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Optimal Timing of Vasopressin Addition in Patients with Septic Shock Refractory to Norepinephrine Infusion: A Systematic Review

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ABSTRACT

Aim: To determine the optimal timing for adding vasopressin as a secondary vasopressor in adult patients with refractory septic shock treated with norepinephrine.

Methods: A systematic review with a quantitative approach using the "evidence-based nursing" methodology, with a PIO-structured question, Boolean operators "AND" and "OR" were used, and words in documentary language in DeCS and MeSH. The search included the following databases: PubMed, SciELO, and EBSCO. Inclusion criteria: Articles from systematic reviews with meta-analyses and systematic reviews, no more than 10 years old, open-access research, excluding duplicates and those that present a risk of bias.

Results: 35 articles were recovered, of which the following were eliminated: 5.71% (2) due to duplication, 11.47% (4) due to the period of time outside the established one, 5.71% (2) for not having access to the primary document, 100% (9) for not being related to the subject of study, the Scottish Intercollegiate Guidelines Network scale was used to evaluate the quality of the evidence in this study, subsequently 25.71% (9) were excluded for not complying with the quality assessment or presenting biases, in the end 25.71% (9) articles were obtained included in the systematic review after applying all the criteria.

Conclusion: The combination of vasopressors improves hemodynamic stability and reduces adverse effects, particularly when norepinephrine doses reach 0.25 and 0.5 mcg/kg/min. In these cases, vasopressin reduces the dose of catecholamines needed to achieve adequate mean arterial pressure and improve organ perfusion.

Keywords: Vasopressor Therapy; Vasopressin; Septic Shock; Refractory Septic Shock; Intensive Care Unit; Recommended Dose; Norepinephrine; Mean Arterial Pressure

Abbreviations: SIRS: Systemic Inflammatory Response Syndrome; ICU: Intensive Care Unit; MAP: Mean Arterial Pressure; DeCS: Health Sciences Descriptors; MeSH: Medical Subject Headings; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SIGN: Scottish Intercollegiate Guidelines Network; FLC: Critical Reading Sheets

Introduction

Sepsis is a complex clinical condition caused by a systemic inflammatory response to infection, leading to tissue damage and organ dysfunction, with a high risk of mortality. The diagnosis of sepsis requires the presence of SIRS (Systemic Inflammatory Response Syndrome) along with evidence or suspicion of infection. Clinically, sepsis is identified when the patient presents signs such as fever (>38.3°C or <36°C), tachycardia (>90 bpm), increased respiratory rate (>20 rpm or pCO2 <32 mmHg), and abnormalities in the white blood cell count (leukocytosis >12,000 or leukopenia <4,000 cells/μL, or >10% of immature forms) [1]. In this context, nurses must be able to quickly identify the signs and symptoms of sepsis, such as fever, tachycardia, hypotension, tachypnea, and altered mental status. These early signs allow for timely treatment to be started, avoiding complications that can put the patient's life at risk [2], nurses have the responsibility to follow strict treatment protocols based on guidelines such as the Surviving Sepsis Campaign and the Clinical Practice Guideline for Septic Shock in Adults. These guidelines indicate that, after the administration of fluids and vasopressors, if blood pressure does not stabilize and signs of hypoperfusion persist, the addition of vasopressin should be considered [3], A decrease in lactate levels and an improvement in peripheral perfusion by monitoring skin temperature, pulse oximetry and capillary refill are usually positive indicators that the treatment is working [4]. In clinical practice, the initial dose of norepinephrine is set between 0.05 and 0.1 mcg/kg/min, adjusted according to the patient's hemodynamic response.

This dose can be gradually increased to a maximum of approximately 1-2 mcg/kg/min, depending on the need to maintain a MAP of at least 65 mmHg. Continuous intravenous infusion is the preferred method to ensure precise dose control and an adequate response to treatment [5], Vasopressin is used at a dose of 0.04 U/min, this dose does not significantly affect blood pressure in normal individuals, but in patients with sepsis it can increase it up to 50 mmHg. [6], Vasopressin is crucial in refractory septic shock by acting on V1 receptors of the vascular endothelium, promoting vasoconstriction through the activation of phospholipase C and the release of calcium [7]. The use of low doses of vasopressin is presented as a promising alternative to conventional therapy based on high doses of catecholamines according to González O, et al. [8], the use of vasopressin as a vasopressor agent is widely debated, highlighting its potent effect in reducing the need for catecholamines (Norepinephrine), according to Bruhn C [9], it is noted that the optimal time to add a second vasopressor is still uncertain. Although it is suggested that a norepinephrine dose of 0.25-0.5 mcg/kg/min could be the threshold to consider the addition of vasopressin.

Materials and Methods

This research is quantitative and based on a systematic review using the Evidence-Based Nursing (EBN) method. The research question was developed following the PIO (Problem, Intervention, Outcome) model (Table 1). Once the clinical research question was formulated, a detailed protocol was established to plan the process of searching for scientific evidence, and a table with words in everyday language was created. These components were converted into an indexed language for document searching, using both the Health Sciences Descriptors (DeCS) [10] and the Medical Subject Headings (MeSH) [11] in Spanish, English, and Portuguese. (Tables 2 & 3).

Table 1: PIO question and its components.

(P) Population	(i) intervention	(O) Results
Patients with refractory septic shock admitted to the Adult Intensive Care Unit.	Optimal timing for vasopressin addition	Stabilization of blood pressure.

Note: Own elaboration Spain V, Ortega S. 2024.

Table 2: Terms for DeCS (Descriptors in Health Sciences).

Concept	Spanish	Portuguese	English
Vasopressor therapy	Vasopressor therapy	Vasopressor therapy	Vasopressor Therapy
Vasopressin	Vasopressin	Vasopressin	Vasopressin
Septic shock	Septic shock	Septic shock	Septic Shock
Refractory septic shock	Refractory septic shock	Refractory septic shock	Refractory Septic Shock
Intensive care unit	Intensive care unit	Intensive care unit	Intensive Care Units
Recommended dose	Recommended dose	Recommended dose	Recommended Dose
Norepinephrine	Norepinephrine	Norepinephrine	Norepinephrine
Mean Arterial Pressure	Mean Arterial Pressure	Average Blood Pressure	Mean Blood Pressure

Note: Own elaboration Spain V, Ortega S. 2024.

Table 3: Terms for MeSH (Medical Subject Headings).

Concept	Spanish	Portuguese	English
Vasopressor agents	Vasopressor agents	Vasopressor agents	Vasoconstrictor Agents
Vasopressors	Vasopressors	Vasopressors	Vasopressors
Combination therapy	Combination therapy	Combination therapy	Combination Drug Therapy
Treatment resistance	Treatment resistance	Treatment resistance	Treatment Failure
Hemodynamics	Hemodynamics	Hemodynamics	Hemodynamics
Intensive care	Intensive care	Intensive care	Critical Care
Shock management	Shock management	Crash management	Shock Management
Mean Arterial Pressure	Mean Arterial Pressure	Average Blood Pressure	Mean Blood Pressure

Note: Own elaboration Spain V, Ortega S. 2024.

Search Protocol

An advanced search was carried out using Boolean operators and specific limiters. These strategies allowed us to reduce the number of evidence aligned with our objective. Limiters such as publication period (articles published between 2014 and 2024), type of study (quantitative studies), and language (English, Spanish, and Portuguese) were applied. For information retrieval, the strategy established that the reviewers filtered according to previously established criteria, which were mainly open access documents. These were stored in a search log. The initial selection was made by reading the title and summary of the evidence located and from there, those related to the research question were selected and discarded, thus allowing us to have better control. The information sources reviewed included PubMed (29 articles), SciELO (4 articles), and EBSCO (2 articles). Search strings designed to maximize the sensitivity and precision of the results were used, such as: (refractory septic shock AND vasopressin AND noradrenaline), (noradrenaline AND septic shock AND vasopressin), (refractory septic shock AND vasopressin), and (noradrenaline AND septic shock). These strategies allowed us to retrieve a significant volume of relevant scientific articles, facilitating access to quality information pertinent to the study. According to the previously defined inclusion criteria, a total of 35 articles were selected for detailed analysis (Table 4). These articles were filtered based on their relevance, methodological quality, and relationship to the research topic. These articles were retrieved using key terms related to vasopressin management in patients with refractory septic shock, applying advanced search strategies that ensure comprehensive coverage of the available literature [12-45].

Table 4: Eligible articles and search string used.

Origin	Year	Design	Qualification	Author	Search string
PubMed	2023	Systematic review	2023 Update on Sepsis and Septic Shock in Adult Patients: Management in the Emergency Department [12].	Guarino M, Perna B, Cesaro AE, Maritati M, Spampinato MD, Contini C, De Giorgio R.	refractory septic shock and vasopressin and noradrenaline
PubMed	2020	Systematic review	Vasopressors for the treatment of refractory septic shock [13].	Meresse Z, Medam S, Mathieu C, Duclos G, Vincent JL, Leone M. Vasopressors to treat refractory septic shock. Minerva Anesthesiol	refractory septic shock and vasopressin and noradrenaline
PubMed	2023	Randomized controlled trial	Early adjuvant treatment with methylene blue in patients with septic shock: a randomized controlled trial [14].	Ibarra-Estrada M, Kattan E, Aguilera-González P, Sandoval-Plascencia L, Rico-Jauregui U, Gómez-Partida CA, Ortiz-Macías IX, López-Pulgarín JA, Chávez-Peña Q, Mijangos-Méndez JC, Aguirre-Avalos G, Hernández G	refractory septic shock and vasopressin and noradrenaline
PubMed	2020	Systematic review	Vasopressors in septic shock: which ones, when and how much? [15]	Shi R, Hamzaoui O, De Vita N, Monnet X, Teboul JL	refractory septic shock and vasopressin and noradrenaline
PubMed	2023	Prospective observational study	Vasopressin Loading Study for Refractory Septic Shock (VALOR): A Prospective Observational Study [16]	Nakamura K, Nakano H, Ikechi D, Mochizuki M, Takahashi Y, Koyama Y, Hashimoto H, Abe T, Hayakawa M, Yamakawa K	refractory septic shock and vasopressin and noradrenaline
PubMed	2008	Systematic review	Eight unanswered and answered questions about the use of vasopressors in septic shock [17]	Hamzaoui O, Goury A, Teboul JL.	refractory septic shock and vasopressin and noradrenaline

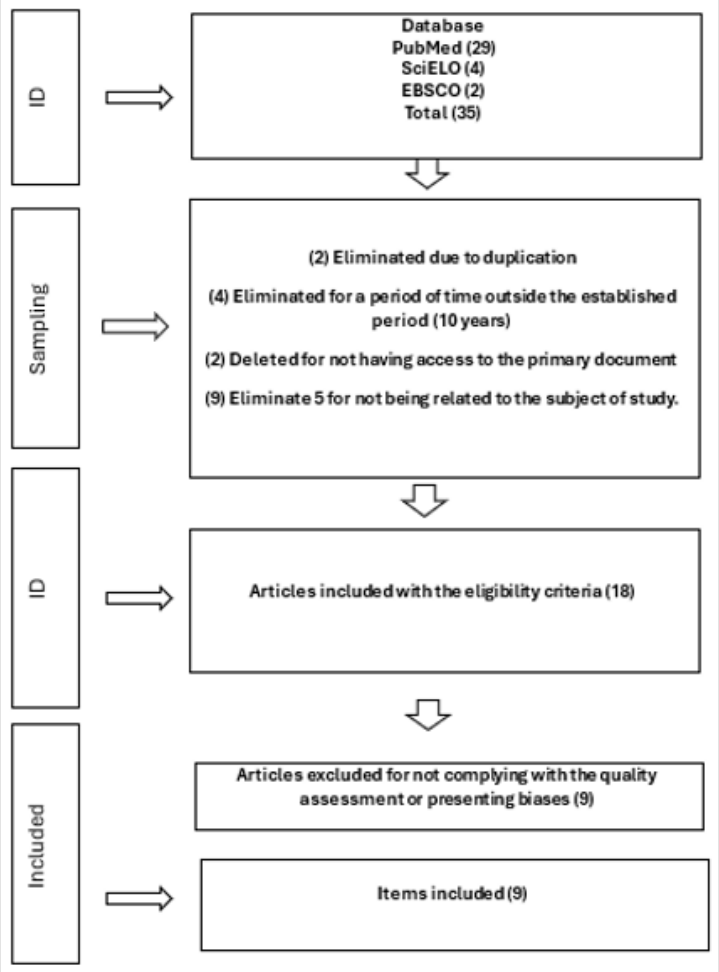
PubMed	2021	Systematic review	Vasopressin loading in refractory septic shock: preliminary analysis of a case series [18]	Nakamura K, Nakano H, Naraba H, Mochizuki M, Takahashi Y, Sonoo T, Hashimoto H, Abe T, Hayakawa M, Yamakawa K	refractory septic shock and vasopressin and noradrenaline
PubMed	2020	Systematic review	Vasopressin for septic shock in a medical-surgical intensive care unit [19]	Patel A, Beauchesne A, Bredenkamp N, McGloin R, Stabler SN, Boyce K.	refractory septic shock and vasopressin and noradrenaline
PubMed	2020	Retrospective cohort study	Vasopressin in combination with norepinephrine in septic shock: a retrospective cohort study from a lower-middle-income country [20]	Raza HA, Arshad A, Ayaz A, Raja MHR, Gauhar F, Khan M, Jamil B	refractory septic shock and vasopressin and noradrenaline
PubMed	2020	Randomized clinical trials	Non-catecholamic vasopressors in the treatment of adult patients with septic shock: evidence from meta-analysis and randomized clinical trial sequential analysis [21]	Zhong L, Ji XW, Wang HL, Zhao GM, Zhou Q, Xie B	refractory septic shock and vasopressin and noradrenaline
PubMed	2023	Retrospective cohort study	EXCHANGE-2: Investigation of the efficacy of supplemental plasma exchange as an adjunctive strategy against septic shock: study protocol for a randomized, prospective, multicenter, open-label, controlled, parallel-group trial [22]	David S, Bode C, Stahl K;	refractory septic shock and vasopressin and noradrenaline
PubMed	2023	Cohorts	Vasopressin loading study for septic shock [23]	Nakamura K, Nakano H, Ikechi D, Mochizuki M, Takahashi Y, Koyama Y, Hashimoto H, Abe T, Hayakawa M, Yamakawa K.	refractory septic shock and vasopressin and noradrenaline
PubMed	2023	Cohorts	Timing of vasopressin initiation in patients with septic shock [24]	Xu J, Cai H, Zheng X.	refractory septic shock and vasopressin and noradrenaline
PubMed	2015	Systematic reviews	Vasopressors for the treatment of septic shock: systematic review and meta-analysis [25]	Avni T, Lador A, Lev S, Leibovici L, Paul M, Grossman A	refractory septic shock AND vasopressin
PubMed	2018	Case series	Use of vasopressin in the treatment of refractory septic shock [26]	Kny KT, Ferreira MAP, Pizzol TDSD	refractory septic shock AND vasopressin
PubMed	2004	Systematic review of the literature	Surviving Sepsis Campaign Guidelines for the Management of Severe Sepsis and Septic Shock [27]	Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM,	Norepinephrine AND Shock Septic
PubMed	2020	systematic review and meta-analysis	Norepinephrine in septic shock: a systematic review and meta-analysis [28]	Ruslan MA, Baharuddin KA, Noor NM, Yazid MB, Noh AYM, Rahman A.	Norepinephrine AND Septic Shock
PubMed	2019	systematic review and meta-analysis	Vasopressin in septic shock: a meta-analysis of individual patient data from randomized controlled trials [29]	Ruslan MA, Baharuddin KA, Noor NM, Yazid MB, Noh AYM, Rahman A.	Norepinephrine AND Shock Septic
PubMed	2022	Systematic review and meta-analysis	Vasopressin versus norepinephrine as a first-line vasopressor in septic shock: a systematic review and meta-analysis [30]	- Sedhai YR, Shrestha DB, Budhathoki P, Memon W, Acharya R, Gaire S, Pokharel N, Maharjan S, Jasaraj R, Sodhi A, Kadariya D, Asija A, Kashiouris MG	Norepinephrine AND Septic Shock
Scielo	2006	Systematic review	Treatment protocol for septic shock in pediatrics [31].	Grela Carolina, Menchaca Amanda, Alberti Marta	Norepinephrine AND septic shock AND vasopressin
Scielo	2024	Systematic review	Septic shock in the intensive care unit. Current approach to treatment [32]	Arriagada S Daniela, Donoso F Alejandro, Cruces R Pablo, Díaz R Franco	Norepinephrine AND septic shock AND vasopressin

Scielo	2021	Descriptive observational	Vasopressor consumption trends in intensive care units in Colombia [33]	Gaviria-Mendoza Andres, Machado-Alba Jorge Enrique, Benitez-Mejia Juan Felipe, Correa-Ruiz Santiago, Restrepo-Lopez Juan Sebastian, Moreno-Gutierrez Paula Andrea	Norepinephrine AND septic shock AND vasopressin
Scielo	2010		Vasopressors and mortality in patients with septic shock in intensive care units [34]	Trujillo Ana Maria, Marquez Ana Maria, Child Mantilla Maria Eugenia, Torres Duenas Diego	Norepinephrine AND septic shock AND vasopressin
PubMed	2022	Systematic review	Efficacy and safety of vasopressin alone or in combination with catecholamines in the treatment of septic shock: a systematic review [35]	Mandal N, Kham NI, Shahid R, Naik SS, Ramphall S, Rijal S, Prakash V, Ekladios H, Mulayamkuzhiyil Saju	Norepinephrine AND Shock Septic
PubMed	2023	Systematic review and meta-analysis	Timing of vasopressor initiation in patients with septic shock: a systematic review [36]	Ye E, Ye H, Wang S, Fang X.	Norepinephrine AND Septic Shock
PubMed	2016	Systematic review	Vasopressors for hypertensive shock [37]	Gamper G, Havel C, Arrich J, Losert H, Pace NL, Müllner M	Norepinephrine AND Shock Septic
PubMed	2020	Systematic review and meta-analysis	Clinical efficacy of vasopressin or its analogues compared with catecholamines alone in patients with septic shock: a systematic review and meta-analysis [38]	Yao RQ, Xia DM, Wang LX, Wu GS, Zhu YB, Zhao HQ, Liu Q	Norepinephrine AND Shock Septic
PubMed	2019	meta-analysis	Effects of norepinephrine and vasopressin discontinuation sequence on the incidence of hypotension in patients with septic shock: a meta-analysis [39]	Duclos G, Baumstarck K, Dünser M, Zieleskiewicz L, Leone	Norepinephrine AND Septic Shock
PubMed	2014	Randomized clinical trial	Protocol for a randomized controlled trial of Vasopressin versus norepinephrine as initial therapy in septic shock (VANISH) [40]	Gordon AC, Mason AJ, Perkins GD, Ashby D, Brett SJ.	refractory septic shock and vasopressin and noradrenaline
EBsco	2018	Prospective trial	Early concomitant therapy with vasopressin and norepinephrine versus initial monotherapy with norepinephrine in septic shock [41]	Hammond DA, Ficek OA, Painter JT, McCain K, Cullen J, Brotherton AL, Kakkera K, Chopra D, Meena N.	refractory septic shock and vasopressin and noradrenaline
EBsco	2019	Systematic review	Effects of norepinephrine and vasopressin discontinuation order in the recovery phase of septic shock: a systematic review and individual patient data meta-analysis [42]	Hammond DA, Sacha GL, Bissell BD, Musallam N, Altshuler D, Flannery AH, Lam SW, Bauer SR.	refractory septic shock and vasopressin and noradrenaline
PubMed	2019	Cohort	Efficacy and safety of early addition of vasopressin to norepinephrine in septic shock [43]	Hammond DA, Cullen J, Painter JT,	refractory septic shock and vasopressin and noradrenaline
PubMed	2019	Cohort	Comparison of initial monotherapy with norepinephrine versus vasopressin for resuscitation in septic shock [44]	Daley MJ, Lat I, Mieure KD, Jennings HR, Hall JB, Kress JP.	refractory septic shock and vasopressin and noradrenaline
PubMed	2016	Randomized clinical trial	Effect of vasopressin versus norepinephrine on renal failure in patients with septic shock [45]	Gordon AC, Mason AJ, Thirunavukkarasu N,	refractory septic shock and vasopressin and noradrenaline

Note: own elaboration Spain V, Ortega S. 2024.

Results

Through an exhaustive review of the literature, a set of studies has been identified that address the topic from diverse perspectives and methodological approaches. For the synthesis, the PRISMA flow diagram was used, this is a tool that helps to visualize the study selection process, from identification to final inclusion, the acronyms of the PRISMA flow are defined by (Preferred, Reporting, Items, for Systematic Reviews and Meta-Analyses). Based on this tool, we proceeded to select our articles of interest following the steps of Identification, Sampling, Eligibility and Inclusion. With a total number of 35 articles. During the sampling, 17 studies were excluded for different reasons: 2 due to duplication, 2 for not having access to the full text, 4 articles because the year of publication was more than 10 years old, and 9 for not being related to the topic of study (Figure 1).



Note: own elaboration Spain V, Ortega S. 2024.
Figure 1: Study selection flowchart 2024.

In total, 18 were eligible, to subsequently go through a critical assessment process (through FLC version 3.0) [46,47] of which 9 were discarded for not complying with the quality evaluation or presenting biases. This process ensures that the evidence used is accurate, up-to-date, and of high quality, meeting the scientific and methodological standards required for informed clinical decision-making. The Scottish Intercollegiate Guidelines Network (SIGN) scale was used to assess the quality of evidence in this study because it offers a structured and rigorous approach to classifying different types of research, such as clinical trials and observational studies (Table 5).

Table 5: Selected articles, degree of recommendation, level of evidence.

Article	Design	Level of evidence	Grade of recommendation	Conclusions
Timing of vasopressor initiation in patients with septic shock [25]	Systematic review and meta-analysis	1++ SIGN	TO	Early initiation of vasopressors (within the first 1–6 hours) in patients with septic shock reduces short-term mortality and improves clinical indicators such as MAP, lactate levels, renal function, and ventilator-free days. Norepinephrine and vasopressin are more effective when administered early, with no significant differences in mortality per hour of delay. No serious adverse effects have been reported with vasopressin, although vasopressors can cause complications such as arrhythmias and tissue damage.
Vasopressin loading in refractory septic shock: preliminary analysis of a case series [18]	Case series	3 SIGN	D	Vasopressin may be effective in patients with refractory septic shock when hypotension persists despite high doses of norepinephrine (>0.2 µg/kg/min). Its use reduces the need for catecholamines, but should be administered based on the patient's clinical response and tolerance to hemodynamic changes. Adverse effects, such as digital and mesenteric ischemia, should be monitored due to the risk of excessive vasoconstriction.
Non-catecholamic vasopressors in the treatment of adult patients with septic shock [21]	Systematic review and meta-analysis	1++ SIGN	TO	The use of vasopressin in combination with norepinephrine in patients with refractory septic shock improves 28-day mortality and several clinical indicators, such as reversal of shock at 6 hours, reduction in heart rate, improvement in renal function, and shorter duration of mechanical ventilation. However, patients treated with high doses of norepinephrine (>0.25 µg/kg/min) may experience adverse effects, such as hyponatremia and digital ischemia, which requires close monitoring and risk assessment.
Timing of vasopressin initiation in patients with septic shock [24]	cohorts	2+	B	The study shows that vasopressin in patients with refractory septic shock receiving low-dose norepinephrine (<0.25 µg/kg/min) significantly reduces 28-day mortality. It is associated with lower norepinephrine use, lower fluid volume, greater urine output, and more days without mechanical ventilation or continuous renal dialysis. Vasopressin should be considered as a second-line treatment, improving perfusion and reducing hemodynamic load without significant adverse effects.
Use of vasopressin in the treatment of refractory septic shock [26]	Case series	3 SIGN	D	Vasopressin treatment in patients with norepinephrine-refractory septic shock in the ICU showed high short-term mortality, with 86.2% of patients dying within 30 days and 75% dying within the first 72 hours. Vasopressin was administered after 5 days of norepinephrine treatment, when the shock was already refractory. Although no adverse effects were reported, vasopressin did not improve mortality, suggesting that its early administration could be key to improving outcomes.
Vasopressin in septic shock: a meta-analysis of individual patient data from randomized controlled trials [29]	Systematic review and meta-analysis	1++ SIGN	TO	Vasopressin did not significantly reduce 28-day mortality compared with other vasopressors. It was associated with greater digital ischemia and a lower incidence of arrhythmias, with no differences in other serious adverse effects. Its effectiveness did not vary according to the timing of initiation or severity of the patients.
Vasopressin versus norepinephrine as a first-line vasopressor in septic shock: a systematic review and meta-analysis [31]	Systematic review and meta-analysis	1++ SIGN	TO	In this meta-analysis, there were no significant differences in 28-day mortality, length of hospital stay, or mean 24-hour arterial blood pressure. However, patients treated with vasopressin were less likely to require renal replacement therapy. Both vasopressors had a similar safety profile, with no differences in serious adverse events.
Vasopressin versus norepinephrine as initial therapy in septic shock (VANISH) [41]	Randomized clinical trial	1++	TO	This study compared vasopressin (0.01–0.06 U/min) with norepinephrine (0–12 mcg/min) in patients with septic shock, assessing organ failure-free days and 28-day survival. Vasopressin, although with a risk of digital ischemia, was effective as an initial vasopressor, and its combination with corticosteroids may improve outcomes.
Early concomitant therapy with vasopressin and norepinephrine versus initial monotherapy with norepinephrine in septic shock [42]	Prospective trial	1++	TO	This study compared early treatment with vasopressin and norepinephrine versus norepinephrine alone in patients with septic shock. The combination achieved target MAP more quickly (5.7 hours vs. 7.6 hours). Although there were no differences in mortality, it accelerated hemodynamic stabilization. Combined use was associated with more positive cultures, especially for infections with nonfermenting gram-negative bacilli, but no differences were observed in serious adverse events.

Discussion

The studies included in this review show that adding vasopressin when norepinephrine doses reach 0.25–0.5 mcg/kg/min may be associated with an improvement in MAP and a reduction in the need for norepinephrine. Some clinical trials, such as the VANISH study, have suggested that early use of vasopressin in combination with norepinephrine reduces the incidence of renal failure and decreases the catecholamine load in patients with less severe septic shock. However, in cases of severe refractory septic shock, the benefit of vasopressin appears to be more limited, possibly due to the characteristic vascular hyporesponsiveness. (Gordon AC, et al. [13]). It is also important to highlight that the Surviving Sepsis Campaign [14] guidelines recommend the use of norepinephrine as a first-line vasopressor to achieve a target MAP of 65 mmHg, supporting the addition of vasopressin at a dose of 0.03 IU/min when norepinephrine doses reach levels of 0.25-0.5 mcg/kg/min.

This seeks to stabilize hemodynamics and reduce adverse effects associated with high doses of norepinephrine, such as arrhythmias, although without a clear impact on long-term mortality [15]. The addition of vasopressin to norepinephrine therapy in patients with refractory septic shock may improve some clinical outcomes; the optimal timing of this vasopressor should be based on a thorough clinical assessment and ongoing patient monitoring to maximize the benefits and minimize the risks associated with its use. Regarding mortality, results are inconsistent. Some observational studies and systematic reviews report a marginal reduction in 28-day mortality when low-dose vasopressin is used in conjunction with norepinephrine compared with norepinephrine alone. However, other studies found no significant differences in mortality, suggesting that the benefits of vasopressin may depend on additional factors, such as the timing of administration and the patient's initial clinical condition. (Sedhai YR, et al. [16]). The reviewed studies also emphasize the importance of individualizing treatment. Patients with different levels of septic shock severity may respond differently to the addition of vasopressin. Thus, the decision to initiate vasopressin should be based not only on the norepinephrine dose, but also on clinical parameters such as MAP, lactate levels, and renal function.

Conclusion

A systematic review of the optimal timing of vasopressin addition in adult patients with refractory septic shock treated with norepinephrine infusion in the ICU indicates that the combination of both vasopressors can improve hemodynamic stability and reduce some adverse effects, particularly when norepinephrine doses reach 0.25–0.5 mcg/kg/min. In these cases, vasopressin acts as a secondary vasopressor, allowing a reduction in the catecholamine dose required to achieve adequate mean arterial pressure (MAP) and improve organ perfusion. However, evidence regarding whether this approach translates into a significant reduction in mortality remains conflicting, with some studies reporting improvements in 28-day survival, while others find no significant differences compared with norepinephrine alone. Regarding the severity of septic shock, studies suggest that vasopressin may be more effective in less severe cases, where there is still some vascular reactivity. In contrast, in severe refractory septic shock, where vascular resistance is severely compromised, the response to vasopressin tends to be less pronounced, underscoring the importance of personalizing treatment according to the patient's hemodynamic response.

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Incompatibility

The authors declare that they have no conflicts of interest in relation to this work.

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