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# Evaluation of vasopressin use in the management of refractory shock in patients admitted to the intensive care unit

**Avaliação do uso de vasopressina no manejo do choque refratário de pacientes em unidade de terapia intensiva**

**Evaluación del uso de vasopresina en el manejo del shock refractario en pacientes ingresados en la unidad de cuidados intensivos**

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**Abstract**
Refractory shock is characterized by hemodynamic instability unresponsive to norepinephrine with a high mortality rate. As there are still doubts regarding the pharmacological benefit of the vasopressin addition, this retrospective study aimed to assess the profile of vasopressin use in the intensive care unit of a university hospital in Paraná, Brazil. The information collected was obtained through the analysis of electronic medical records. 73 patients with refractory shock, mainly of septic etiology (61.6%), were included. The dose (μg/Kg/minute) and duration of norepinephrine, upon finding refractoriness, was 35.6% infusion < 1, 34, 3% of 1-1.9, 30.1% > 2 and mean time of 1.5 days. High mortality (80.8%) was observed, with a mean hospital stay of 8.2 days. Median survival after vasopressin infusion was 4.5 days until the unfavorable outcome. Still, 80.5% of patients used other adjuvant therapy, 71.2% being corticotherapy and 9.6% dobutamine. Due to the great variability, it was not possible to define a pattern of use. There were limitations in the analysis due to the lack of clinical and prognostic information. However, the need for deepening scientific discussions and continuous updating of protocols that guide management is highlighted.
**Keywords:** Shock; Critical care; Intensive care units; Vasopressins; Norepinephrine; Vasoconstrictor agents.

**Resumo**
O choque refratário é caracterizado pela instabilidade hemodinâmica não responsiva à norepinefrina com alta taxa de mortalidade. Como ainda há dúvidas quanto ao benefício farmacológico da adição de vasopressina, este estudo retrospectivo teve como objetivo avaliar o perfil do uso de vasopressina na unidade de terapia intensiva de um hospital universitário do Paraná, Brasil. As informações coletadas foram obtidas por meio da análise de prontuários eletrônicos. Foram incluídos 73 pacientes com choque refratário, principalmente de etiologia séptica (61,6%). A dose (μg/Kg/minuto) e duração da norepinefrina, ao definir refratariedade, foi de 35,6% para infusão < 1, 34, 3% de 1-1,9, 30,1% para infusão > 2 e tempo médio de 1,5 dias. Observou-se alta mortalidade (80,8%), com média de internação de 8,2 dias. A sobrevida mediana após a infusão de vasopressina foi de 4,5 dias até o desfecho desfavorável. Ainda, 80,5% dos pacientes utilizaram outra terapia adjuvante, sendo 71,2% corticoterapia e 9,6% dobutamina. Devido à grande variabilidade, não foi possível definir um padrão de uso. Houve limitações na análise devido à falta de informações clínicas e prognósticas. No entanto, destaca-se a necessidade de aprofundamento das discussões científicas e atualização contínua dos protocolos que orientam a tomada de decisão médica.
**Palavras-chave:** Choque; Cuidados críticos; Unidades de terapia intensiva; Vasopressinas; Norepinefrina; Vasoconstritores.

**Resumen**
El shock refractario se caracteriza por inestabilidad hemodinámica que no responde a la norepinefrina con una alta tasa de mortalidad. Como aún existen dudas sobre el beneficio farmacológico de la adición de vasopresina, este estudio retrospectivo tuvo como objetivo evaluar el perfil de uso de vasopresina en la unidad de cuidados intensivos de un hospital universitario de Paraná, Brasil. La información recolectada se obtuvo a través del análisis de historias clínicas electrónicas. Se incluyeron 73 pacientes con shock refractario, principalmente de etiología séptica (61,6%). La dosis (μg/kg/minuto) y la duración de la norepinefrina, al definir la refractariedad, fueron 35,6% para infusión < 1, 34, 3% para infusión < 1,9, 30,1% para infusión > 2 y tiempo promedio de 1,5 días. Se observó una alta mortalidad (80,8%), con una estancia hospitalaria media de 8,2 días. La mediana de supervivencia después de la infusión de vasopresina fue de 4,5 días hasta un resultado desfavorable. Asimismo, el 80,5% de los pacientes utilizaban otra terapia adyuvante, de los cuales el 71,2% eran corticoides y el 9,6% dobutamina. Debido a la gran variabilidad, no fue posible definir un patrón de uso. Hubo limitaciones en el análisis debido a la falta de información clínica y pronóstica. Sin embargo, se destaca la necesidad de profundizar las discusiones científicas y la actualización continua de los protocolos que orientan la toma de decisiones médicas.
**Palabras clave:** Choque; Cuidados críticos; Unidades de cuidados intensivos; Vasopresinas; Norepinefrina; Vasoconstrictores.

## 1. Introduction

Circulatory shock syndrome is characterized by hypoperfusion of peripheral organs and tissues with imbalance in oxygen demand and supply, leading to changes in hemodynamic parameters and consequent multiorgan failure (Standl *et al.* 2018). Clinical signs range from a drop in cardiac output (CO), a decrease in mean arterial pressure (MAP) and an unchanged or reduced heart rate (HR) (Kislitsina *et al*. 2019).

The diversity of clinical manifestations makes shock management difficult, due to the variability of therapeutic measures depending on the type of shock. The classification is defined according to the etiology, being mainly categorized as hypovolemic, distributive, cardiogenic and obstructive (Standl *et al.* 2018, Kislitsina *et al*. 2019).

Hypovolemic shock is caused by the loss of intravascular volume, with or without acute hemorrhage (Standl *et al.* 2018). Cardiogenic shock occurs due to systolic or diastolic cardiac dysfunction with reduced ejection fraction or ventricular filling, and must be distinguished from obstructive shock, which results from physical obstruction of blood vessels (Standl *et al.* 2018, Kislitsina *et al*. 2019).

Distributive shock is the most frequent in intensive care, being classified by loss of regulation of vascular tone and permeability, with extravasation of intravascular volume into the interstitium. And, further, it can be subdivided into septic, anaphylactic or neurogenic etiology (Standl *et al.* 2018, Kislitsina *et al*. 2019).

Fluid resuscitation and the use of norepinephrine (NA) are the first steps in management to restore hemodynamic parameters. The norepinephrine dose is titrated according to the previously established MAP target (> 65 mmHg). Some studies suggest that a higher MAP target improves prognosis and reduces the risk of acute kidney injury. However, it is also related to the increase in adverse effects (Russell *et al*. 2021).

Early approaches and rapid diagnosis are essential to prevent the worsening of the clinical situation and the progression of circulatory shock into catecholamine-refractory shock. Refractory can occur in up to 7% of critically ill patients and is identified when the hemodynamic response remains inadequate and with significant vasoplegia, even at high doses of norepinephrine. Doses above 1 μg/kg/min are related to an increase in adverse effects and a mortality rate higher than 80%, and therefore, the dose of the vasopressor is a great predictor of mortality in circulatory shock (Meresse *et al*. 2020, Knotzer, Poidinger & Kleinsasser, 2019).

There is some evidence already described regarding adjuvant therapies for the management of refractory shock. Among them, the use of corticosteroids to reduce vasodilation caused by the generalized systemic inflammation of septic shock, and the association of vasopressin or adrenaline. The use of sedatives should also be re-evaluated due to the adverse effect of myocardial

depression and systemic vasodilation that can hinder the return of adequate hemodynamic parameters (Jentzer *et al*. 2018, Barola & Shabbir, 2021).

To help the patient return to stability, correction of acidosis should be considered. Infusion of sodium bicarbonate can reverse cases of metabolic acidosis, and supplementation with thiamine also helps to correct lactic acidosis. Another important factor is that the responsiveness of the vasopressor is decreased in acidic media, and the use of a glucose solution for infusion of the vasopressor is recommended (Jentzer *et al*. 2018).

There are still many questions regarding the effective treatment of shock refractory to norepinephrine. Several managements are described in the literature and demonstrated in clinical trials and observational studies. In general, they guide the management with the association of vasopressin together with adjuvant therapies (Patel *et al*. 2020).

However, prescription practices are still not well standardized and the risk-benefit and effectiveness of these treatments in terms of duration of shock, length of stay in the intensive care unit (ICU) and mortality rate of these patients remain controversial (Patel *et al*. 2020).

The widely reported management option to combat refractoriness is the association of norepinephrine with vasopressin. Vasopressin (VP) is the antidiuretic hormone, which is stored and released by the posterior pituitary, and promotes vascular contraction and water reabsorption in the renal collecting tubules. This pharmacotherapeutic association of vasopressors makes it possible to reduce norepinephrine doses, avoiding undesirable adverse effects. And yet, some studies correlate it with a reduction in the high mortality rate of circulatory shock in critically ill patients (Jentzer *et al*. 2018, Annane *et al*. 2018).

Several questions still permeate the scientific discussions involving the use of vasopressin in the management of refractory shock in relation to the start of infusion, recommended dosage and treatment time according to the clinical response and the patient's prognosis.

Considering the points raised and in order to contribute to the scientific community in the therapeutic management of refractory shock, this research aimed to assess the profile of vasopressin use in the adult Intensive Care Unit (ICU) of the Regional University Hospital of Campos Gerais.

## 2. Methodology

This study has an observational character with a retrospective design, based on the analysis of the electronic medical record of the computerized system used at the Regional University Hospital of Campos Gerais.

The information evolved in electronic medical records of patients who had a record of vasopressin dispensing, were hospitalized in the adult intensive care unit from June 2019 to June 2020, and who used the vasopressor with therapeutic indication for shock refractory to norepinephrine.

According to institutional protocol, vasopressin is recommended when there is therapeutic refractoriness to norepinephrine, in cases of circulatory shock.

Patients who had a prescription and electronic vasopressin dispensing record in the institution's computerized system, but were admitted to other units of the hospital or used this drug with a therapeutic purpose other than refractory shock, were excluded from this study.

The tabulated and analyzed data refer to anthropometric measurements, age, shock classification, time of vasopressor use, use of adjuvant drugs (corticosteroids and/or dobutamine) and C-reactive protein (CRP) dosage at the beginning of vasopressin use, length of stay in the ICU and clinical outcome. To assess severity and prognosis, the Glasgow Coma Scale obtained at the time of initiation of vasopressin therapy was also used.

Data were included in Microsoft Excel® data sheets and evaluated by descriptive analysis. The study was approved by the Research Ethics Committee involving Human Beings at the State University of Ponta Grossa and by the National Research

Ethics Committee (CAAE 48479321.60000.0105).

## 3. Results

In an attempt to evaluate the use and define a pattern of VP prescription in refractoriness, this study included 73 patients with refractory circulatory shock who were treated with vasopressin over a period of one year. The age of the patients ranged between 20 and 94 years with a median of 67 years and a predominance of elderly people aged 60 years or over (67.1%). There was no significant difference between men (52%) and women (48%) (Table 1).

**Table 1.** Frequency of demographic variables during vasopressor therapy for refractory shock.

| VARIABLES | SUBVARIABLES | n | % |
|---|---|---|---|
| GENDER | MALE | 38 | 52 |
| | FEMALE | 35 | 48 |
| AGE GROUP (years) | 20 – 39 | 10 | 13,7 |
| | 40 – 59 | 14 | 19,2 |
| | ≥ 60 | 49 | 67,1 |

n – freqüência absoluta; % - freqüência relativa. Source: Authors.

Most patients had a shock of septic etiology (61.6%). Hemorrhagic, cardiogenic and mixed shock (two or more different etiologies) were diagnosed in 21.9%, 5.5% and 11% of patients, respectively. The Glasgow scale performed on the day on which refractoriness was defined had a prevalence of score 3 (80.8%). The average length of stay in the intensive care unit was 8.2 ± 8 days and the mortality rate was 80.8% (Table 2).

The clinical-laboratory variables are interesting to be evaluated together, allowing the correlation with the severity and prognosis during vasopressor therapy. C-reactive protein (CRP) dosage was the clinical and laboratory variable that could be evaluated for all patients. Of these, the majority (46.6%) had CRP greater than 20 mg/L indicating severe infections, 28.8% systemic inflammation (5.1 - 20 mg/L), 20.5% mild inflammation (1 - 5 mg /L) and only 3 patients had a reference value of CRP < 1 mg/L (4.1%) (Table 2).

The mean duration of treatment with norepinephrine during the ICU stay, prior to the initiation of vasopressin, was 1.5 ± 2 days. And the management with vasopressin lasted an average of 1.7 + 1 day. The dose of NA when verifying refractoriness and starting VP was quite variable, with 35.6% having an infusion dose of less than 1 µg/Kg/minute, 34.3% from 1 to 1.9 µg/Kg/minute and 30.1% of the cases had an infusion greater than 2 µg/Kg/minute (Table 3).

**Table 2.** Frequency of clinical variables during vasopressor therapy for refractory shock.

| VARIABLES | SUBVARIABLES | n | % |
|---|---|---|---|
| SHOCK CLASSIFICATION | SEPTIC | 45 | 61,6 |
| | CARDIOGENIC | 4 | 5,5 |
| | HEMORRHAGIC | 16 | 21,9 |
| | MIXED | 8 | 11 |
| GLASGOW | 3 | 59 | 80,8 |
| | 4 - 6 | 8 | 11 |
| | ≥ 7 | 6 | 8,2 |
| CRP | <1 | 3 | 4,1 |
| | 1 a 5 | 15 | 20,5 |
| | 5,1 a 20 | 21 | 28,8 |
| | > 20 | 34 | 46,6 |

n – absolute frequency; % - relative frequency. Source: Authors.

**Table 3.** Noradrenaline dose in refractoriness and duration of vasopressin therapy.

| VARIABLES | SUBVARIABLES | n | % |
|---|---|---|---|
| NORADRENALINE DOSE AT THE BEGINNING OF VASOPRESSIN USE (μg/kg/minute) | ≤ 0,5 | 10 | 13,7 |
| | 0,6 - 0,9 | 16 | 21,9 |
| | 1 - 1,9 | 25 | 34,3 |
| | ≥ 2 | 22 | 30,1 |
| VASOPRESSIN USE (days) | 1 | 43 | 58,9 |
| | 2 | 17 | 23,3 |
| | 3 | 8 | 11 |
| | 4 | 5 | 6,8 |

n – absolute frequency; % - relative frequency. Source: Authors.

The survival of patients was on average 4.5 days, being considered after the start of VP in those whose final outcome was unfavorable. Most of the cases analyzed died in just 1 day after vasopressin infusion (50.8%) and only 15.3% had a survival rate of more than 10 days, the largest of which was 44 days (Table 4).

The use of adjuvant therapy has already been described in the literature, with greater relevance for the management of refractory septic shock with the use of corticosteroid therapy. In this context, this study found that most patients (80.5%) used one or more adjuvant therapy analyzed. Corticosteroid therapy was used by 71.2% of patients and only 9.6% were associated with norepinephrine, vasopressin and dobutamine (Table 4).

**Table 4.** Characteristics of vasopressor therapy in refractory shock.

| VARIABLES | SUBVARIABLES | n | % |
|---|---|---|---|
| COADJUVANT THERAPY | CORTICOTHERAPY | 52 | 71,2 |
| | DOBUTAMINE | 7 | 9,6 |
| CLINICAL EVOLUTION | DISCHARGE FROM ICU | 14 | 19,2 |
| | DEATH | 59 | 80,8 |
| SURVIVAL AFTER VASOPRESSIN USE (days) | 1 | 30 | 50, 8 |
| | 2 a 9 | 20 | 33,9 |
| | > 10 | 9 | 15,3 |

n – absolute frequency; % - relative frequency. Source: Authors.

## 4. Discussion

Circulatory shock is one of the most common syndromes found in intensive care units, with refractoriness being a determining factor for high mortality (65 - 100%) present in up to 7% of critically ill patients (Barola & Shabbir, 2021, Wu *et al*. 2020). This study described 73 patients diagnosed with refractory circulatory shock using vasopressin, regardless of the underlying etiology.

The high mortality rate that was found (80.8%) is common in refractory shock and corroborates other studies, demonstrating the severity of these cases. Comparatively, in the study by Kny et al. 2018, 75% of deaths were observed within 72 hours and 86.2% within 30 days, in 80 cases of refractory septic shock, the majority with a hospital stay of up to 10 days (Kny et al., 2018).

The poor prognosis and high mortality in refractory circulatory shock is related to the severity of the cases. Biochemical parameters such as CRP can be an important marker of the evolution of these inflammatory processes (Ríos-Toro *et al*. 2017, Cui et al., 2019).

CRP values above 5.1 are related to systemic inflammation, and above 20 to serious infections. In this study, it is noted that 75.1% of patients had cases of systemic inflammation (28.8%) or severe infections (46.3%), demonstrating the severity of the clinical conditions included in the study.

Clinical scores to assess the severity and probability of complications are widely used in intensive care units and can help in studies on the correlation of pharmacotherapy and mortality and efficiency of clinical management. Acute Physiology, and Chronic Health Evaluation II (APACHE II) is used as a predictor of mortality assessed by physiological changes and clinical variables. The Sequential Organ Failure Assessment Score (SOFA) scale assesses the morbidity of critically ill septic patients based on the quantification of the degree of organ dysfunction in the clinical evolution (Kądziołka et al., 2019).

Although these scores are used in this institution, there were no records in the electronic medical record, which is an important limitation of a retrospective study.

Given the severity explained so far, the scientific literature continues to seek answers to establish clinical criteria for refractory shock and reduce the high probability of an unfavorable outcome. What is the best time to start and discontinue vasopressor therapy, what is the indicated dose and expected response, and what therapeutic options are necessary to combat refractory hypotension are questions that still permeate professionals in intensive care.

The recommended first pharmacological choice for reversal of circulatory shock is norepinephrine. A potent vasoconstrictor, an α1 receptor agonist with less β agonist activity, ensures an increase in pressure and blood flow and, consequently, an improvement in cardiac function with little or no change in CO. However, prolonged infusion and the use of high doses of norepinephrine can have a toxic effect on cardiac myocytes (Kislitsina *et al*., 2019).

Several studies have shown that the combined administration of low dose vasopressin (0.01 – 0.04 IU/min) increases MAP and decreases the need for NA and its adverse effects. However, high doses of vasopressin can cause mesenteric ischemia and are often recommended only as a rescue in refractory vasodilatory shock (Kislitsina *et al*. 2019, Annane *et al.* 2018, Hammond *et al*. 2018, Guinot *et al*. 2021). The definition of ceiling doses and/or effective doses of VP together with NA can determine a treatment with a lower risk of side effects and better therapeutic response (Evans *et al.* 2021).

Vasopressin is a potent endogenous vasopressor released by the posterior pituitary in response to hypotension and hypernatremia. Its pharmacological action is due to the stimulation of receptors V1a (vasoconstriction independent of norepinephrine), V1b (corticotropin release), V2 (antidiuretic action), oxytocin (vasodilation) and purinergic receptors (potential therapeutic target being studied in sepsis). Another factor that justifies the association of VP is the depletion of this hormone already observed at the beginning of septic shock and the increase in vascular sensitivity to NA, which can increase its pressure effects (Kislitsina *et al*. 2019, Annane *et al.* 2018).

Experts defined recommendation guidelines on the use of vasopressin for septic shock in the Surviving Sepsis Campaign (SSC). VP was considered as a second or third choice vasopressor after the use of NA, with evidence of moderate quality (Evans *et al.*, 2021). For cardiogenic shock, the American Heart Association (AHA) consensus also reported that there is insufficient evidence to guide the pharmacological management judiciously, however it described all the pharmacological possibilities for hemodynamic return (van Diepen *et al*. 2017). The association of dobutamine is normally used as a rescue alternative for cardiogenic shock in an attempt to improve cardiac contractility (Kim et al., 2020, Thiele et al., 2015).

The recommendation for VP dosage in the SSC guidelines is continuous infusion at a fixed dose of 0.03 IU/min to prevent adverse events. VP does not have a titrated dose like other vasopressors and some clinical trials used doses of 0.06 IU/min (Evans *et al.* 2021). However, it is noteworthy that the half-life of the drug is 10 to 35 min, requiring a longer time to reach steady state and adequate pharmacological response. For this reason, bolus administration is often used in medical practice due to the severity of refractoriness cases (Nakamura *et al*. 2021).

In this study, it was not possible to collect information about the dose of vasopressin that was started and maintained due to the absence of this record in the medical records of the included patients. The evaluated dosage referred to the infusion of norepinephrine when refractoriness was found.

One of the hypotheses for the high mortality rate is the late onset of vasopressin. In a review, Udupa e Shetty (2018) defined refractoriness from doses greater than 0.5 μg/kg/min of norepinephrine after correct fluid resuscitation (Udupa, & Shetty, 2018). However, Wu et al. (2019) describe an increase in mortality from 65 to 100% with an infusion of > 1 μg/kg/min of NA (Wu *et al*. 2020). The SSC describes the VP association as a weak recommendation and moderate quality evidence, which should be started when the NA is between 0.25 to 0.5 μg/kg/min in order not to increase the NA infusion (Evans *et al.*, 2021).

The infusion of VP in the patients analyzed in this study did not have an onset pattern for refractoriness. The patients described in this study had concomitant administration of NA and VP after infusion of less than 1μg/Kg/minute (35.6%), from 1 to 1.9 μg/Kg/minute (34.3%) and also greater than 2 μg/Kg/minute (30.1 %).

Considering that a dose greater than 1 μg/Kg/minute determines refractoriness, as mentioned by Wu et al. (2019), this study demonstrates a probable late start of VP infusion, since 64.4% of patients started VP in doses high (Wu *et al*. 2020). This criterion may be related to the high mortality found in this and other studies mentioned above. On the other hand, Russell et al (2020) questioned the correlation of VP with reduced mortality, as some studies were unable to correlate these factors (Russell *et al*. 2021).

However, the onset of vasopressin was, on average, after 1.5 days of norepinephrine, ranging from immediate onset (0 days) to 9 days after NA infusion, and it cannot generalize the late onset or not. Standardizing the use of VP would allow a better assessment of this aspect, and it is a possible hypothesis that could be challenged in a future study. Also, data were not collected from a control group, without the use of VP, in order to verify the ceiling dose of NA used in cases of circulatory shock in the intensive care unit of this institution.

Also regarding the recommendation to start VP, Huang et al. (2021), in a systematic review, demonstrated that the infusion of vasopressin within 6 hours of the onset of septic shock was not associated with a reduction in mortality and length of stay, but seems to reduce the use of renal replacement therapy (Huang *et al*. 2021). In addition, a prospective open-label trial by Hammond et al. (2018) found that the VP and NA group as first choice reached the MAP goal (65 mmHg) faster than the group that used only NA (Hammond *et al*., 2018).

Another question regarding refractory shock is when to discontinue the association of vasopressin. The ideal approach seems controversial, and several studies are being carried out in an attempt to define a recommendation and stimulate scientific discussion. The VASST study showed no significant difference in the duration of VP therapy, but its use was associated with a lower dose of NA and longer survival in patients with shock, preventing renal failure (Mehta *et al*. 2013, Russell *et al*. 2008).

Wu et al. (2020) and Duclos et al. (2019) performed a meta-analysis regarding discontinuation and found no significant change in mortality and length of hospital stay in VP removal before NA and vice versa. However, VP withdrawal first may increase the incidence of hypotension, not associated with worse outcomes (Wu *et al*. 2020, Duclos et al., 2019).

On the other hand, the concomitant use of corticosteroids, commonly prescribed in septic shock, has suggested a potential interaction between VP reducing the chance of rebound hypotension and the mortality rate. VP binds to V1b receptors and allows the release of adrenocorticotropic hormone, and the beneficial effect of this association can be explained by the effect of corticosteroids in restoring cytokine-mediated negative regulation of VP receptors (Duclos et al., 2019).

The Guidelines recommend the association of adjuvant therapies in cases of shock to reduce the high mortality shown. In this study, it was found that in most patients in shock, the medical team decided to use adjuvant therapy (80.5%) described in the literature, in addition to the use of VP (Evans *et al.* 2021, van Diepen *et al*. 2017).

Corticosteroid therapy is highly recommended in septic shock, being the most evident etiology in this research and the most frequent adjuvant therapy (71.2%). Another rescue attempt observed in this study was the association of dobutamine by 9.6% of patients.

According to the various points described in this article, the need for scientific in-depth knowledge in the management of refractory shock is highlighted. The study methodology of this article and the data collected to discuss possible conflicts between prescribing practices were limited, not being able to define dose, duration of treatment and benefits. The lack of a control group restricted the assessment of causality and relevant clinical aspects. The high variability in prescribing practices and information in electronic medical records observed in this study made the analysis of the results even more difficult.

Also, the lack of records on clinical parameters such as MAP, HR and CD, use of renal replacement therapy and mechanical ventilation, in addition to scales that assess severity and prognosis such as Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment Score (SOFA) did not allow further study and a conclusion regarding the correlation between mortality and vasopressin use.

Despite the numerous limitations found, this study is similar to the high variability in the available literature that guides the use of PV in shock, and the correlation with the final clinical outcome is not conclusive. The adequacy of information for a future study is of great value and, thus, allow the standardization of the administration of vasopressin in refractory shock in this institution and deepen the clinical discussions of this management.

## 5. Final Considerations

There were limitations in the study due to the lack of information regarding the clinical parameters and prognosis of the patients. Based on these data, it was not possible to define a standard profile of vasopressin use in this institution due to the great diversity related to the initiation of vasopressin, demonstrating that there are still doubts regarding this management.

However, this study highlights the need to deepen scientific discussions regarding care in refractory shock and seeks to encourage the scientific community for future studies. In addition, there is urgency in the emergence of more clinical studies that allow to define management guidelines in refractory shock with vasopressin more clearly and objectively in terms of benefit and efficacy.

The definition of a protocol and its continuous updating are essential to support the medical team's decisions and guarantee an evidence-based practice. The standardization of the use of vasopressin can help the medical team to decide according to the patient's clinical conditions and enable a better clinical evolution for the patient with refractory circulatory shock. Therefore, we encourage further studies regarding the dose and initiation of vasopressin use according to the parameters of noradrenaline-refractory patients.

## References

Annane, D., Ouanes-Besbes, L., de Backer, D., DU, B., Gordon, A. C., Hernández, G., Olsen, K. M., Osborn, T. M., Peake, S., Russell, J. A., & Cavazzoni, S. Z. (2018). A global perspective on vasoactive agents in shock. *Intensive care medicine*, *44*(6), 833–846. https://doi.org/10.1007/s00134-018-5242-5

Barola S, Shabbir N. Refractory Shock. [Updated 2021 Oct 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK564427/

Cui, N., Zhang, H., Chen, Z., & Yu, Z. (2019). Prognostic significance of PCT and CRP evaluation for adult ICU patients with sepsis and septic shock: retrospective analysis of 59 cases. *The Journal of international medical research*, *47*(4), 1573–1579. https://doi.org/10.1177/0300060518822404

Duclos, G., Baumstarck, K., Dünser, M., Zieleskiewicz, L., & Leone, M. (2019). Effects of the discontinuation sequence of norepinephrine and vasopressin on hypotension incidence in patients with septic shock: A meta-analysis. *Heart & lung: the journal of critical care*, *48*(6), 560–565. https://doi.org/10.1016/j.hrtlng.2019.05.007

Evans, L., Rhodes, A., Alhazzani, W., Antonelli, M., Coopersmith, C. M., French, C., Machado, F. R., Mcintyre, L., Ostermann, M., Prescott, H. C., Schorr, C., Simpson, S., Wiersinga, W. J., Alshamsi, F., Angus, D. C., Arabi, Y., Azevedo, L., Beale, R., Beilman, G., Belley-Cote, E., & Levy, M. (2021). Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Intensive care medicine*, *47*(11), 1181–1247. https://doi.org/10.1007/s00134-021-06506-y

Guinot, P.-G., Martin, A., Berthoud, V., Voizeux, P., Bartamian, L., Santangelo, E., Bouhemad, B., & Nguyen, M. (2021). Vasopressor-Sparing Strategies in Patients with Shock: A Scoping-Review and an Evidence-Based Strategy Proposition. *Journal of Clinical Medicine*, *10*(14), 3164. https://doi.org/10.3390/jcm10143164

Hammond, D. A., Ficek, O. A., Painter, J. T., McCain, K., Cullen, J., Brotherton, A. L., Kakkera, K., Chopra, D., & Meena, N. (2018). Prospective Open-label Trial of Early Concomitant Vasopressin and Norepinephrine Therapy versus Initial Norepinephrine Monotherapy in Septic Shock. *Pharmacotherapy*, *38*(5), 531–538. https://doi.org/10.1002/phar.2105

Huang, H., Wu, C., Shen, Q., Xu, H., Fang, Y., & Mao, W. (2021). The effect of early vasopressin use on patients with septic shock: A systematic review and meta-analysis. *The American journal of emergency medicine*, *48*, 203–208. https://doi.org/10.1016/j.ajem.2021.05.007

Jentzer, J. C., Vallabhajosyula, S., Khanna, A. K., Chawla, L. S., Busse, L. W., & Kashani, K. B. (2018). Management of Refractory Vasodilatory Shock. *Chest*, *154*(2), 416–426. https://doi.org/10.1016/j.chest.2017.12.021

Kądziołka, I., Świstek, R., Borowska, K., Tyszecki, P., & Serednicki, W. (2019). Validation of APACHE II and SAPS II scales at the intensive care unit along with assessment of SOFA scale at the admission as an isolated risk of death predictor. *Anaesthesiology intensive therapy*, *51*(2), 107–111. https://doi.org/10.5114/ait.2019.86275

Kim, J. H., Sunkara, A., & Varnado, S. (2020). Management of Cardiogenic Shock in a Cardiac Intensive Care Unit. *Methodist DeBakey cardiovascular journal*, *16*(1), 36–42. https://doi.org/10.14797/mdcj-16-1-36

Kislitsina, O. N., Rich, J. D., Wilcox, J. E., Pham, D. T., Churyla, A., Vorovich, E. B., Ghafourian, K., & Yancy, C. W. (2019). Shock - Classification and Pathophysiological Principles of Therapeutics. *Current cardiology reviews*, *15*(2), 102–113. https://doi.org/10.2174/1573403X15666181212125024

Knotzer, H., Poidinger, B., & Kleinsasser, A. (2019). Pharmacologic Agents for the Treatment of Vasodilatory Shock. *Current pharmaceutical design*, *25*(19), 2133–2139. https://doi.org/10.2174/1381612825666190704101907

Kny, K. T., Ferreira, M. A. P. & Pizzol, T. S. D. (2018). Use of vasopressin in the treatment of refractory septic shock. *Revista Brasileira de Terapia Intensiva*, *30*(4), 423-428. Epub December 13, 2018.https://doi.org/10.5935/0103-507x.20180060

Mehta, S., Granton, J., Gordon, A. C., Cook, D. J., Lapinsky, S., Newton, G., Bandayrel, K., Little, A., Siau, C., Ayers, D., Singer, J., Lee, T. C., Walley, K. R., Storms, M., Cooper, D. J., Holmes, C. L., Hebert, P., Presneill, J., Russell, J. A., & Vasopressin and Septic Shock Trial (VASST) Investigators (2013). Cardiac ischemia in patients with septic shock randomized to vasopressin or norepinephrine. *Critical care (London, England)*, *17*(3), R117. https://doi.org/10.1186/cc12789

Meresse, Z., Medam, S., Mathieu, C., Duclos, G., Vincent, J. L., & Leone, M. (2020). Vasopressors to treat refractory septic shock. *Minerva anestesiologica*, *86*(5), 537–545. https://doi.org/10.23736/S0375-9393.20.13826-4

Nakamura, K., Nakano, H., Naraba, H., Mochizuki, M., Takahashi, Y., Sonoo, T., Hashimoto, H., Abe, T., Hayakawa, M., & Yamakawa, K. (2021). Vasopressin Loading for Refractory Septic Shock: A Preliminary Analysis of a Case Series. *Frontiers in medicine*, *8*, 644195. https://doi.org/10.3389/fmed.2021.644195

Patel, A., Beauchesne, A., Bredenkamp, N., McGloin, R., Stabler, S. N., & Boyce, K. (2020). Vasopressin for Septic Shock in a Medical-Surgical Intensive Care Unit. *The Canadian journal of hospital pharmacy*, *73*(3), 209–21

Ríos-Toro, J. J., Márquez-Coello, M., García-Álvarez, J. M., Martín-Aspas, A., Rivera-Fernández, R., Sáez de Benito, A., & Girón-González, J. A. (2017). Soluble membrane receptors, interleukin 6, procalcitonin and C reactive protein as prognostic markers in patients with severe sepsis and septic shock. *PloS one*, *12*(4), e0175254. https://doi.org/10.1371/journal.pone.0175254

Russell, J. A., Walley, K. R., Singer, J., Gordon, A. C., Hébert, P. C., Cooper, D. J., Holmes, C. L., Mehta, S., Granton, J. T., Storms, M. M., Cook, D. J., Presneill, J. J., Ayers, D., & VASST Investigators (2008). Vasopressin versus norepinephrine infusion in patients with septic shock. *The New England journal of medicine*, *358*(9), 877–887. https://doi.org/10.1056/NEJMoa067373

Russell, J. A., Gordon, A. C., Williams, M. D., Boyd, J. H., Walley, K. R., & Kissoon, N. (2021). Vasopressor Therapy in the Intensive Care Unit. *Seminars in respiratory and critical care medicine*, *42*(1), 59–77. https://doi.org/10.1055/s-0040-1710320

Standl, T., Annecke, T., Cascorbi, I., Heller, A. R., Sabashnikov, A., & Teske, W. (2018). The Nomenclature, Definition and Distinction of Types of Shock. *Deutsches Arzteblatt international*, *115*(45), 757–768. https://doi.org/10.3238/arztebl.2018.0757

Thiele, H., Ohman, E. M., Desch, S., Eitel, I., & de Waha, S. (2015). Management of cardiogenic shock. *European heart journal*, *36*(20), 1223–1230. https://doi.org/10.1093/eurheartj/ehv051

Udupa, A., & Shetty, R. (2018). Advanced cardiovascular support in refractory shock. *Indian Journal of Respiratory Care*, *7*(2), 67. https://doi.org/10.4103/ijrc.ijrc_2_17

van Diepen, S., Katz, J. N., Albert, N. M., Henry, T. D., Jacobs, A. K., Kapur, N. K., Kilic, A., Menon, V., Ohman, E. M., Sweitzer, N. K., Thiele, H., Washam, J. B., Cohen, M. G., & American Heart Association Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Mission: Lifeline. (2017). Contemporary management of cardiogenic shock: A scientific statement from the American heart association. *Circulation*, *136*(16), e232–e268. https://doi.org/10.1161/CIR.0000000000000525

Wu, K. S., Gu, D. Y., Wang, T. T., Yu, B. W., Pan, K. H., & Zhou, J. C. (2020). Factors associated with outcomes of septic shock patients receiving high dose noradrenaline according to three primary infection sites. *The Journal of international medical research*, *48*(2), 300060519874545. https://doi.org/10.1177/0300060519874545

Wu, Z., Zhang, S., Xu, J., Xie, J., Huang, L., Huang, Y., Yang, Y., & Qiu, H. (2020). Norepinephrine vs Vasopressin: Which Vasopressor Should Be Discontinued First in Septic Shock? A Meta-Analysis. *Shock (Augusta, Ga.)*, *53*(1), 50–57. https://doi.org/10.1097/SHK.0000000000001345