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A Recent Development in Sepsis Management: A Literature Review

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1. ABSTRACT

Sepsis is when the host's abnormal immune response leads to multi-organ failure. It is also one of the most common causes of death worldwide. The pathogenesis of sepsis is very complex; in sepsis, the body's first response to the external antigen is phagocytosis by the macrophage, which activates the immune system, resulting in a cytokine storm due to immune dysfunction. Mitochondrial damage is seen, which causes decreased ATP production, and an increase in free radical production leads to oxidative stress and alters cellular metabolism. These reactions eventually result in cell death, endoplasmic reticulum stress, and blood coagulability changes. Management involves early diagnosis of sepsis, initial empirical treatment with broad-spectrum antibiotics, and fluid resuscitation to maintain the mean arterial blood pressure necessary for restoring normal tissue perfusion with the usage of inotropic

agents when initial fluid resuscitation is unable to meet the tissue requirements. This review aims to provide information about the updates in managing sepsis.

Keywords: Continuous Renal Replacement Therapy (CRRT); Intermittent Hemodialysis (IHD); Sequential Organ Failure Assessment (SOFA); Systemic Inflammatory Response Syndrome (SIRS); Sepsis

2. INTRODUCTION AND BACKGROUND

Sepsis is regarded as a medical emergency, so early diagnosis is important, which can be done with tools like systemic inflammatory response syndrome criteria and a quick version of sequential organ failure assessment for triaging. After the diagnosis of sepsis, broad-spectrum antimicrobial therapy with fluid administration should be started as soon as possible. The empirical antimicrobial treatment should be selected based on patient demographics, like endemic diseases, common environmental pathogens, and local infection sites. After the antibiotic culture sensitivity is done, treatment should be changed from a broad to a narrow spectrum. Even biomarkers like procalcitonin can help guide the proper usage of antibiotics.[1] Long-term use of broad-spectrum antibiotics results in antimicrobial resistance and pseudomembrane colitis due to clostridium difficulty and may even lead to death. Therefore, a de-escalation strategy is necessary to prevent the adverse effects of broad-spectrum medicines.[2]

Fluid resuscitation is required to correct the decrease in blood volume. However, many times the patient becomes unresponsive to the fluid therapy after a few phases of therapy, leading to decreased oxygen perfusion to the organ and worsening the patient's condition. Along with fluid therapy, vasoactive agents like norepinephrine cause vasoconstriction and maintain arterial blood pressure.[3] Now new therapeutic approaches are coming up that aim at balancing the immune dysfunction and abnormal systemic inflammatory responses by the body. Anticoagulants are also used to prevent abnormal thrombus formation or any other further complications.[4] Therefore, low doses of corticosteroids are also used for their anti-inflammatory property and thus eventually reducing Mortality.[5]

2.1 Sepsis Recent Definitions

Initial sepsis definitions were established at a consensus conference in 1991, with a subsequent update in 2001 that merely expanded the list of sepsis symptoms to reflect clinical bedside experience.

Initial categorization of sepsis included

- Sepsis (systemic inflammatory response syndrome [SIRS] and infection suspicion),
- Severe sepsis (sepsis and organ dysfunction), and
- Septic shock (sepsis with low blood pressure despite adequate fluid resuscitation).

The Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) convened a 19-member international task force to revise the current sepsis and septic shock definitions. This group developed the new Sepsis-3 definitions using an expert Delphi consensus procedure. They distanced themselves from the correlation between infection and inflammation and abandoned SIRS criteria entirely.

Sepsis is a life-threatening illness with host response dysregulation to infection and organ dysfunction.[6] The clinical criteria of sepsis consist of infection, whether suspected or confirmed. Moreover, an acute increase of at least two Sequential Organ Failure Assessment points (SOFA) represents organ dysfunction. Septic shock is a subtype of sepsis in which the underlying circulatory and cellular/metabolic abnormalities are severe enough to increase Mortality drastically. Even with sufficient rehydration measures, vasopressor therapy is required to elevate mean arterial pressure to 65 mm Hg and lactate level to more than two mmol/L (18 mg/dL).[7]

According to the new septic shock definition, the mortality rate for septic shock was found to be 40%, which is higher if compared to the 10% rate mortality rate associated with the new definition of sepsis.

A systematic review identified 44 studies reporting septic shock outcomes, and the Delphi process identified hypotension, lactate concentration, and vasopressor therapy as clinical diagnostic criteria for septic shock patients.[8]

In risk-modified differentiation, the group necessitated therapy with vasopressors to sustain mean arterial pressure of 65 mm Hg or greater and a lactate concentration > two mmol/L (18 mg/dL) following rehydration management (group 1) had a greater mortality rate (42.3%). Patients who met the Sepsis-2 criteria for septic shock (group 2) with hypotension, necessitating vasopressors, but without lactate elevation also had a mortality rate of 30.1%. The new sepsis-3 definition for septic shock was developed after these analysis results.

The trial design in septic shock was significantly implicated by the greater mortality rate related to the new septic shock definition. It may limit future septic shock trials to use a smaller sample size. Incorporating lactate in the Sepsis-3 septic shock definition, particularly lactate measurement above two mmol/L) used in the report remain controversial.[9]

Mortality.[10] Patients meeting the Sepsis-3 definition of septic shock had a higher mortality rate than patients meeting the Sepsis-2 definition (38.9% vs. 34.0%), but only lactate values of 6 mmol/L were associated with increased ICU. Others have expressed concern that lactate is a sensitive but non-specific indicator of cellular or metabolic stress as opposed to "shock."

2.2 Volume Resuscitation

Sepsis can cause rapid tissue hypoperfusion and circulatory shock, which can be fatal.[11] Initial management of sepsis involves assessment and management of the airway and breathing; for adequate oxygen delivery to tissues, oxygen saturation of greater than 93% must be maintained. Simultaneously with resuscitative efforts, the initial history, examination, and evaluation should be conducted urgently. Collection of basic blood tests and relevant cultures and administer the first dose of antibiotics as soon as possible. Guidelines from the surviving sepsis

campaign recommend measuring serum lactate at admission as a marker of tissue hypoperfusion.[12] Most patients with septic shock should have a jugular or subclavian Central Venous Catheter (CVC) inserted for rapid administration of fluids, initiation of medications, hemodynamic monitoring, and possibly central venous oxygen saturation monitoring (SCvO2). A randomized, single-center study concluded that early resuscitation aimed at achieving and maintaining specific physiological variables within the first six hours of septic shock improved survival compared to standard care.[13]

The following targets are included in the study. The Central Venous Pressure (CVP) of 8-12 mmHg, a mean arterial pressure (MAP) equal to or greater than 65 mmHg, a urine output equivalent to or greater than 0.5 mL/kg/hour, and a SCvO2 greater than 70%. However, if the SCvO2 was less than 70% despite adequate volume resuscitation, the interventions of PRBC transfusion to attain hemoglobin more significant than 10g/dl and dobutamine infusions were sequentially implemented to improve global oxygen delivery. Nonetheless, this study has been criticized for a variety of reasons:[14]

1. The primary resuscitation goal (SCvO2 70%) has been questioned because, unlike this study, other studies indicated a minor proportion of septic patients with low admittance SCvO2.
2. Using SCvO2 as a proxy for the mixed venous oxygen saturation (SVO2) is not widely accepted.
3. A normal SVO2 (0.70%) seldom indicates adequate oxygen delivery, as tissue extraction and oxygen utilization are also abnormal in septic patients, which may result in a near-normal or even supranormal SVO2 despite the presence of active tissue hypoxia.
4. The rationale for red blood cell transfusion has been called into question because the improvement in the oxygen-carrying capacity of transfused blood may be suboptimal due to several factors associated with its shelf life.

Additionally, the risks associated with the transfusion may outweigh any benefits. In this study, dobutamine was administered without documentation or measurement of cardiac function. Despite evidence of similar results from multiple subsequent observational studies compared to their historical controls, this approach still needs to be proven in a large multicenter Randomized Controlled Trial (RCT). Currently, three such trials are being conducted in North America, the United Kingdom, and Australia, with results anticipated in 2013.

Recently, a randomized trial of 300 patients with severe sepsis evaluated serum lactate clearance as a substitute for SCvO2 and found similar outcomes when resuscitation was targeted to a lactate clearance of 10% or greater or a SCvO2 of 70% or greater.[15] No universally applicable CVP and MAP cutoffs can be endorsed for all patients with sepsis. CVP can be significantly altered by right ventricular compliance and tricuspid valve pathology, along with intrathoracic, intra-abdominal, and pericardial pressures; therefore, it does not always accurately reflect the actual right ventricular preload in a given patient.

Furthermore, no CVP value can predict whether a patient's cardiac output will increase in response to a fluid challenge. Despite this, the Surviving Sepsis Campaign recommends a CVP between 8 and 12, believing that most patients will not experience significant intravascular volume depletion at these levels.[12] Similarly, although the Surviving Sepsis Campaign recommends a MAP greater than 65 mmHg, the pressure-flow Relationship varies significantly between individuals and organs within the same individual.[12] For instance, end-stage liver disease patients may have adequate perfusion at a lower MAP. In contrast, a patient with chronic hypertension may require a significantly higher MAP for adequate perfusion. Therefore, it is essential to recognize that guideline-recommended cutoffs serve only as benchmarks during resuscitation and should be used with clinical judgment for all septic patients.

As a resuscitation fluid, there has been controversy regarding the superiority of colloids over crystalloids. There is no consensus on the type and quantity of fluids to administer to septic patients during resuscitation. The usage of eighter 4% albumin or 0.9% saline for fluid resuscitation in a large multicenter RCT of ICU. Patients resulted in similar 28-day outcomes.[16] However, a planned subgroup analysis revealed albumin to be harmful to patients with traumatic brain injury, whereas albumin appeared beneficial for patients with sepsis. Albumin was also favored in a subsequent meta-analysis of studies on fluids for fluid resuscitation in sepsis.[17] In a recent multicenter trial involving 800 patients with sepsis, hydroxyl ethyl starch was found to be related to a greater incidence of acute kidney injury and an increased risk of death within 90 days compared to crystalloids of comparable volume.[18] A trial using pentastarch demonstrated a similar signal.[19] Therefore, it is advisable to prevent using hydroxyl ethyl starch for resuscitation in sepsis patients.

Using fluid boluses outside the ICU or modern emergency department is even more controversial. A large trial in Africa compared fluid boluses (20-40mL/kg body weight) with saline or albumin solution to no fluid boluses in 3,141 children with sepsis, most of whom had malaria.[20] Twenty children with severe hypotension or decompensated shock were given either albumin or 0.9% saline boluses. In the albumin-bolus, saline-bolus, and control groups, the mortality rate at 48 hours was 10.6%, 10.5%, and 7.3%, respectively (P 0.001). In the three groups, Mortality at four weeks was 12.2%, 12.0%, and 8.7%, respectively (P140004). However, the mortality rate was comparable in patients with or without decompensated shock, and It is plausible that the increment in the mortality rate observed in the cases that received fluid boluses was due to multiple factors, including increased capillary permeability, augmented interstitial edema (pulmonary and cerebral edema), with a higher rate of the fluid boluses associated adverse effects. The fluid resuscitation must be tailored to the patient's physiology, and frequent assessments of response with the tolerance to fluid boluses are required to balance the under-resuscitation and fluid overload. Dynamic preload indices, such as pulse pressure or stroke volume variation, can better predict fluid responsiveness than static measures, such as CVP.[21] Once dynamic indices indicate that a patient is unresponsive to fluid administration, it is prudent to discontinue fluid administration, as both the magnitude and duration of fluid overload have been associated with increased Mortality.[22,23]

2.3 Early and Appropriate Antibiotics

Identifying the source of sepsis and administering the correct antibiotics are crucial steps in stabilizing septic shock. An observational study by Kumar and colleagues established the association of an effective antimicrobial therapy initiation within an hour of documented hypotension, with increased survival to hospital discharge, in septic shock patients.[24] Every lateness in administering antimicrobials over the next six hours was associated with an average 7.6% decrease in survival. The starting time for the antimicrobial therapy was the strongest predictor of outcome in this study's multivariate analysis. Timing appears to have an effect on all organism types, including gram-positive, gram-negative, and candida species.

Similarly, numerous studies have revealed that incorrect initial empiric antibiotic treatment in septic shock is associated with decreased survival.[25]

An antimicrobial administration strategy of "hit early, hit hard, and hit broad" is essential for increasing survival in patients with septic shock. Therefore, in the course of empiric antibiotic therapy prescription, the initial choice must be adequately wide to cover the organisms in question.[26] The clinician should correctly detect the cause(s) of sepsis, predict the possible pathogens, and recognize the local resistance patterns with the pharmacokinetic and pharmacodynamic principles of the antibiotics used to select the optimal initial antimicrobial treatment. Because the volume of distribution, metabolism, and clearance of antimicrobial drugs are unpredictably altered in septic shock, therapeutic drug-level monitoring must be used to titrate the following maintenance doses for the highest efficacy.

Antibiotics are frequently ineffective when administered alone to patients with undrained abscesses or necrotic tissues. Cultures should be obtained for subsequent antimicrobial adjustment. As indicated, early identification of the infection's source, drainage, and surgical debridement should also be performed.

2.4 Organ Aid in a Septic Case

Following initial stabilization and the initiation of antimicrobial therapy, the following treatment objective is organ support. The targets of subsequent supportive critical care are maintaining and supporting organ function while attenuating and minimizing organ injury expansion.

2.4.1 Lung-Protective Strategies

In patients with acute lung injury (ALI), the overdistension and recurrent opening and shutting of alveoli can worsen lung injury and increase Mortality. The airway must be secured when it gets compromised, and mechanical ventilation is initiated. There has been a demonstrated survival benefit by low tidal volume ventilation (6 mL/kg of predicted body weight) and maintenance of airway pressures of less than 30 cm of water (to prevent the overdistension of the alveoli).[27] The sufficient maintenance of positive end-expiratory pressure ventilation prevents alveolar collapse and improves oxygenation, but it does not affect the survival of patients with acute lung injury

(ALI). In patients with ALI who are not in shock (i.e., with no evidence of organs low perfusion), a supportive fluid plan (CVP, four mmHg) achieved with fluid restriction with or without diuresis improves functions of the lungs. It decreases the length of mechanical ventilation and intensive care compared to a liberal fluid strategy without increasing non-pulmonary organ failures (CVP 10-14 mmHg).[28,29]

2.5 Management of Shock

In patients with septic shock who do not respond to fluid resuscitation alone or are hypotensive despite preload optimization, Vassopressor therapy was recommended. As previously discussed, although Surviving Sepsis guidelines recommend a MAP target of more than 65 mmHg, this must be individualized based on patient pathophysiology.[12] Different organs have different pressure-flow characteristics, with the kidneys being the most sensitive to pressure changes during shock. In a recent prospective observational study of 217 patients with sustained hypotension, Badin and colleagues found that a greater MAP (72-82 mmHg) was shown to reduce the risk of AKI at 72 hours in patients with septic shock and AKI at 6 hours.[30] However, due to the study's observational nature, it is impossible to determine if increasing MAP benefits kidney function or if patients capable of achieving a higher MAP have a lower risk of severe AKI. Norepinephrine is recommended as the initial agent. A recent randomized controlled trial found no difference in survival between shock patients treated with dopamine as the initial vasopressor and those treated with norepinephrine.[31] In this study, however, the use of dopamine was associated with increased adverse events. If cardiac contractility is impaired, it is also recommended to administer an inotropic agent. In such patients, adding dobutamine as an inotrope to norepinephrine or using epinephrine as both a vasopressor and an inotrope are equally acceptable options.[32]

Vasopressin, a potent vasoconstrictor hormone, is initially released in the circulation of patients with septic shock. Due to the depletion of stored vasopressin, vasopressin levels drop precipitously to an unsafely low level.[33] Patients in septic shock who are already receiving at least 5 mg/minute of norepinephrine may benefit from adding low-dose vasopressin (0.01-0.03 units/minute). According to a recent study, adding vasopressin to norepinephrine did not significantly alter the 28- or 90-day mortality rates.[34] In a subsequent analysis of this study, the same authors discovered that the interaction between low-dose vasopressin and corticosteroids decreased Mortality and organ dysfunction.[35]

2.6 Steroids' value in Septic Shock

One should suspect corticosteroid deficiency due to a critical illness in hypotensive patients who react weakly to fluids and vasopressors therapies. Cortisol production is suboptimal in critical illnesses, including septic shock. Additionally, tissue corticosteroid resistance creates a condition of relative adrenal insufficiency known as corticosteroid insufficiency related to critical illness.[36]

Previous research utilizing significant corticosteroid doses in septic shock did not demonstrate a survival benefit.[37] Recently, two large, randomized trials assessed the efficacy of low-dose corticosteroids in septic shock patients.[38]

Within 8 hours of the onset of septic shock, patients in the first study were randomly assigned to receive a placebo or hydrocortisone (50 mg intravenously every 6 hours) plus fludrocortisone (50 mg enterally once a day).[39] All 39 patients underwent a high-dose adrenocorticotrophin hormone (250 mg) stimulation test and were classified as responders (increase in serum cortisol of 0.9 mg/dL from baseline) or non-responders (increase in serum cortisol of 0.9 mg/dL from baseline). There was a significant decrease in Mortality with hydrocortisone in the subgroup of non-responders but not in the group of responders. The withdrawal rates of vasopressors were higher and more rapid in the hydrocortisone group. In a comprehensive study, Corticosteroids Therapy of Septic Shock (CORTICUS) trial assigned hydrocortisone (50mg) or placebo intravenously every 6 hours for five days with a subsequent tapering regimen to 499 patients with septic shock.[40]

40 Similar to the previous study, non-responders and responders were distinguished using high-dose adrenocorticotrophin hormone stimulation. Hydrocortisone did not enhance survival in the total patient population or either subgroup.

The discrepancy between the results of these two studies is likely attributable to the fact that the CORTICUS study evaluated fewer critically ill patients and enrolled patients up to 72 hours after the onset of shock, making the treatment less effective after such a delay. However, the shock was reversed more rapidly in the group of patients administered hydrocortisone. Based on these findings, it is a typical practice to begin norepinephrine infusion for vasodilatory shock in septic patients and to take into consideration initiating hydrocortisone or low-dose vasopressin in patients with refractory shock. If there is still no response, we will administer both drugs after 4 to 8 hours.

2.7 Renal function maintenance in Septic Shock

As previously discussed, in severe sepsis and septic shock patients, AKI is highly prevalent and significantly increases morbidity and Mortality.[41] The only available strategies to prevent AKI are intravascular volume replacement, appropriate resuscitation, satisfactory perfusion pressure maintenance, and refraining from exposure to nephrotoxic agents.[41] No single MAP value is recommended as adequate for the prevention of AKI. Individual needs must be considered when adjusting MAP, taking into account the patient's blood pressure at rest and clinical/laboratory evidence of end-organ perfusion. Low-dose dopamine does not reduce the incidence of AKI or Mortality associated with AKI; therefore, it should not be used to protect the kidneys.[42,43]

Even though loop diuretics are commonly used in oliguric AKI, the studies revealed that they did not reduce the demand for Renal Replacement Therapy (RRT), the time invested in RRT, or the risk of death.[44] There is some evidence of an increase in Mortality.[45] Therefore, diuretics should be used for only fluid overload prevention and management rather than the treatment of AKI.[46] The conventional practice of prescribing diuretics to patients with oliguria is unjustified and potentially harmful. However, it is appropriate to use diuretics and other measures (RRT) to prevent volume overload. Once established, severe AKI will require RRT to support kidney function. RRT is essential for clinical indications such as life-threatening fluid overload, hyperkalemia, and metabolic acidemia

unresponsive to medical therapy in AKI patients whose care has not been restricted by advance directives for end-of-life care. The clinical benefit of early initiation of RRT is unproven, and there are no standard cutoff limits for the level of azotemia at which we can initiate it.[47] Early initiation of RRT may permit stabilization of drug dosing, but randomized trials have not evaluated this hypothesis. Changes in glomerular function and volume of distribution are additional factors to consider in septic patients complicated with AKI, as they can make antibiotic management exceptionally challenging.

Indefinite Advantage has been identified between Intermittent Hemodialysis (IHD) and Continuous Renal Replacement Therapy (CRRT) for patients, including those with sepsis, who can receive either modality.[48] The Cochrane Collaboration analyzed 15 RCTs involving 1,550 AKI patients and concluded the hospital and ICU. Mortality, hospitalization span, and renal recovery (discharge from hospital without dialysis) were not disparate for critically ill AKI patients treated with CRRT versus IHD.[49] However, most trials excluded patients with hypotension, and the high crossover rate between treatment modalities makes it challenging to interpret these studies. The Kidney Disease Improving Global Outcomes AKI guideline recommends continuous and intermittent RRT as complementary therapies, recognizing that local practice varies but that most centers use IHD and CRRT for AKI patients.[50] However, CRRT is desired over standard IHD in hemodynamically unstable and AKI patients with acute brain injury or other reasons for elevated intracranial pressure or diffuse brain edema.[50]

2.8 Glycemic Control

Stress hyperglycemia results from an increase in hormones that induce hyperglycemia, such as cortisol, catecholamines, glucagon, and growth hormone, as well as an increase in insulin resistance. Recent evidence indicates that uncontrolled hyperglycemia is linked to poor outcomes in critically ill patients.[51] Subsequently, several studies have evaluated the optimal glucose level in critically ill patients that positively influence their prognosis.[52,53] Randomized trials involving medical, septic, and mixed medical and surgical patients have conclusively demonstrated that glucose values of less than 180 mg/dL have comparable outcomes to glucose levels between 80 and 100 mg/dL.[53,54] In all of these studies, tighter glucose control was associated with a much higher incidence of hypoglycemia, which may have nullified any beneficial effect of the glycemic control. Therefore, the majority of experts advise reducing blood glucose to less than 180 mg/dL in all septic patients while avoiding excessively "tight" control. Avoiding hypoglycemia and large fluctuations in glucose levels also positively affects the outcome.

2.9 Adjunctive Therapies

Several novel approaches have been evaluated to modulate the inflammatory response and alter outcomes in patients with septic shock. Although activated protein C has been thoroughly assessed, other substances are still in the experimental phase.

2.9.1 Recombinant Activated Protein C

A recent Randomized Controlled Trial (RCT.) PROWESS-SHOCK enrolled 1,696 patients with vasopressor-dependent septic shock and randomly assigned them to get recombinant activated protein C (rhAPC) or a placebo. The study revealed that rhAPC did not impact Mortality, encouraging the drug's removal from the market.[55]

2.10 Intravenous Immunoglobulin

It was hypothesized that polyclonal intravenous immunoglobulin (IVIG) would benefit sepsis patients by binding endotoxin; therefore, their use in sepsis patients was evaluated. The results of studies are contradictory, with one randomized controlled trial demonstrating no benefit to Mortality and some meta-analyses studies displaying a benefit from IVIG therapy. However, all meta-analyses exhibited substantial heterogeneity and failed to demonstrate a use when analyzing only high-quality trials. IVIG cannot be routinely recommended for treating severe sepsis and septic shock patients based on the available evidence.[56-58]

2.11 Blood Purification Extracorporeal

Several researchers have attempted extracorporeal blood purification techniques to nonspecifically remove inflammatory mediators and attenuate the entire inflammatory process in response to this understanding. Targeting a specific molecule in the inflammatory cascade was unlikely to attenuate this response or affect outcomes. This result was due to the complexity and redundancy of the inflammatory response.

Overall, increasing the intensity of RRT in patients with AKI beyond conventionally recommended levels (e.g., ultrafiltrate rates of 20-25 mL/kg/hour for CRRT) does not improve survival or kidney recovery, and subgroup analyses did not reveal any benefit for patients with sepsis. Small trials conducted on patients with sepsis and no AKI found no benefit for renal intensity CRRT compared to standard care. In addition, they were unable to demonstrate the modulation of inflammatory mediators. These findings led to the development of High-Volume Hemofiltration (HVHF) with flow rates exceeding 60 mL/kg/hour. Although small initial trials with HVHF in septic patients demonstrated an improvement in hemodynamics and other physiological parameters, these results have yet to be confirmed by subsequent large randomized trials.[59-62]

Hemoperfusion has been significantly more effective in removing inflammatory mediators, and animal studies indicate that this technique improves survival and reduces organ damage. A specialized form of hemoperfusion employs polymyxin-bound fibers to eliminate endotoxins. Sixty-four patients with severe sepsis or septic shock who underwent emergency surgery for intra-abdominal infection were randomized to receive either standard therapy or standard therapy, plus two sessions of poly-myxine B hemoperfusion. The trial was ended prematurely.[63-67]

Polymyxin B hemoperfusion appeared to decrease Mortality at 28 days, but the results were inconclusive. Ongoing blood purification trials, including HVHF and hemoperfusion, should enhance our understanding of these therapies and their potential role in sepsis management. However, these therapies are currently only used in clinical trials or as "rescue" therapy.

3. DISCUSSION

The definition and management of sepsis have evolved with a better understanding of the pathophysiological changes that occur in this multisystem disorder. Over the past three decades, high-level randomized control trials have provided high-quality, evidence-based strategies that continue to emphasize early recognition and resuscitation, source control, prompt and broad antibiotic therapy, and organ support as essential in improving outcomes. Differentiating sepsis from conditions that resemble it remains a challenge, especially in the pre-ICU phases of care. Improved sepsis definitions have allowed better risk stratification, which may have potential implications in clinical trial enrollment. In addition, ventilation with low tidal volumes to minimize alveoli overdistension has been shown to improve survival. As it pertains to sepsis management, fluid resuscitation has historically been assessed using specific physiological parameters such as central venous pressure, mean arterial blood pressure, urine output, and SCvO2 to determine the adequacy of perfusion. However, these endpoints should not be viewed as substitutes for clinical judgment, and resuscitation should be individualized based on patient-specific comorbidities, preferably with more dynamic and objective indices. The timing of antibiotics administration must be early and broad enough to cover all likely pathogens for the suspected source of infection.

Vasopressors like norepinephrine should be initiated if hypotension persists after adequate fluid resuscitation, and corticosteroids should be considered in patients with refractory shock. The limitation of renal injury *via* timely fluid resuscitation, avoidance of nephrotoxic agents, judicious use of diuretics, and initiation of renal replacement therapy has been shown to improve patient outcomes. In addition, hyperglycemia (especially >180 mg/dl) and tight blood control have consistently negatively impacted sepsis outcomes. Despite the enormous strides made in the management of sepsis, knowledge gaps still exist, particularly in the pre-ICU and ICU. Phases of care need to be addressed further to reduce the observed high hospital mortality rate of sepsis. For instance, more evidence is required to guide resuscitation's timing, dosage, and choice of intravenous fluids. Future trials need to enroll risk-stratified cohorts similarly to allow for better interpretation of trial results across different patient populations. In addition, more well-designed research studies are needed on the utility of adjunctive therapies such as intravenous immunoglobulin, corticosteroids, and blood purification techniques in sepsis management. Finally, as we strive for precision-based, patient-centered care, there is also a need for the identification and validation of novel biomarkers that could not only aid early sepsis diagnosis but could potentially also have a prognostic value by informing the early use of adjunct therapies in patients at risk of organ dysfunction and Mortality.

4. CONCLUSIONS

The fundamental principles of sepsis management are early recognition, early and titrated fluid resuscitation, adequate source control, prompt and extensive antibiotic therapy, and organ support. It remains challenging to distinguish sepsis from conditions that resemble it. Specific physiological parameters such as CVP, MAP, urine output, and SCvO2 are frequently recommended to evaluate the adequacy of perfusion. However, these endpoints are not meant to replace clinical judgment. Antibiotics should be administered promptly and must be broad enough

to cover all potential pathogens for the suspected infection source. If hypotension persists after adequate fluid replacement, norepinephrine should be administered. Patients with refractory shock should be considered for treatment with vasopressors and corticosteroids. Dopamine has no function as a kidney-protective agent. While providing organ support, specific organ-specific objectives must be met. Before using adjunctive therapies such as hemofiltration, hemoperfusion, or IVIG routinely in patients with septic shock, additional research is required.

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