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SEPTIC SHOCK: A NARRATIVE REVIEW OF MANAGEMENT AND THERAPY

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Abstract: Goal: To present the main concepts of septic shock, focusing on management and therapy. **Literature review:** Septic shock is defined as a condition of persistent hypotension that requires vasopressors to maintain blood pressure greater than or equal to 65 mmHg, together with the presence of a serum lactate level greater than 18 mg/dL or 2 mmol/L even with volume replacement. The Modified Early Warning Score (MEWS) is one of the tools used, upon admission to the emergency room and during hospitalization in the ward, to recognize patients at risk of clinical deterioration. Once sepsis and septic shock are suspected, it is necessary to immediately begin patient management. Priorities include identifying and controlling the source of infection, as well as treating it with appropriate antibiotics and continually reassessing the patient and their vital signs. **Final considerations:** Early detection is essential for the rapid initiation of treatment. Management involves collecting cultures and lactate, prompt administration of broad-spectrum antimicrobials, infusion of fluids, and use of vasopressor substances. Patients recovering from septic shock may face long-term challenges, including persistent organ dysfunction and complications.

Keywords: "Septic Shock", "Sepsis" and "Therapeutics"

INTRODUCTION

Sepsis is an organic dysfunction caused by a dysregulated host response to infection (LAZZARIN T, et al., 2023). This organ dysfunction continues to be one of the significant causes of morbidity and mortality in critically ill patients worldwide, despite the use of broad-spectrum antibiotics, advances in intensive care units (ICU), resuscitation strategies and protocols (RUSLAM MA, et al., 2021).

Septic shock represents a major global

health challenge, being responsible for 6 million deaths annually. In-hospital mortality for sepsis is greater than 10%, while septic shock exceeds 40% (ALLEN JM, et al., 2019). Septic shock consensuses prior to 2016 defined it as a cardiovascular dysfunction associated with an infection and unexplained by other causes (SHANKAR-HARI M, et al., 2016). Currently, it is defined as sustained hypotension despite adequate fluid resuscitation, requiring vasoactive drugs to maintain mean arterial pressure greater than 65 mmHg and serum lactate level greater than 2 mmol/L (SINGER M, et al., 2016).

The signs and symptoms of sepsis are nonspecific and usually mimic several other diseases, being characterized as a syndrome. As there is no "gold standard" test for diagnosis, the ideal thing to do is to continuously evaluate the patient to investigate other possible diagnoses (EVANS L, et al., 2021). The most common symptoms observed in the first 6 hours in patients suffering from septic shock are increased heart rate, respiratory rate above 20 breaths per minute (IRPM), leukopenia or leukocytosis, peripheral oxygen saturation (SpO2) below 90%, body temperature greater than 38.3°C or less than 36°C (BILRO MM, et al., 2021).

Adequate management of sepsis and septic shock encompasses the prompt and accurate identification of the condition, followed by prompt and adequate administration of antibiotics, as well as the immediate reversal of hypoperfusion (ALLEN JM, et al., 2019). The 1-hour package recommended by the Sepsis Survival Campaign (CSS) consists of adopting measures to be taken, including measuring the lactate level, obtaining cultures before starting antibiotic therapy (as long as the start of medication is not delayed), administer broad-spectrum antibiotics, intravenous fluid and vasopressors if necessary (LOHN A, et al., 2021).

It is certain that this condition is associated with an unrestrained systemic inflammatory response that is caused by a generalized infection. Estimates indicate that millions of people are affected annually and with a mortality rate that varies between a third and a sixth of affected individuals (EVANS L, et al., 2021). Furthermore, the incidence of this disorder is increasing, mainly influenced by an aging population with multiple comorbidities, increased use of immunosuppressive therapy and high-risk interventions (KEELEY A, et al., 2017).

The present study aims to present the main concepts of septic shock, focusing on its management and therapy.

METHODS

A narrative review of the literature was carried out based on 28 articles that varied between 2001 and 2023, in the months of July to September 2023. The articles covered the English, Portuguese and Spanish languages and were taken from the PubMed and Scielo databases. The descriptors used were "Septic Shock", "Sepsis" and "Therapeutics".

LITERATURE REVIEW

Septic shock is defined as a condition of persistent hypotension requiring vasopressors to maintain a blood pressure greater than or equal to 65 mmHg, together with the presence of a serum lactate level greater than 18 mg/dL or 2 mmol/L even with replacement. of adequate volume (SINGER M, et al., 2016). It is considered the main cause of death among critically ill patients, being responsible for more than 6 million deaths annually, representing a hospital mortality rate of more than 40% (ALLEN JM, et al., 2019). However, the use of tools for early detection and clinical deterioration allows the development of proactive and reactive strategies, providing quality and safety (LIU AC, et al., 2020).

There are numerous microbiological causative agents, with bacteria such as Staphylococcus aureus, Streptococcus pneumoniae or Neisseria meningitidis being most commonly found. Regarding viruses, adenovirus and cytomegalovirus are common, followed by parasites, notably Toxoplasma gondii. Finally, fungi such as Candida sp can be infectious agents that trigger septic shock (GARZA M, et al., 2018).

For early screening, the National Early Warning Score (NEWS) is a score that can be applied when suspected sepsis, consisting of indicators of respiratory rate, oxygen saturation, temperature, systolic blood pressure, heart rate, level of consciousness and use of auxiliary oxygen, as well as a specific assessment for patients with hypercapnic respiratory failure, such as, for example, Chronic Obstructive Pulmonary Disease (COPD). Your final score is calculated by values assigned to each of the items, ranging between 0 (best prognosis) and 23 (worst prognosis). However, this scale is not recommended for evaluating individuals aged < 16 years and pregnant women, and is calculated based on physiological parameters and the use of auxiliary oxygen (OLIVEIRA APA, et al., 2020).

The Modified Early Warning Score (MEWS) is one of the tools used, especially upon admission to the emergency room and during hospitalization in the ward, to recognize patients at risk of clinical deterioration (DUNDAR ZD, et al., 2016). The MEWS is a score composed of five physiological parameters: systolic blood pressure, heart rate, respiratory rate, axillary temperature and level of consciousness. Any value outside the range considered normal, it receives a score between 1 and 3, with the total score varying between 0 and 14 (SUBBE CP, et al., 2001; TAVARES RC, et al., 2008). International literature demonstrates that NEWS has superior results when compared to MEWS (JARVIS SW, et al., 2015).

In addition to the scores already mentioned, the SOFA score was developed, which is calculated on patients upon admission to the ICU and every 24 hours. It consists of a score from 0 to 4 for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems. The higher the score, the greater the worsening of organic dysfunction (EVANS L, et al., 2021). Although SOFA is a robust mortality stratification tool, it is difficult to calculate and requires laboratory values that are not readily available for rapid triage of patients outside the ICU (SINGER M, et al., 2016).

Therefore, it was necessary to improve it for screening measures, called quick-SOFA (qSOFA or rapid assessment of sequential organ failure). It is calculated for patients outside the ICU, with a worse prognosis and unfavorable evolution, who have 2 or more of the following criteria: Glasgow score less than 13, systolic blood pressure < 100 or respiratory rate (RR) 22 (SINGER M, et al, 2016). SOFA and quick-SOFA are less recommended according to the 2021 International Surviving Sepsis Campaign guidelines and must not be used in isolation (EVANS L, et al., 2021).

In the management of sepsis, patients can be grouped into two groups. The first is probable sepsis. In this case, they are patients with organic dysfunction and suspected or confirmed focus, with or without hypotension. In these individuals, the sepsis protocol must be opened and maintained, with the 1-hour package completed. On the other hand, there are patients defined as possible sepsis. In this group, patients presented with systemic inflammatory response syndrome (SIRS) and the absence of infectious risk factors. Therefore, follow-up within 3 hours must be ensured to assess the presence of associated infection or not (configuring sepsis). If the suspicion remains, the administration of antibiotics is

suggested (EVANS L, et al., 2021).

Once sepsis and septic shock are suspected, it is necessary to immediately begin patient management. Priorities include identifying and controlling the source of infection, as well as treating it with appropriate antibiotics and continually reassessing the patient and their vital signs. Treatment must be initiated pending additional diagnostic studies. Blood cultures must be collected as early as possible and urine cultures must be collected if a urinary tract infection is suspected. Imaging exams must be aimed at investigating the infectious focus (THOMPSON K, et al., 2019).

Broad-spectrum antimicrobial therapy, intravenously, within the first hour and after culture collection, must be considered a priority for patients with probable shock or sepsis (i.e., when there are risk factors such as immunosuppression, severe comorbidities, or age). advanced). In the absence of these risk factors, sepsis is determined to be only possible, therefore, it is suggested that an investigation be carried out looking for infectious and non-infectious causes of shock, as long as it does not last longer than three hours; If this rapid investigation is not possible, antimicrobial therapy must be started as soon as possible (EVANS L, et al., 2021). In situations where there is a low probability of infection and there are no signs of shock, continuous observation of the patient and monitoring of signs of sepsis is carried out, without empirical administration of antimicrobials (OCZKOWSKI S, et al., 2022).

Furthermore, the choice of initial therapy must be based on the patient's clinical situation, considering the primary focus, presence of immunodeficiencies, history of previous infections, recent use of antimicrobials and local microbiology. In situations where infection by resistant germs is suggested, such as, for example, infection by methicillin-resistant Staphylococcus aureus (MRSA), identified by the local microbiota or by the patient's clinical situation, treatment with combined therapy must be chosen, with two or three drugs. Furthermore, if you are at high risk of MRSA infection, empirical antimicrobials that have coverage for this microorganism must be included (EVANS L, et al., 2021).

After identifying the pathogen, it is essential that there is a daily assessment of the reduction in the spectrum of the antimicrobial, making it more specific, so that there is no unnecessary exposure to broad-spectrum antimicrobials. Studies revealed that this de-escalation, when possible, improved patient outcomes, in addition to reducing hospital stay, costs and patient antimicrobial resistance (EVANS L, et al., 2021; OCZKOWSKI S, et al., 2022).

Regarding the suspension of the medication, it is necessary to analyze parameters such as the resolution of fever, leukocytosis, or through the use of biomarkers that allow evaluating the evolution of the patient in a serious condition, such as, for example, procalcitonin (PEPPER DJ, et al., 2019). Procalcitonin is a pro-inflammatory biomarker that has shown promise in individualizing the use of antibiotics. Evidence from a recent Cochrane review shows that this biomarker can be used to guide the initiation and duration of antibiotic therapy, resulting in lower risks of mortality, inadequate antibiotic consumption and side effects related to antibiotic therapy (EVANS L, et al, 2021).

Patients with arterial hypotension or tissue hypoperfusion (serum lactate greater than or equal to 36 mg/dL) must preferably receive at least 1000 ml of Ringer lactate serum during initial volume expansion (RHODES A, et al, 2017). If necessary, administer vasopressors together, aiming for an initial MAP of 65 mmHg. In this context, norepinephrine is usually the first choice, followed by vasopressin or epinephrine (RUSLAN M, et al., 2021;

DELLINGER RP, et al., 2008). Randomized trials comparing the use of dopamine versus norepinephrine as the initial agent showed higher incidences of tachyarrhythmias and worse mortality with dopamine (DE BACKER DP, et al., 2010).

Noradrenaline is preferable due to its effects of improving oxygenation, organ perfusion and less arrhythmic risks. Its main effect is to increase organ perfusion, controlling vascular dilation. The use of norepinephrine resulted in significant reductions (36% and 45%) in the incidence of arrhythmias compared with other vasopressors and placebo. This is due to the beta-1 effect of norepinephrine, which increases cardiac contractility and coronary blood flow. Therefore, norepinephrine is considered the gold standard in the treatment of septic shock (RUSLAM, M.A. et al, 2021).

Currently, clinical practice guidelines have no preference between the use of balanced crystalloid salt solutions (BSSs) or normal saline (NS). However, comparison studies between the solutions demonstrated lower mortality in patients using BSS (25.2% vs 29.4%), especially in patients with a previous history of renal replacement therapy (ALLEN JM, et al., 2019).

Therefore, the 1-hour package was created, which is a set of interventions to be carried out within the first hour after the recognition of sepsis or septic shock that aim to improve the results obtained and reduce the mortality rate of these patients. The package consists of the assessment of the arterial and laboratory serum lactate level (blood count, creatinine, arterial blood gas analysis, bilirubin, coagulogram), the collection of two blood cultures from different sites, the administration of broad-spectrum antimicrobials, volume resuscitation and vasopressors if necessary. Furthermore, analyze the need for supplemental oxygen and monitor capillary blood glucose every 1-2 hours. It is worth mentioning that lactate is a crucial biomarker for the diagnosis and progression of septic shock, and is also the best predictor of in-hospital mortality in septic shock (BILRO MM, et al., 2021).

After analyzing the results of the tests carried out in the 1-hour package, the 6-hour reassessment begins, with the aim of reassessing the patient's volume status and tissue perfusion. A priori, the need to continue fluid resuscitation is analyzed through the presence of signs of poor peripheral perfusion (analyzed by vital signs, cold extremities, diuresis, capillary refill time greater than 3 seconds or presence of livedo) and/ or arterial hypotension. If necessary, administer a new volume expansion of 500-1000 ml of crystalloids (EVANS L, et al., 2021).

Erythrocyte transfusion in the management of septic shock is based on improving oxygen supply and cellular respiration, as low hemoglobin levels are related to higher mortality. On the other hand, there is evidence that erythrocyte transfusions are disadvantageous in patients without comorbidities and with stable pathology. Furthermore, guiding erythrocyte transfusions targeting metabolic or physiological variables rather than hemoglobin (Hb) levels demonstrates benefit in clinical practice (ARANGO-GRANADOS MC, et al., 2021).

In case of mild respiratory failure, supplemental oxygen can be used through a nasal catheter or face mask. However, if there is severe hypoxemia, orotracheal intubation with mechanical ventilation is necessary. Corticosteroids must only be used in indicated cases, such as when there is a strong suspicion of adrenal insufficiency or in patients who require increasing doses of noradrenaline (above 0.25-0.5 micrograms/kilogram/ minute), which may constitute refractory shock. It is in this same scenario of refractory shock that the application of vasopressin

in conjunction with noradrenaline must be considered (EVANS L, et al., 2021).

The transition from the Intensive Care Unit (ICU) to the general floor and hospital discharge is a vulnerable moment for patients, as it presents a risk of loss of information between sectors. For these reasons, there is already evidence that monitoring by ICU professionals after patient transfer can reduce in-hospital mortality and the risk of readmission to the sector. Furthermore, follow-up with a professional after discharge is a step in the recovery process, due to the high risk of readmission (approximately 40%), which has been associated with higher mortality and discharge to palliative care (EVANS L, et al., 2021).

When analyzing the factors that establish a worse prognosis, it is possible to highlight the involvement of the origin in the central nervous system, whether disseminated or associated with intestinal ischemia; longer duration of hemodynamic impairment (MAP<65 mmHg or SvO2<70%) with greater need for vasopressor therapy; increased lactate concentration and/or decreased clearance; and greater severity of the chaos, due to the number of failing organs and the evolution of their dysfunction (DUBIN A, et al., 2017).

Patients who are discharged after septic shock or sepsis have a high risk of clinical deterioration in the following months and years due to the possibility of organ dysfunction that may be persistent (PRESCOTT HC, et al., 2014; KRUMHOLZ HM, et al, 2013). Around one-sixth of patients experience severe persistent physical disability or cognitive impairment in long-term follow-up. In this context, around 50% require hospitalization within 3-6 months after discharge from the intensive care unit (IWASHYNA TJ, 2010; PRESCOTT HC, et al., 2015). Furthermore, a higher risk of aspiration pneumonia, neurological damage and metabolic disorders (hyper and hypoglycemia) was identified (HOPKINS RO, et al., 2016).

FINAL CONSIDERATIONS

Septic shock is a critical condition with high mortality. Its early detection is essential for the rapid initiation of treatment, thus avoiding an increase in negative outcomes. The identification of sepsis can be carried out using scores such as MEWS and NEWS. Management involves collecting cultures and lactate, prompt administration of broad-spectrum antimicrobials, infusion of fluids, and use of vasopressor substances. Frequent reassessment of the patient is essential to assess the response to treatment. Patients recovering from septic shock may face long-term challenges, including persistent organ dysfunction and complications. Therefore, a comprehensive and continuous approach is essential to ensure effective management of this clinical condition.

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