Review

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Recent trends in septic shock management: a narrative review of current evidence and recommendations

Mariam Akram Nofal, MD[a], Jawad Shitawi, MD[d], Hashem Bassam Altarawneh, MD[b], Sallam Alrosan, MD[e], Yanal Alqaisi, MD[b], Al-Mothaffer Al-Harazneh, MD[c], Ammar Masoud Alamaren, MD[b], Mohammad Abu-Jeyyab, MD[b,*]

Abstract

Septic shock stands for a group of manifestations that will cause a severe hemodynamic and metabolic dysfunction, which leads to a significant increase in the risk of death by a massive response of the immune system to any sort of infection that ends up with refractory hypotension making it responsible for escalating the numbers of hospitalized patients mortality rate, Organisms that are isolated most of the time are *Escherichia coli, Klebsiella, Pseudomonas aeruginosa,* and *Staph aureus*. The WHO considers sepsis to be a worldwide health concern; the incidence of sepsis and septic shock have been increasing over the years while being considered to be under-reported at the same time. This review is a quick informative recap of the recent studies regarding diagnostic approaches using lactic acid (Lac), procalcitonin (PCT), Sequential Organ Failure Assessment (SOFA) score, acute physiology and chronic health evaluation II (APACHE II) score, as well as management recommendations for using vasopressors, fluid resuscitation, corticosteroids and antibiotics that should be considered when dealing with such type of shock.

Keywords: antibiotics, corticosteroids, diagnosis, fluids, immunotherapy, sepsis, septic shock, treatment, vasopressors

Introduction

According to the Third International Consensus Definitions, septic shock is considered to be a manifestation of sepsis that causes hemodynamic and metabolic dysfunction so severe that it significantly increases the risk of death; thus, prompt detection and proper treatment are vital to enhance its outcome[1]. Organisms that are responsible for developing septic shock can vary, but the ones isolated most of the time are *Escherichia coli, Klebsiella, Pseudomonas aeruginosa*, and *Staph. aureus*[2,3].

The WHO considers sepsis to be a worldwide health concern; the incidence of sepsis and septic shock have been increasing over the years while being considered to be under-reported at the same time. The pathophysiology of sepsis is quite complicated and reliant on the causative agent and the host, with tissue damage resulting from the pathogen itself and the following pro-inflammatory response early on, while lately, the patient becomes more susceptible to infections due to the anti-inflammatory response[4–6].

Early features of septic shock include increased body temperature, tachycardia, tachypnea, and leukocytosis, after these, shock ensues. Septic shock imposes a 40% risk of mortality, which makes it a feared complication of sepsis, this risk depends on the causative organism, its sensitivity to antibiotics, the extent of organ damage, and the patient's age, the increased likelihood of mortality is also carried on the long term. Additionally, these patients can be affected by complications that would impact their general quality of life, such as chronic kidney disease (CKD) and prolonged ICU admission complications, leading to considerable

HIGHLIGHTS

- Septic shock causes life-threatening organ failure and high mortality rates.
- This study used various tools to diagnose and predict outcomes of septic shock patients.
- Balanced crystalloids were used for fluid resuscitation to improve hemodynamic stability.
- Broad-spectrum antibiotics and multi-drug regimens were initiated within one hour of septic shock onset.
- Norepinephrine was the first-line vasopressor to maintain blood pressure.
- Low-dose corticosteroids were given to patients who needed vasopressors, with individualized dosing and clinical evaluation.
- Septic shock management involves a comprehensive and personalized approach.

[a]School of Medicine, Jordan University Hospital, Amman, Jordan, [b]School of Medicine Mutah University Amman, Jordan, [c]Internal Medicine, Al-Karak Governmental Hospital, Amman, Jordan, [d]Internal Medicine, Epsom and St Helier University Hospitals NHS Trust, Sutton, GBR, UK and [e]Internal Medicine, Saint Luke's Health System, Kansas City, MO, USA

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*Corresponding author. Address: School of Medicine, Mutah University, Amman 60217, Jordan. Tel.: +962 796 383 747. E-mail: mabujeyyab@yahoo.com (M. Abu-Jeyyab).

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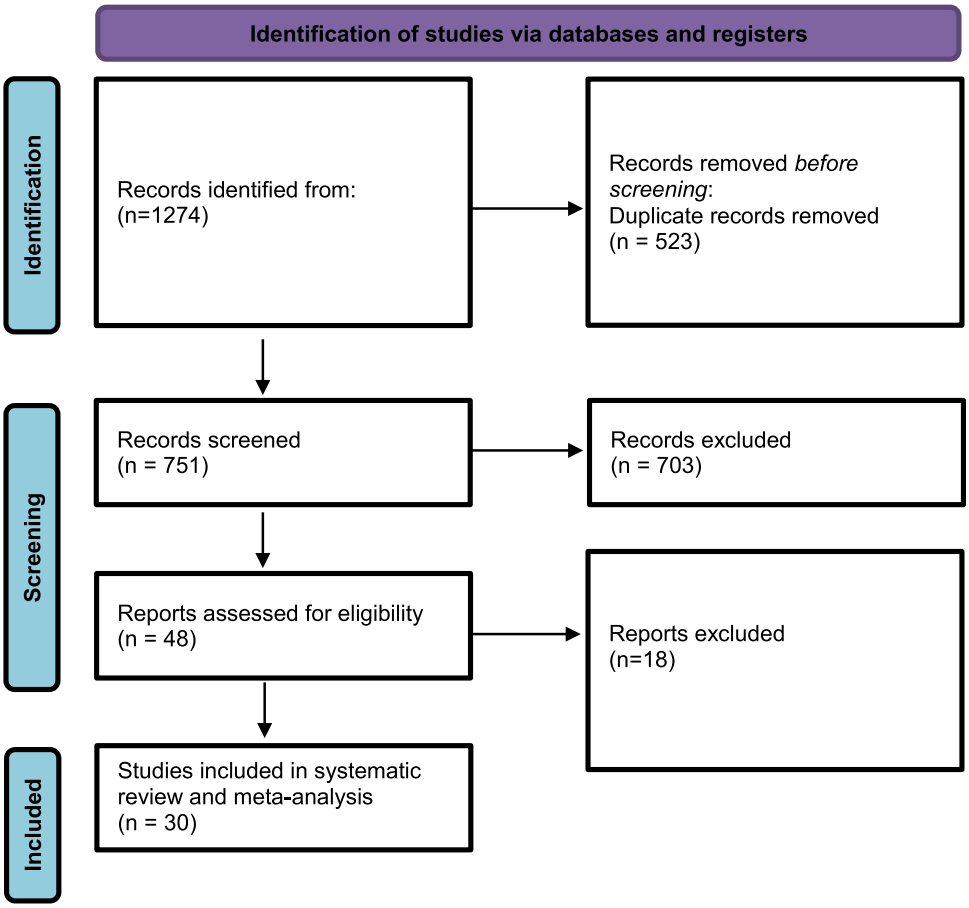

Figure 1. PRISMA flow diagram of database searching and screening.

morbidity[3]. In this paper, the latest trends in the management of septic shock are addressed to provide medical professionals with an updated, evidence-based, and concise view of its guidelines for them to go over readily.

To maintain the relevance and currentness of the data being provided, it has been decided to exclusively consider papers that were published from the year 2018 and beyond in PubMed.

Methods

We systematically searched PubMed for articles considering the diagnosis and management of septic shock published recently from 2018 to January 2023. We used the following keywords: "septic shock" OR "sepsis" AND "diagnosis" OR "management" OR "treatment" OR "recommendations" OR: Guidelines" OR "recent" OR "current" OR "trends".

Results

After searching the databases and removal of duplicates, the screening process yielded a total of 30 articles that investigated recent advances in the management of sepsis. (Fig. 1)

Diagnosis of septic shock

Reducing organ system damage and mortality requires early detection of septic shock and adequate treatment with antibiotics, fluids, and vasopressors[5]. In a variety of healthcare settings and contexts, the Sequential Organ Failure Assessment (SOFA) (Table 1), has been extensively validated as a tool for evaluating the acute morbidity of critical illness at the community level[7]. The SOFA score (Table 1), qsOFA score, and △SOFA score were found to be abnormally expressed in patients with sepsis and to be risk factors for the severity of the patient's condition and prognosis. These scores also had some value in diagnosing sepsis and assessing the condition and prognosis, with the combined value of the three being higher. The efficiency of lactic acid (Lac), procalcitonin (PCT), SOFA score (Table 1), acute physiology and chronic health evaluation II (APACHE II) score (Table 2), and other measures in determining the severity and prognosis of septic shock were investigated in a retrospective study. In patients with septic shock, age, PCT, SOFA score (Table 1), APACHE II score (Table 2), and Lac were independent risk factors for death. These variables had a higher diagnostic value and were more accurate in predicting the short-term prognosis of septic shock than a single variable[7]. The Third International Consensus Definitions for Sepsis and Septic Shock (sepsis-3) states that an increase in the SOFA score (Table 1) of two points or more indicates organ failure and is linked to an in-hospital mortality rate of more than 10%.

Systemic inflammatory response syndrome (SIRS), SOFA, Quick Sepsis-related Organ Failure Assessment (qSOFA), and National Early Warning Score (NEWS) were compared in a meta-

analysis by Qiu *et al.*[8]. for the diagnosis of sepsis and the prediction of unfavorable outcomes in septic shock. qSOFA displayed poor sensitivity (0.42) but high specificity (0.98), SIRS showed high sensitivity (0.85) but low specificity (0.41), and NEWS showed both high sensitivity (0.71) and specificity (0.85) about sepsis prediction. The SOFA had the highest sensitivity (0.89) and specificity (0.69) for predicting in-hospital mortality. SIRS demonstrated a high sensitivity (0.87) and a high specificity (0.75) in predicting the 7/10/14-day mortality. In comparison to qSOFA, which showed poor sensitivity (0.41) but high specificity (0.88), SOFA had high sensitivity (0.97) but low specificity (0.14) for predicting 28/30-day mortality. Thus, this study concluded that NEWS, particularly in high-income nations, independently showed good diagnostic capabilities for sepsis. In low-income nations, SOFA can be used as a screening tool for 28/30-day mortality and turns out to be the best option for predicting in-hospital death.

Eighty new individual biomarkers have emerged during the past ten years, according to a previous thorough study that found 5367 studies examining the use of biomarkers for sepsis[9]. Of these, 21 biomarkers on average were evaluated expressly for the diagnosis of sepsis in fundamental research studies, clinical investigations, and studies that combined the two methods. Among these were cytokines, microRNAs, proteins, receptors, calprotectin, and others.

The term "septic shock" refers to a subtype of sepsis in which there is a higher risk of death from very severe circulatory, cellular, and metabolic abnormalities than from infection alone. Clinical markers for septic shock patients include the need for a vasopressor to maintain a mean arterial pressure of 65 mm Hg or higher and, in the absence of hypovolemia, a serum lactate level greater than 2 mmol/l (>18 mg/dl). Over 40% of hospital mortality rates are linked to this combo. Whether in an emergency room, ordinary hospital ward, or out-of-hospital situation, If adult patients with suspected infection meet at least two of the clinical criteria that together form a new bedside clinical score called qSOFA—respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100 mmHg or less—they can be quickly identified as being more likely to have poor outcomes typical of sepsis[1]. In addition to providing more consistency for epidemiologic studies and clinical trials, these revised definitions and clinical criteria should take the place of earlier ones. They should also make it easier to identify and treat individuals who have sepsis or are at risk of developing sepsis sooner rather than later[1].

Table 1[10], Tables 2,3,4[11]

Table 1; The SOFA score is a scoring system that assesses the performance of several organ systems in the body (neurologic, blood, liver, kidney, and blood pressure/hemodynamics) and assigns a score based on the data obtained in each category.

Tables 2,3,4; APACHE II score is a general measure of disease severity based on current physiologic measurements, age and previous health conditions. The score can help in the assessment of patients to determine the level and degree of diagnostic and therapeutic intervention.

In the Apache scoring system for sepsis, the column headings 4, 3, 2, 1, 0, 1, 2, 3, 4 indicate the severity grades assigned to different physiological parameters. Here's a breakdown of each grade: -Grade 4: This indicates the most severe derangement or abnormality in a physiological parameter. It represents a critical deviation from the normal range. -Grade 3: This indicates a

Table 1
SOFA Score.

Organ system	Corresponding parameter	0	1	2	3	4
Cardiovascular,	Hypotension, mm Hg	MAP; > 70 mm without vasopressors	MAP < 70 mm without vasopressors	Dopamine ≤ 5 or dobutamine (any dose)	Dopamine > 5 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1
Respiratory	Pao2/Fio2 mm Hg	> 400	< 400	< 300	< 200 with respiratory support	< 100 with respiratory support
Renal	Creatinine, mg/dl	< 1.2	1.2–1.U	2.0–3.4	3.5–4.U	> 5.0
Hematology	Platelet count, $*10^3/mm^3$	> 150	< 150	< 100	< 50	< 20
Hepatic	Bilirubin, mg/dl	< 1.2	1.2–1.U	2.0–5.U	G.0–11.U	> 12.0

The numbers in the headings indicate how much points does the patient would have according to the specific category.
FiO2, fraction of inspired oxygen; MAP, mean arterial blood pressure; mg/dl, milligrams per deciliter; mmHg, millimeters of mercury; Pao2, measured the partial pressure of oxygen in arterial blood; SOFA, Sequential Organ Failure Assessment.

Table 2

APACHE II scoring system A: total acute physiology score.

	4	3	2	1	0	1	2	3	4
Body temp. (Celsius)	≤ 2U.U	30–31.U	32–33.U	34–35.U	3G–38.4	38.5–38.U		3U–40.U	≥41
Mean Bp (mmHg)	≤4U		50–GU		70–10U		110–12U	130–15U	≥1G0
Pulse (/min)	≤3U	40–54	55–GU		70–10U		110–13U	140–17U	≥180
Respiratory rate (/min)	≤5		G–U	10–11	12–24	25–34		35–4U	≥50
A-a Do2(Fio2 > =0.5) PaO2(Fio 2 < 0.5)	< 55	55–G0		G1–70	< 200 > 70		200–34U	350–4UU	≥500
Arterial blood PH	< 7.15.	7.15–7.24	7.25–7.32		7.33–7.4U	7.50–7.5U		7.G0–7.GU	≥7.70
HCO3	< 15	15–17.U	18–21.U		22–31.U	32–40.U		41–51.U	≥52
Serum sodium (mol/l)	≤110	111–11U	120–12U		130–14U	150–154	155–15U	1G0–17U	≥180
Serum potassium (mmol/l)	< 2.5		2.5–2.U	3.0–3.4	3.5–5.4	5.5–5.U		G–G.U	≥7.0
Serum creatinine (mg/dl)			< 0.G		0.G–1.4		1.5–1.U	2.0–3.4	≥3.5
Hematocrit (%)	< 20		20–2U.U		30–45.U	4G–4U.U	50–5U.U		≥G0
WBC (*10^3/mm^3)	< 1		1–2.U		3–14.U	15–1U.U	20–3U.U		≥40
Glasgow coma scale	Score = 15 minus the actual GCS	Score = 15 minus the actual GCS	Score = 15 minus the actual GCS	Score = 15 minus the actual GCS	Score = 15 minus the actual GCS	Score = 15 minus the actual GCS	Score = 15 minus the actual GCS	Score = 15 minus the actual GCS	Score = 15 minus the actual GCS

Respiratory Rate (per min); how many times the patient take breath per 1 min.
Pulse (per minute); how many times the heart contract per 1 min.
APACHE II, acute physiology and chronic health evaluation II; GCS, Glasgow Coma Scale; mg/dl, milligrams per deciliter; mol/l; moles per litre; mmHg; millimeters of mercury; mmol/l; millimoles per litre.

significant abnormality that is closer to the severe end but not as extreme as grade 4. -Grade 2: This indicates a moderate abnormality, that is an intermediate deviation from normal. -Grade 1: This indicates a mild abnormality or a minor deviation from the normal range. -Grade 0: This indicates that the physiological parameter is within the normal range. The reason the number is repeated twice (1, 2, 3, 4, 0, 1, 2, 3, 4) is because the scoring system assesses the severity of physiological parameters based on both high and low values. For some parameters, a higher value may represent a more severe abnormality, while for others, a lower value may indicate greater severity. By including both high and low values, the scoring system can capture a wider range of abnormalities in different physiological parameters. It's important to note that these grades may be assigned differently for each physiological parameter being assessed, depending on the specific parameter and its clinical relevance. The Apache scoring system considers various physiological parameters such as heart rate, blood pressure, temperature, respiratory rate, etc., and assigns grades based on their deviation from normal ranges[11,12].

Fluid resuscitation in septic shock

Fluid resuscitation is the cornerstone of managing septic shock[13]. Patients with septic shock generally have a mean arterial pressure (MAP) below 65 mmHg, which indicates that the amount of tissue perfusion to vital organs is reduced[14]. Rapid initiation of fluid therapy is considered the first line of management of septic shock. 2021 Surviving Sepsis Campaign (SSC) guidelines recommend an initial bolus of 30 ml/kg of crystalloids within 3 h of detecting septic shock[15]. Balanced crystalloids—Plasma-lyte, Ringer's lactate—are preferred over 0.9% normal saline, as normal saline has been associated with hyperchloremia, metabolic acidosis, and acute kidney injury. Moreover, albumin administration is suggested in patients who have received large amounts of crystalloids[16]. Hemodynamic stability must be ensured, but aggressive fluid administration cannot be applied to all patients with septic shock. Fluid overload is linked to worse long-term outcomes, especially in patients with comorbidities such as cardiac dysfunction and chronic kidney disease. A retrospective study was conducted on 275 patients with a mean age of 65 years, in France to see the impact of fluid overload (FO) on SOFA score kinetics from day 0 to 5 following the detection of septic shock, FO was found to be an independent determinant of SOFA, and patients with FO have more prolonged organ failure. Patients without FO had better outcomes[16]. Recent studies have recommended that a more restrictive fluid strategy may be more beneficial than a liberal strategy[16].

Fluid therapy should be individualized and based on the patient's response to fluids and monitored using clinical parameters to help guide clinical decisions The ANDROMEDA-SHOCK randomized clinical trial compared two different resuscitation strategies for septic shock: One targeted peripheral perfusion status (CRT), while the other focused on normalizing serum lactate levels. No significant difference was shown in reducing all causes of 28-day mortality[17]. Fluid therapy in septic shock is complex. Thus the need for restoring hemodynamic stability should be balanced with the potential risks of fluid overload, but progress is being made in reducing mortality among patients with septic shock. Promising studies are underway to develop better assessments of responsiveness to fluid therapy and de-resuscitation (REDUCE) protocols

Table 3

APACHE II Scoring system B: age points.

Age (years)	Score
≤44	0
45–54	2
55–G4	3
G5–74	5
≥75	G

Age; in years.
APACHE II = [A] APS + [B] Age points + [C] CHP.
APACHE II, acute physiology and chronic health evaluation II.

Table 4

APACHE II scoring system C: chronic health points.

Chronic organ insufficiency	Score
Non-operative	5
Emergent-operative	5
Elective-operative	2

APACHE II = [A] APS + [B] Age points + [C] CHP.
APACHE II, acute physiology and chronic health evaluation II.

which aim to achieve negative fluid balance (input is less than output) in patients with fluid overload[18,19].

Tseng *et al.*[20]. conducted a network meta-analysis to compare the safety and effectiveness of various fluids. There were found to be fifty-eight trials (n = 26 351 patients). Seven different kinds of fluids were assessed. Compared to saline and low molecular weight hydroxyethyl starch (L-HES), balanced crystalloids and albumin improved survival, reduced acute kidney injury, and required fewer blood transfusion volumes in patients undergoing surgery or experiencing sepsis. Balanced crystalloids in sepsis patients significantly decreased mortality [odds ratio (OR) 0.84; 95% CI 0.74–0.95], acute renal damage (OR 0.80; 95% CI 0.65–0.99), and saline (OR 0.81; 95% CI 0.69–0.95). Nevertheless, out of all the fluid types, they needed the largest volume for resuscitation, particularly for trauma patients. Saline and L-HES were found to have a decreased death rate in traumatic brain injury patients when compared to albumin and balanced crystalloids. Of these, saline was found to be considerably better than iso-oncotic albumin (OR 0.55; 95% CI 0.35–0.87). Thus, this meta-analysis demonstrated that balanced crystalloids and albumin reduced mortality in sepsis patients more than L-HES and saline did; in patients with traumatic brain injury, on the other hand, saline or L-HES performed better than iso-oncotic albumin or balanced crystalloids.

Antibiotic therapy in septic shock

As it has been well established in the literature, antibiotics are essential for the management of sepsis and play a key role in eradicating the invading agent and halting and reversing the progression of the disease.

Numerous guidelines suggest antibiotic therapy should be started within one hour of presentation, using broad-spectrum antibiotics, until the results of the blood culture performed on a sample taken before antibiotic administration reveal the causative agent upon which targeted antibiotic therapy should be used[21]. however, there remains conflating evidence regarding both the timing and appropriateness of antibiotic therapy. Regarding timing, a study found a drop in survival rate of 7.6% for every hour delay before starting therapy[21]. However, there remains a concern that such a practice could lead to increased antibiotic resistance as more research should be done in this field[22]. In regards to appropriateness and administration, it should be known that antibiotics are not without side effects[23] and indiscriminate use could lead to increasing the risk of side effects on the patient as well as increasing resistance[22].

Having said the above, a critical question remains unanswered: What specific single or multiple antibiotics should be used as empiric treatment? No one can sufficiently address this question. However, a series of recommendations issued by the SSc aimed to help clinicians tackle this issue. Broad-spectrum carbapenems (e.g. meropenem, imipenem/cilastatin), extended-range penicillin/β-lactamase inhibitors (e.g. piperacillin/tazobactam, ticarcillin/clavulanate), and third or higher-generation cephalosporins constitute a suitable choice for a single-drug empiric treatment[24]. The SSC, however, recommends adopting a multi-drug approach as multi-drug resistant pathogen variants could be the causative agent[21]. Examples of this method include supplementing the empiric treatment with a Gram-negative agent to further increase the coverage and adding an anti-MRSA agent like vancomycin in case of MRSA infection suspicion[21]. When treating sepsis and septic shock, the use of antibiotics is necessary, but it is important to use them carefully and consider reducing or stopping the therapy as soon as the clinical condition permits.

The effect of immediate (0–1 h after commencement) versus early (1–3 h after onset) antibiotics on mortality in patients with severe sepsis or septic shock was examined in a meta-analysis about antibiotic scheduling[25]. According to this meta-analysis, patients receiving antibiotics in the immediate vs early phases did not vary in mortality (OR 1.09; 95% CI 0.98–1.21). This was based on a pooling of data from 33 863 participants. Higher mortality was observed in the immediate vs early periods (OR 1.29; 95% CI 1.09–1.53) in an analysis of severe sepsis studies involving 8595 participants.

Despite its unclear efficacy, the prolonged β-lactam infusion method has become the conventional treatment for septic shock or sepsis[26]. To evaluate the impact of continuous versus intermittent β-lactam antibiotic infusion on outcomes in patients with sepsis or septic shock, Kondo *et al.*[26]. conducted a meta-analysis. According to the study's pooled analysis, the longer infusion group's hospital mortality did not drop [risk ratio (RR) 0.69 (95% CI 0.47–1.02)]. In the prolonged infusion group, there was a substantial improvement in both the clinical cure and the attainment of the target plasma concentration [RR 0.40 (95% CI 0.21–0.75) and RR 0.84 (95% CI 0.73–0.97), respectively]. However, there were no appreciable variations between the groups in terms of adverse events or the prevalence of bacteria resistant to antibiotics [RR 1.01 (95% CI 0.95–1.06) and RR 0.53 (95% CI 0.10–2.83), respectively].

Vasopressor therapy in septic shock

New guidelines released in 2020 state that loss of normal sympathetic vascular tone causes tissue hypoperfusion and persistent hypotension even after adequate fluid resuscitation. This leads to vasodilation, neurohormonal imbalances, myocardial depression, micro-circulatory dysregulation, and mitochondrial dysfunction. Vasopressors and inotropes increase cardiac output and arterial pressure, respectively, to restore oxygen delivery to tissues[27].

The ideal blood pressure to aim for during resuscitation is the mean arterial pressure. The first target that is advised is 65 mmHg. Individuals with end-stage liver disease, elderly individuals, and those with decreased systolic function may tolerate a lower target more easily than those with a higher objective of 80–85 mm Hg[27].

Our understanding of the autoregulation of blood flow in the vascular beds of major organs—the brain, heart, and kidneys—forms the basis for these recommendations. Tissue perfusion reduces linearly as blood pressure drops below a crucial level. The aim can then be tailored based on global and regional perfusion as measured with urine output, mental state, or lactate clearance.

That crucial threshold can differ between organ systems and individuals. The possible risks of titrating vasopressors to meet targets for mean arterial pressure should be weighed against the possibility of arrhythmias, cardiovascular events, and ischemia[27].

Norepinephrine is the first-line vasopressor

To date, there aren't many extensive multicenter randomized controlled trials that have examined the best initial and supplemental vasoactive drugs for septic shock. Compared to dopamine, norepinephrine has been demonstrated to improve survival and have a decreased risk of arrhythmia. However, two systematic reviews did not find any difference between norepinephrine and epinephrine, vasopressin, terlipressin, or phenylephrine in terms of clinical outcomes or mortality[27].

The SSC guidelines strongly recommend norepinephrine as the preferred vasopressor for achieving the target mean arterial pressure, even though the evidence supporting it is only of moderate quality. This is because there isn't enough evidence to support other agents as first-line therapy for septic shock[28,29].

Adding a second vasopressor or inotrope

Another sympathomimetic drug such as vasopressin or epinephrine can be used to either achieve target mean arterial pressures or decrease the norepinephrine requirement. A second vasopressor is routinely added when norepinephrine doses exceed 40 or 50 μg/min[27].

Vasopressin. Septic shock involves relative vasopressin deficiency. Adding vasopressin as a replacement hormone has been shown to have a sparing effect on norepinephrine, resulting in a lower dose needed. A randomized controlled trial comparing vasopressin plus norepinephrine vs. vasopressin monotherapy failed to show any survival benefit or reduction in kidney failure. Evidence supporting the use of vasopressin over norepinephrine as a first-line agent remains limited, but vasopressin remains the preferred adjunct with norepinephrine[30,31].

The SSC guidelines suggest epinephrine as a second-line vasopressor. Strong beta- and alpha-adrenergic activity raises cardiac output and vasomotor tone, which raises mean arterial pressure. The substantial risk of tachycardia, arrhythmia, and temporary lactic acidosis limits the use of epinephrine[32].

Due to its tendency to cause tachyarrhythmia and considerably decrease outcomes in this situation, dopamine usage is avoided in sepsis[33,34].

Although there is little information regarding the safety and effectiveness of phenylephrine, a pure alpha-adrenergic agonist, it is frequently used in septic shock. Using phenylephrine in septic shock was linked to higher mortality, according to a multicenter cohort study carried out by Vail *et al.*[35]. amid a norepinephrine shortage. Until further research is done to confirm its advantages, phenylephrine should only be used in cases of septic shock worsened by severe tachyarrhythmia or as a refractory vasodilatory shock adjunct[28].

Recently, the vasopressor angiotensin II was licensed for the treatment of septic shock. Vasoconstriction is encouraged by activating angiotensin type 1a and 1b receptors, which raise intracellular calcium in smooth muscle. There is a recent experiment that provides clinical data on its use, although it only shows that adding angiotensin II to high-dose vasopressor-treated patients with refractory vasodilatory shock reduced blood pressure[36]. Its safety is still the subject of limited research, and its exact function in refractory shock treatment algorithms is still unknown.

Patients with inadequate cardiac output following fluid resuscitation because of combined shock or sepsis-induced cardiomyopathy may need to be given inotropic medications. Although there is little information available regarding the best inotropic drug for septic shock, dobutamine and adrenaline are the most often utilized[37,38]. When septic shock was treated with norepinephrine + dobutamine versus epinephrine, there was no difference in shock duration, adverse effects, or mortality[38]. Studies have been done on milrinone and levosimendan, which are not authorized in the US, but the evidence for their superiority over dobutamine is weak[39]. It is recommended to measure alterations in cardiac output, central venous oxygen saturation, or other tissue perfusion indices to track the response to inotrope administration.

Corticosteroid therapy in septic shock

Corticosteroids contribute to regulating the immune response and reducing the generation of inflammatory agents. This is particularly significant in the context of septic shock, a condition of vasodilation resulting from excessive release of pro-inflammatory cytokines. The physiologic rationale for administering corticosteroids in septic shock is grounded in their anti-inflammatory properties, which help in improving blood vessels' responsiveness to vasoconstrictors[40].

The SSC 2016 guidelines discouraged the use of IV hydrocortisone if hemodynamic stability was able to be restored with fluids and vasopressors. The 2021 guidelines, however, recommend using low-dose IV corticosteroids for adult septic shock patients who need vasopressors, this change is based on moderate quality evidence[41].

Many clinical trials have been conducted to evaluate the role of corticosteroids in septic shock. Two prior randomized controlled trials; ADRENAL and APROCCHSS[42] investigated corticosteroid treatment in septic shock. In the ADRENAL trial where 3800 patients were assigned to receive hydrocortisone (200 mg/day for 7 days or placebo), the results indicated that hydrocortisone had no significant impact on 90-day mortality. However, it did reduce the duration of vasopressor use. In contrast, the APROCCHSS trial[42] (with 1241 patients assigned to receive hydrocortisone 200 mg/day plus fludrocortisone 50 mcg/day or placebo) showed a significant improvement in reducing mortality in the group treated with corticosteroids[43].

This discrepancy may be attributed to variations in the inclusion and exclusion criteria used in these studies, plus the addition of fludrocortisone in the APROCCHSS study[42]. To investigate further a post hoc analysis was conducted on the ADRENAL trial to assess the effects of hydrocortisone in patients who met the criteria for septic shock according to the APROCCHSS inclusion criteria. The analysis revealed that hydrocortisone did not reduce 90-day mortality in patients with septic shock, regardless of the inclusion criteria used. Nonetheless, hydrocortisone did lead to a more rapid resolution of shock, along with a reduced need for mechanical ventilation and a shorter duration of stay in the ICU[43]. Regarding the effectiveness of combining fludrocortisone with hydrocortisone compared to hydrocortisone alone, there is insufficient clinical data available, and the literature remains uncertain[44].

However, a recent cohort study in the United States, conducted on 88275 patients with septic shock who were receiving norepinephrine, aimed to compare the effectiveness of Fludrocortisone and Hydrocortisone versus hydrocortisone Alone. The results indicated that the combination of fludrocortisone with hydrocortisone outperformed the use of hydrocortisone[45].

The timing of initiation of corticosteroid therapy plays a vital role in determining the outcomes. A retrospective cohort study was conducted on adult patients, with 844 patients included: 553 in the early group -less than 12 h after initiation of vasopressors- and 291 in the late group -more than 12 h after initiation of vasopressors-. The results have shown a significant improvement in both short-term and long-term mortality, as well as a reduction in hospital stays[46].

The optimal dosage and duration of corticosteroid therapy remain areas of ongoing research; lower doses, such as stress-dose hydrocortisone, are often recommended to avoid potential adverse effects associated with higher doses. These potential side effects include hyperglycemia and secondary infections[44]. Administering corticosteroids as a continuous infusion to minimize hyperglycemia or implementing a taper to prevent rebound hypotension does not seem to offer any significant benefits[47].

Corticosteroids in septic shock are not a one-size-fits-all solution. Individualized dosing and ongoing evaluation of clinical response are found to be critical components of using corticosteroids in septic shock.

According to a meta-analysis by Liang *et al.*[48], corticosteroid therapy for sepsis increased the incidence of adverse events like hyperglycemia and hypernatremia, as well as days without a vasopressor and ventilation-free period. It also increased the incidence of shock reversal on days 7 and 28. Corticosteroids have been linked to a lower chance of shock resolution time and hospital stay duration. Nevertheless, a lower risk of corticosteroids on the duration of ICU stay and unfavorable outcomes, like superinfection and gastric hemorrhage, were not mentioned in this study. It was also difficult to determine the adverse events in the trials that qualified, which could have led to a poor evidence rank.

According to recent guidelines, the only side effects associated with corticosteroids in trials were hyperglycemia, hypernatremia, and hypertension; superinfections did not rise[27,49]. Current guidelines recommend hydrocortisone 200 mg per day intravenously as a continuous drip or 50 mg bolus in 4 divided doses for at least 3 days if corticosteroids are used in septic shock. This recommendation is based on a systematic review that found a longer course of low-dose steroids is associated with a lower mortality rate[50]. Since bigger randomized clinical trials did not include a tapering method and showed no difference in shock recurrence, there is no clear consensus on whether steroids should be tapered or if abrupt withdrawal is suitable[42,43]. Most of the time, stopping vasopressors is followed by stopping steroids[27].

Recommendations

Lac, PCT, SOFA score (Table 1), APACHE II score (Table 2) were more accurate in predicting the short-term prognosis of septic shock than a single variable, while the Sequential Organ Failure Assessment, or SOFA score (Table 1), has been extensively validated as a tool for evaluating the acute morbidity of critical illness.

Rapid initiation of fluid therapy is considered the first line of management of septic shock, 2021 SSC guidelines recommend an initial bolus of 30 ml/kg of crystalloids within three hours of detecting septic shock and balanced crystalloids (Plasma-lyte, Ringer's lactate) are preferred over 0.9% normal saline. However, aggressive fluid administration cannot be applied to all patients with septic shock, especially in patients with comorbidities such as cardiac dysfunction and chronic kidney disease. Fluid therapy should be individualized and based on the patient's response to fluids and monitored using clinical parameters to help guide clinical decisions, on another hand Vasopressors are Often needed to maintain mean arterial blood pressure alongside fluid therapy starting with Norepinephrine as a first-line vasopressor.

The SSC Campaign in 2021 guidelines recommend using low-dose IV corticosteroids for adult septic shock patients who need vasopressors; a combination of fludrocortisone with hydrocortisone outperformed the use of hydrocortisone alone. However, a stress-dose hydrocortisone is often recommended to avoid potential adverse effects associated with higher doses.

Antibiotic therapy should be started within one hour of presentation, using broad-spectrum antibiotics, until the results of the blood culture, Broad-spectrum carbapenems, extended-range penicillin/β-lactamase inhibitors, and third or higher-generation cephalosporins constitute a suitable choice for a single-drug empiric treatment while a multi-drug approach is recommended when a multi-drug resistant pathogen variant could be the causative agent.

Although we gathered the recommendations from recent studies, and guidelines with high evidence (e.g. meta-analyses with large sample sizes), there exist some limitations such as the low or absence of evidence regarding the dosing recommendations and timing of some drugs. In addition, cases differ from each other depending on many confounders such as comorbidities and drugs. Moreover, some differences exist between different guidelines.

Conclusion

In terms of diagnostics, the SOFA score remains the standard, which also alongside other mentioned parameters is used to determine the severity of septic shock. Once diagnosed, IV fluid replacement should be commenced, preferably with balanced crystalloids, to regain hemodynamic stability while being careful of causing fluid overdose. Concurrently, a blood culture is to be collected, and broad-spectrum antibiotics should be administered. Vasopressors, ideally norepinephrine, should be used if the patient fails to maintain the target MAP value despite proper fluid therapy. Patients who receive vasopressors are recommended to have low-dose corticosteroids administered, according to the moderate quality evidence of recent guidelines.

Ethical approval

As the article is a secondary research, it does not need any IRb as per Jordanian guidelines.

Consent

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Author contribution

Conceptualization: M.A.N. and M.A.J. Investigation: J.S. and H.T. Methodology: S.A. Project administration: M.A.J. Supervision: J.S. and M.A.J. Writing—original draft: M.A.N., Y.A., H.S., M.A., and A.M.A. Writing—review and editing: M.A.J., S.A., and J.S.

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