone for adults with septic shock. *New England Journal of Medicine, 378*(9), 809-818. doi: 10.1056/NEJMoa1705716				
Purpose	Study Design	Sample Demographics	Mortality Endpoint	Corticosteroid
To evaluate the effect of hydrocortisone plus fludrocortisone therapy versus placebo in patients with septic shock. (Originally purpose was to evaluate effect of hydrocortisone plus fludrocortisone therapy, drotrecogin alpha, the combination of the three drugs, or their respective placebos but drotrecogin alpha removed from market during trial).	A multicenter, double-blind, randomized trial with two-group parallel design. 34 participating centers. Patients recruited from Sept 2, 2008 through June 23, 2015. Inclusion criteria: indisputable or probable septic shock for less than 24 hours. Exclusion criteria: presence of septic shock for at least 24 hours, a high risk of bleeding, pregnancy or lactation, underlying conditions that could affect short-term survival, or previous treatment with corticosteroids.	1,241 patients: 626 hydro/fludro group, 614 placebo group Age (mean $\pm$ SD): hydrocortisone group = 66 $\pm$ 14, placebo group = 66 $\pm$ 15 Male gender: hydro/fludro group = 402 (65.5%), placebo group = 424 (67.7%) SOFA score: hydro/fludro group = 12 $\pm$ 3, placebo group = 11 $\pm$ 3	90-day all-cause mortality. Secondary outcomes included all-cause mortality at ICU discharge, hospital discharge, and day 28, and vasopressor free days by day 28.	Hydrocortisone was administered as a 50-mg intravenous bolus every 6 hours, and fludrocortisone was given as a 50-µg tablet through a nasogastric tube once daily in the morning. This was administered for 7 days without tapering.

Appendix E

E1: Data Collection Tool 2

Sprung, C. L., Annane, D., Keh, D., Moreno, R., Singer, M., Freivogel, K., … Briegel, J. (2008). Hydrocortisone therapy for patients with septic shock. *The England Journal of Medicine, 358*(2), 111-124.				
Identified Placebo	Mortality Rate at Day 28		Key Findings	Limitations
	Corticosteroid	Placebo (No corticosteroid)		
Exact placebo not mentioned. Vials containing placebo were identical to those containing hydrocortisone.	86 (34.3%)	78 (31.5%)	There was no significant difference between the two study groups in the rate of death at 28 days among overall patients and those with and without a response to corticotropin. Overall: hydrocortisone group = 34.3% (95% CI., 28.3 to 40.2), placebo group = 31.5% (95%, 25.5 to 37.3; P = 0.51). No corticotropin response: hydrocortisone group = 39.2% (95% CI, 30.5 to 47.9), placebo group = 36.1% (95% CI, 26.9 to 45.3; P=0.69).	Authors note a lack of adequate power since only 500 patients were enrolled instead of the projected 800. They attributed this to slow recruitment, termination of funding, and expiration date of the trial drug. 21 patients received open-label corticosteroids (4.2%). Authors believed this was unlikely to have an effect on the outcome.

Identified Placebo	Mortality Rate at Day 28		Key Findings	Limitations
	Corticosteroid	Placebo (No corticosteroid)		
			Corticotropin response: hydrocortisone group = 28.8% (95% CI, 20.6 to 37.0), placebo group = 28.7% (95% CI, 21.2 to 36.3; P = 1.00). ICU discharge 28-day mortality: hydrocortisone group = 40.6%, placebo group = 36% (P=0.31). Hospital discharge 28-day mortality: hydrocortisone group = 44.6%, placebo group = 40.8 (P=0.47). Reversal of shock was similar among all patients. Hydrocortisone group = 79.7%, placebo group = 74.2% (P=0.18). Median time until reversal of shock was shorter in the hydrocortisone group: hydrocortisone group = 3.3 days, placebo group = 5.28 days.	

Identified Placebo	Mortality Rate at Day 28		Key Findings	Limitations
	Corticosteroid	Placebo (No corticosteroid)		
			LOS was similar in both groups. In ICU: hydrocortisone group = 19 ± 31, placebo group = 18 ± 17 (P=0.51). In hospital: hydrocortisone group = 34 ± 41, placebo group = 34 ± 37 (P=0.47). In the hydrocortisone group there was an increased incidence of superinfections (new episodes of sepsis or septic shock), hyperglycemia, and hypernatremia.	

E2: Data Collection Tool 2

Arabi Y. M., Aljumah A., Dabbagh O., Tamim H. M., Rishu A. H., Al-Abdulkareem, A., … Cherfan A. (2010). Low-dose hydrocortisone in patients with cirrhosis and septic shock: A randomized controlled trial. *Canadian Medical Association Journal, 182*(18), 1971-7. doi: 10.1503/cmaj.090707				
Identified Placebo	Mortality Rate at Day 28		Key Findings	Limitations
	Corticosteroid	Placebo (No corticosteroid)		
Normal saline (placebo) given in same manner as hydrocortisone.	33 (85%)	26 (72%)	There was no significant difference between the hydrocortisone and placebo groups in 28-day mortality (33 [85%] v. 26 [72%], RR 1.117, 95% CI 0.92-1.49, p=0.19). There was no difference between the two groups in ICU (P=0.86) or hospital LOS (P=0.90). ICU mortality was 24 (62%) in hydrocortisone group and 24 (67%) in placebo group (P=0.64). Hospital mortality was 34 (87%) in hydrocortisone group and 32 (89%) in placebo group (P=0.82).	Limitations included the setting of the study at a single-centre which may affect its generalizability. The length of the randomization window was long at 72 hours. Etomidate was used in some patients which has been shown to cause adrenal suppression.

Identified Placebo	Mortality Rate at Day 28		Key Findings	Limitations
	Corticosteroid	Placebo (No corticosteroid)		
			The hydrocortisone showed improved hemodynamic parameters. Shock reversal: hydrocortisone group = 24 (62%), placebo group 14 (39%) (P=0.05). Mean vasopressor-free days: hydrocortisone group = 6.8, placebo group = 5.6 (P=0.54). Hydrocortisone was associated with higher rates of severe hyperglycemia: hydrocortisone group = 34 (87%), placebo group = 25 (69%). Also, there was a significant increase in the risk of gastrointestinal bleeding: hydrocortisone group = 13 (33%), placebo group = 4 (11%).	

E3: Data Collection Tool 2

<table>
<tr><td colspan="5">Gordon, A. C., Mason, A. J., Perkins, G. D., Stotz, M., Terblanche, M., Ashby, D., & Brett, S. J. (2014). The interaction of vasopressin and corticosteroids in septic shock: a pilot randomized controlled trial. Critical Care Medicine 42(6), 1325-1333.</td></tr>
<tr><td rowspan="2">Identified Placebo</td><td colspan="2">Mortality Rate at Day 28</td><td rowspan="2">Key Findings</td><td rowspan="2">Limitations</td></tr>
<tr><td>Corticosteroid</td><td>Placebo
(No corticosteroid)</td></tr>
<tr><td>Placebo was 0.5 mL 0.9% saline given in same manner as hydrocortisone.</td><td>7 (23%)</td><td>7 (23%)</td><td>There was no difference in mortality rates.
28-day mortality: hydrocortisone group = 23%, placebo group = 23% (-0.01*).
ICU mortality: hydrocortisone group = 23%, placebo group = 27% (-0.04*).
Hospital mortality: hydrocortisone group = 26%, placebo group = 30% (-0.04*).
*Difference in proportions: (vaso + hydro) – (vaso + placebo).

Patients in the hydrocortisone group were weaned off vasopressin more quickly with a 3.1 day (P=0.001) shorter duration of vasopressin infusion and a halving of the</td><td>The study was prospectively powered to detect a difference in plasma vasopressin levels at single point after reaching maximum rate of vasopressin infusion and corticosteroid administration. Not all patients reached the max vasopressin rate even though additional existing catecholamines were weaned off quickly. This reduced the sample size and potential power in the analysis of plasma levels

There were 5 crossovers from the placebo group to hydrocortisone group due to refractory shock (although results remained unchanged).

The use of 61 patients resulted in limited power to detect differences in clinical outcomes measures.</td></tr>
</table>

Identified Placebo	Mortality Rate at Day 28		Key Findings	Limitations
	Corticosteroid	Placebo (No corticosteroid)		
			total dose (P=0.001) of vasopressin required than placebo group. Hydrocortisone = 2.5 $\pm$ 2.4 days of vasopressor, placebo group = 2.8 $\pm$ 4 days. There was no difference in plasma vasopressin levels. 14 adverse events reported although none attributed directly to hydrocortisone.	

E4: Data Collection Tool 2

Lv, Q., Gu, X., Chen, Q., Yu J., & Zheng, R. (2017). Early initiation of low-dose hydrocortisone treatment for septic shock in adults: A randomized clinical trial. *American Journal of Emergency Medicine, 35*(12), 1810-1814. doi: 10.1016/j.ajem.2017.06.004				
Identified Placebo	Mortality Rate at Day 28		Key Findings	Limitations
	Corticosteroid	Placebo (No corticosteroid)		
Normal saline (Administration procedure same as hydrocortisone)	23 (39.7%)	19 (31.7%)	There were no significant differences in 28-day (P=0.365) or hospital all-cause mortality length of stay in the ICU or hospital between patients treated with hydrocortisone or placebo. In-hospital mortality: hydrocortisone group = 23 (39.7%), placebo group = 19 (31.7%, P=0.365) LOS in ICU, days: hydrocortisone group = 10.9 $\pm$ 17.5, placebo group = 10.2 $\pm$ 13.1 (P=0.799)	Only short-term outcomes, 28-day and in-hospital mortality, were collected and therefore any long-term difference between treatment groups cannot be assessed. The study was likely to be underpowered to detect a statistically significant difference by the recruitment of patients with lower mortality. Authors note the original calculated sample size was based on a control mortality of 60% using findings from a large prior study, but this study's control mortality was about half. The sample size was relatively small, and only one center was involved, which may affect its generalizability.

Identified Placebo	Mortality Rate at Day 28		Key Findings	Limitations
	Corticosteroid	Placebo (No corticosteroid)		
			LOS in hospital, days: hydrocortisone group = 23.7 ± 36.8, placebo group = 21.7 ± 21.7 (P=0.711) Shock reversal was similar in both groups. Hydrocortisone group = 65.6%, placebo group = 70.0% (P=0.602) Early administration of hydrocortisone enabled earlier titration off vasoactive therapy. Norepinephrine duration: hydrocortisone group = 2.5 ± 2.4, placebo group = 2.8 ± 4.0 (P=0.639) The early initiation of low-dose hydrocortisone did not decrease the risk of mortality or the length of stay in the ICU or hospital in adults with septic shock. These findings do not support the use of hydrocortisone in these patients.	

E5: Data Collection Tool 2

Venkatesh, B., Finfer, S., Cohen, J., Rajbhandari, D., Arabi, Y., Bellomo, R., … Myburgh, J. (2018). Adjunctive glucocorticoid therapy in patients with septic shock. *The New England Journal of Medicine, 379*(9), 797-808.				
Identified Placebo	Mortality Rate at Day 28		Key Findings	Limitations
	Corticosteroid	Placebo (No corticosteroid)		
Masked vial reconstituted to produce an equivalent volume of placebo (200ml). (Administration procedure same as hydrocortisone)	410 (22.3%)	448 (24.3%)	Among patients with septic shock undergoing mechanical ventilation, a continuous infusion of hydrocortisone did not result in lower 90-day mortality than placebo (P=0.50). There was no significant difference in mortality at 28 days (P=0.13). Hydrocortisone group = 410 (22.3%), placebo group = 448 (24.3%) The resolution of shock was shorter (days) in the hydrocortisone group (P<0.001). Hydrocortisone group = 3, placebo group = 4 .	The authors did not identify adverse events themselves. Data on adverse events were judged by the treating clinicians thought to be related to the trial regimen. This judgement was not adjudicated. This may weaken inferences about adverse events. Data were not collected regarding all possible secondary infections. Only bacteremia and fungemia data was recorded. The appropriateness of antibiotic therapy was not adjudicated.

Identified Placebo	Mortality Rate at Day 28		Key Findings	Limitations
	Corticosteroid	Placebo (No corticosteroid)		
			Patients receiving hydrocortisone had a shorter time to ICU discharge (days) ($P<0.001$). Hydrocortisone group = 10, placebo group = 12 There was a higher percentage of adverse events in the hydrocortisone vs placebo group (1.1% vs 0.3%, $P=0.009$) the most prevalent being hyperglycemia	

E6: Data Collection Tool 2

Annane, D., Renault, A., Brun-Buisson, C., Megarbane, B., Quenot, J. P., Siami, S., … Bellissant, E. (2018). Hydrocortisone plus fludrocortisone for adults with septic shock. *New England Journal of Medicine, 378*(9), 809-818. doi: 10.1056/NEJMoa1705716				
Identified Placebo	Mortality Rate at Day 28		Key Findings	Limitations
	Corticosteroid	Placebo (No corticosteroid)		
Respective placebos given in same manner. Hydrocortisone placebo = mannitol (133.6mg), disodium phosphate (8.73mg), and sodium phosphate (0.92mg). Fludrocortisone placebo = microcrystalline cellulose (59.098mg), magnesium stearate (0.6mg), and colloidal	207 (33.7%)	244 (38.9%)	The relative risk of death was 0.88 (95% CI, 0.78 to 0.99) in favor of hydro/fludro therapy. Death occurred in 43% in hydro/fludro group and 49.1% in placebo group. Mortality at day 28 was 33.7% for the hydro/fludro group and 38.9% for the placebo group (P=0.06). Mortality was significantly lower in hydro/fludro group than placebo group at ICU discharge (35.4% vs 41%, P=0.04) and hospital discharge (39% vs 45.3%, P=0.02).	No limitations were reported by the authors in this study. The trial was suspended twice: First, from October 2011 to May 2012 after the withdrawal of drotrecogin alpha from the market. Second, from July 2014 to October 2014 at the request of the data and monitoring board to check the quality of the trial drugs and reported serious adverse events. After drotrecogin alpha withdraw, the trial continued as a two-group parallel design.

Identified Placebo	Mortality Rate at Day 28		Key Findings	Limitations
	Corticosteroid	Placebo (No corticosteroid)		
anhydrous silica (0.3mg).			The hydro/fludro group had more vasopressor-free days (17 $\pm$ 11) than placebo group (15 $\pm$ 11) by day 28 ($P<0.001$). The risk of secondary infection, GI bleeding, or neurological events was not significantly higher in the hydro/fludro group although the risk of hyperglycemia was significantly higher in the hydro/fludro group.	

Appendix F1

Study: Sprung, C. L., Annane, D., Keh, D., Moreno, R., Singer, M., Freivogel, K., … Briegel, J. (2008). Hydrocortisone therapy for patients with septic shock. *The England Journal of Medicine, 358*(2), 111-124.			
Section A: Are the results of the trial valid?	Yes	Can't tell	No
1. Did the trial address a clearly focused issue?	✓		
2. Was the assignment of patients to treatments randomised?	✓		
3. Were all of the patients who entered the trial properly accounted for at its conclusion? *One patient withdrew consent after randomization.*			✓
4. Were patients, health workers and study personnel 'blind' to treatment? *Of note, 4.4% of the hydrocortisone group and 4.0% of the placebo group received open-label corticosteroids after study enrollment due to allergic reactions, laryngeal edema, bronchospasm, brain edema, replacement of long-term corticosteroid therapy whose history was unknown at enrollment, acute respiratory distress syndrome, and septic shock.*	✓		
5. Were the groups similar at the start of the trial?	✓		
6. Aside from the experimental intervention, were the groups treated equally?	✓		
Section B: What are the results?			
7. How large was the treatment effect? *The mortality rate at 28 days was 34.3% (86/251 deaths) in the hydrocortisone group and 31.5% (78/248 deaths) in the placebo group.*			
8. How precise was the estimate of the treatment effect? *A sample size of 800 patients was needed to achieve a statistical power of 80% to detect an absolute decrease in mortality of 10% from an existing death rate of 50% in patients who did not have a response to corticotropin (40% of total group).*			
Section C: Will the results help locally?	Yes	Can't tell	No
9. Can the results be applied to the local population, or in your context?	✓		
10. Were all clinically important outcomes considered?	✓		
11. Are the benefits worth the harms and costs?	✓		

Critical Appraisal Skills Programme (CASP) Randomised Controlled Trials Checklist (2018)

Appendix F2

Study: Arabi Y. M., Aljumah A., Dabbagh O., Tamim H. M., Rishu A. H., Al-Abdulkareem, A., … Cherfan A. (2010). Low-dose hydrocortisone in patients with cirrhosis and septic shock: A randomized controlled trial. *Canadian Medical Association Journal, 182*(18), 1971-7. doi: 10.1503/cmaj.090707			
Section A: Are the results of the trial valid?	Yes	Can't tell	No
1. Did the trial address a clearly focused issue?	✓		
2. Was the assignment of patients to treatments randomised?	✓		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	✓		
4. Were patients, health workers and study personnel 'blind' to treatment? *Of note, blinding was opened for one patient at the request of the primary physician, but the therapy (placebo) was continued as planned per the study protocol.*	✓		
5. Were the groups similar at the start of the trial?	✓		
6. Aside from the experimental intervention, were the groups treated equally? *Five patients in the placebo group were given rescue corticosteroids for the treatment of life-threatening hypotension and were considered crossovers.*			✓
Section B: What are the results?			
7. How large was the treatment effect? *The mortality rate at 28 days was 85% (33/39 deaths) in the hydrocortisone group and 72% (26/36 deaths) in the placebo group.*			
8. How precise was the estimate of the treatment effect? *Based on an estimated baseline 28-day mortality of 90% and an estimated absolute risk reduction of 20%, 75 patients were required in each group using a two-sided type I error of 5% and power of 80%.* *A planned interim analysis was performed after randomly allocating 75 patients and found a trend towards excess 28-day mortality with the hydrocortisone group. At this point the trial was stopped since it was highly unlikely that a significant treatment benefit would be evident if the trial were completed to the targeted sample size.*			
Section C: Will the results help locally?	Yes	Can't tell	No
9. Can the results be applied to the local population, or in your context?	✓		
10. Were all clinically important outcomes considered?	✓		
11. Are the benefits worth the harms and costs?	✓		

Appendix F3

Study: Gordon, A. C., Mason, A. J., Perkins, G. D., Stotz, M., Terblanche, M., Ashby, D., & Brett, S. J. (2014). The interaction of vasopressin and corticosteroids in septic shock: a pilot randomized controlled trial. *Critical Care Medicine 42*(6), 1325-1333.			
Section A: Are the results of the trial valid?	Yes	Can't tell	No
1. Did the trial address a clearly focused issue?	✓		
2. Was the assignment of patients to treatments randomised?	✓		
3. Were all of the patients who entered the trial properly accounted for at its conclusion? *Two patients met exclusion criteria after randomization, but before administration of the study drug.*		✓	
4. Were patients, health workers and study personnel 'blind' to treatment?	✓		
5. Were the groups similar at the start of the trial?	✓		
6. Aside from the experimental intervention, were the groups treated equally? *Due to emergency situations, not all patients received vasopressin as the initial vasopressor. 30% received vasopressin as the initial vasopressor and 50% were transitioned to vasopressin within the first 4 hours of the onset of shock. Also, eleven patients did not reach maximum vasopressin requirements so did not receive the study drug.*			✓
Section B: What are the results?			
7. How large was the treatment effect? *The mortality rate at 28 days was 23% (7/31 deaths) in the hydrocortisone group and 23% (7/30 deaths) in the placebo group.*			
8. How precise was the estimate of the treatment effect? *30 patients were required in each treatment group in order to study the primary outcome of the difference in plasma vasopressin concentration between groups. The group sizes were calculated in order to detect a 33 pmol/L difference in vasopressin levels at 6-12 hours post corticosteroid administration assuming a SD of 45 pmol/L with a significance level of 0.05 and 80% power.*			
Section C: Will the results help locally?	Yes	Can't tell	No
9. Can the results be applied to the local population, or in your context?	✓		
10. Were all clinically important outcomes considered?	✓		
11. Are the benefits worth the harms and costs?	✓		

Appendix F4

Study: Lv, Q., Gu, X., Chen, Q., Yu J., & Zheng, R. (2017). Early initiation of low-dose hydrocortisone treatment for septic shock in adults: A randomized clinical trial. *American Journal of Emergency Medicine, 35*(12), 1810-1814. doi: 10.1016/j.ajem.2017.06.004			
Section A: Are the results of the trial valid?	Yes	Can't tell	No
1. Did the trial address a clearly focused issue?	✓		
2. Was the assignment of patients to treatments randomised?	✓		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	✓		
4. Were patients, health workers and study personnel 'blind' to treatment?	✓		
5. Were the groups similar at the start of the trial? *The initial SOFA score was higher in the hydrocortisone group compared to the placebo group and was statistically significant (P<0.001).*			✓
6. Aside from the experimental intervention, were the groups treated equally?	✓		
Section B: What are the results?			
7. How large was the treatment effect? *The mortality rate was 39.7% (23 deaths) in the hydrocortisone group and 31.7% (19 deaths) in the placebo group.*			
8. How precise was the estimate of the treatment effect? *The study was likely to be underpowered to detect a statistically significant difference by the recruitment of patients with lower mortality. The original sample size collection was based on a control mortality of 60% originating from the findings of the largest prior study, but the control 28-day mortality in this study was almost half that.*			
Section C: Will the results help locally?	Yes	Can't tell	No
9. Can the results be applied to the local population, or in your context?	✓		
10. Were all clinically important outcomes considered?	✓		
11. Are the benefits worth the harms and costs?	✓		

Appendix F5

Study: Venkatesh, B., Finfer, S., Cohen, J., Rajbhandari, D., Arabi, Y., Bellomo, R., … Myburgh, J. (2018). Adjunctive glucocorticoid therapy in patients with septic shock. *The New England Journal of Medicine, 379*(9), 797-808.			
Section A: Are the results of the trial valid?	Yes	Can't tell	No
1. Did the trial address a clearly focused issue?	✓		
2. Was the assignment of patients to treatments randomised?	✓		
3. Were all of the patients who entered the trial properly accounted for at its conclusion? *Of the 3800 patients enrolled, 114 patients either withdrew or did not have informed consent obtained, and 28 patients were lost to follow-up at 90 days.*			✓
4. Were patients, health workers and study personnel 'blind' to treatment?	✓		
5. Were the groups similar at the start of the trial?	✓		
6. Aside from the experimental intervention, were the groups treated equally?	✓		
Section B: What are the results?			
7. How large was the treatment effect? *The mortality rate at 28 days was* 22.3% *(410/1832 deaths) in the hydrocortisone group and 24.3% (448/1826 deaths) in the placebo group.*			
8. How precise was the estimate of the treatment effect? *A population of 3800 patients provided the trial with 90% power to detect an absolute difference of 5% in 90-day all-cause mortality from an estimated baseline mortality of 33%, at an alpha level of 0.05. This allowed for a rate of withdrawal and loss to follow-up of 1%.*			
Section C: Will the results help locally?	Yes	Can't tell	No
9. Can the results be applied to the local population, or in your context?	✓		
10. Were all clinically important outcomes considered?	✓		
11. Are the benefits worth the harms and costs?	✓		

Appendix F6

Study: Annane, D., Renault, A., Brun-Buisson, C., Megarbane, B., Quenot, J. P., Siami, S., … Bellissant, E. (2018). Hydrocortisone plus fludrocortisone for adults with septic shock. *New England Journal of Medicine, 378*(9), 809-818. doi: 10.1056/NEJMoa1705716			
Section A: Are the results of the trial valid?	Yes	Can't tell	No
1. Did the trial address a clearly focused issue?	✓		
2. Was the assignment of patients to treatments randomised?	✓		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	✓		
4. Were patients, health workers and study personnel 'blind' to treatment?	✓		
5. Were the groups similar at the start of the trial?	✓		
6. Aside from the experimental intervention, were the groups treated equally?	✓		
Section B: What are the results?			
7. How large was the treatment effect? *The mortality rate at 28 days was 33.7% (207/1241 deaths) in the hydrocortisone group and 38.9% (244/1241 deaths) in the placebo group.*			
8. How precise was the estimate of the treatment effect? *A 90-day mortality of 45% among patients with septic shock was anticipated. 320 patients were needed in each group to detect an absolute difference of 10% in 90-day mortality (*α=0.05 and power at 95%).			
Section C: Will the results help locally?	Yes	Can't tell	No
9. Can the results be applied to the local population, or in your context?	✓		
10. Were all clinically important outcomes considered?	✓		
11. Are the benefits worth the harms and costs?	✓		

Appendix G

Cross Study Analysis

	Author, Year	Mortality Rate at Day 28	Resolution of Shock	Vasopressor Usage	Length of Stay (LOS)	
					ICU	Hospital
1	Sprung et al., 2008	Corticosteroid: 34.3% Placebo: 31.5 P=0.51	Corticosteroid: 79.7% Placebo: 74.2% P=0.18 *Median time to Reversal (days)* Corticosteroid: 3.3 Placebo: 5.28	Not reported	Corticosteroid: 19±31 Placebo:18+17 P=0.51	Corticosteroid: 34+41 Placebo: 34+37 P=0.47
2	Arabi et al., 2010	Corticosteroid: 85% Placebo: 72% P=0.19	Corticosteroid: 62% Placebo: 39% P=0.05	*Vasopressor-free days* Corticosteroid: 6.8 Placebo: 5.6 P=0.54	Corticosteroid: 9.2 Placebo: 9.6 P=0.86	Corticosteroid: 27.2 Placebo: 43.3 P=0.90
3	Gordon et al., 2014	Corticosteroid: 23% Placebo: 23%	Not reported	*Days on Vasopressor* Corticosteroid: 2.5±2.4 Placebo: 2.8±4 P=0.001	Not reported	Not reported

	Author, Year	Mortality Rate at Day 28	Resolution of Shock	Vasopressor Usage	Length of Stay (LOS)	
					ICU	Hospital
4	Lv et al., 2017	Corticosteroid: 39.7% Placebo: 31.7% P=0.365	Corticosteroid: 65.6% Placebo: 70.0% P=0.602	*Days on Vasopressor* Corticosteroid: 2.5±2.5 Placebo: 2.8±4.0 P=0.639	Corticosteroid: 10.9±17.5 Placebo: 10.2±13.1 P=0.799	Corticosteroid: 23.7±36.8 Placebo: 21.7±21.7 P=0.711
5	Venkatesh et al, 2018	Corticosteroid: 22.3% Placebo: 24.3% P=0.13	*(Days)* Corticosteroid: 3 Placebo: 4 P=<0.001	Not reported	Corticosteroid: 10 Placebo: 12 P<0.001	Corticosteroid: 39 Placebo: 43 P=0.13
6	Annane et al, 2018	Corticosteroid: 33.7% Placebo: 38.9% P=0.06	Not reported	*Vasopressor-free days* Corticosteroid: 17±11 Placebo: 15±11 P<0.001	Not reported	Not reported