

**METHYLENE BLUE IN REFRACTORY SEPTIC SHOCK: AN INTEGRATIVE REVIEW OF THE EVIDENCE ON HEMODYNAMIC EFFICACY AND CLINICAL IMPACT**

**AZUL DE METILENO NO CHOQUE SÉPTICO REFRACTÁRIO: REVISÃO INTEGRATIVA DAS EVIDÊNCIAS SOBRE EFICÁCIA HEMODINÂMICA E IMPACTO CLÍNICO**

**AZUL DE METILENO EN EL SHOCK SÉPTICO REFRACTARIO: UNA REVISIÓN INTEGRADORA DE LA EVIDENCIA SOBRE LA EFICACIA HEMODINÂMICA Y EL IMPACTO CLÍNICO**



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## **ABSTRACT**

Refractory septic shock remains associated with high mortality despite early fluid resuscitation, appropriate antimicrobial therapy, and stepwise vasopressor support. Exaggerated activation of the nitric oxide–cGMP pathway constitutes a central mechanism of septic vasoplegia, providing the pathophysiological rationale for the use of methylene blue as a guanylate cyclase inhibitor. Recent evidence suggests hemodynamic benefit; however, uncertainties persist regarding its impact on robust clinical outcomes. This integrative review critically analyzed the evidence published over the last decade concerning the efficacy, safety, and administration strategies of methylene blue as adjunctive therapy in refractory septic shock. The review was conducted according to the framework proposed by Whittmore and Knafl, with a systematic search performed in PubMed/MEDLINE, SciELO, and ScienceDirect databases covering the period from 2014 to 2024. Randomized controlled trials demonstrated a significant reduction in vasopressor duration and increased mean arterial pressure with early administration of methylene blue. Recent meta-analyses reported a possible reduction in short-term mortality, as well as decreased vasopressor exposure and lower serum lactate levels, although with low certainty of evidence due to methodological heterogeneity and limited sample size. Observational evidence supports hemodynamic improvement in extreme refractory settings, although variability in dosing regimens and lack of therapeutic standardization remain relevant limitations. In conclusion, methylene blue demonstrates consistent hemodynamic benefit in refractory septic shock; however, despite signals suggesting short-term mortality reduction, the overall quality of evidence remains low to moderate, and routine clinical incorporation depends on large, multicenter randomized controlled trials with standardized protocols and long-term outcome assessment.

**Keywords:** Septic Shock. Methylene Blue. Vasoplegia. Vasopressors. Critical Care.

## **RESUMO**

O choque séptico refratário permanece associado a elevada mortalidade, apesar do manejo baseado em ressuscitação volêmica precoce, antibioticoterapia adequada e uso escalonado de vasopressores. A ativação exacerbada da via óxido nítrico–GMPc constitui mecanismo central da vasoplegia séptica, fundamentando o racional fisiopatológico para o uso do azul de metileno como inibidor da guanilato ciclase. Evidências recentes sugerem benefício hemodinâmico, porém persistem incertezas quanto ao impacto em desfechos clínicos robustos. Esta revisão integrativa analisou criticamente as evidências publicadas na última década acerca da eficácia, segurança e estratégias de administração do azul de metileno como terapia adjuvante no choque séptico refratário. A revisão foi conduzida conforme o referencial metodológico de Whittmore e Knafl, com busca sistematizada nas bases PubMed/MEDLINE, SciELO e ScienceDirect, no período de 2014 a 2024. Ensaios clínicos

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randomizados demonstraram redução significativa da duração do suporte vasopressor e aumento da pressão arterial média com a administração precoce do fármaco. Meta-análises recentes identificaram possível redução da mortalidade de curto prazo, além de diminuição do tempo de uso de vasopressores e redução do lactato sérico, embora com baixo grau de certeza devido à heterogeneidade metodológica e ao tamanho amostral limitado. Evidências observacionais corroboram o benefício hemodinâmico em cenários de refratariedade extrema, embora persista variabilidade nos regimes posológicos e ausência de padronização terapêutica. Conclui-se que o azul de metileno apresenta benefício hemodinâmico consistente no choque séptico refratário; contudo, apesar de sinais favoráveis quanto à mortalidade de curto prazo, a qualidade global da evidência permanece baixa a moderada, e sua incorporação rotineira depende da realização de ensaios clínicos multicêntricos robustos, com protocolos padronizados e avaliação de desfechos clínicos de longo prazo.

**Palavras-chave:** Choque Séptico. Azul de Metileno. Vasoplegia. Vasopressores. Terapia Intensiva.

## RESUMEN

El choque séptico refractario continúa asociándose con una alta mortalidad, a pesar del manejo basado en la reanimación precoz con líquidos, la terapia antibiótica adecuada y el uso progresivo de vasopresores. La activación exacerbada de la vía del óxido nítrico-GMPc constituye un mecanismo central de la vasoplejía séptica, lo que proporciona la justificación fisiopatológica para el uso del azul de metileno como inhibidor de la guanilato ciclase. La evidencia reciente sugiere un beneficio hemodinámico, pero persisten incertidumbres sobre su impacto en resultados clínicos robustos. Esta revisión integrativa analizó críticamente la evidencia publicada en la última década sobre la eficacia, seguridad y estrategias de administración del azul de metileno como terapia adyuvante en el choque séptico refractario. La revisión se realizó de acuerdo con el marco metodológico de Whittemore y Knafl, con una búsqueda sistemática en las bases de datos PubMed/MEDLINE, SciELO y ScienceDirect, abarcando el período de 2014 a 2024. Los ensayos clínicos aleatorizados demostraron una reducción significativa en la duración del soporte vasopresor y un aumento de la presión arterial media con la administración temprana del fármaco. Metaanálisis recientes han identificado una posible reducción de la mortalidad a corto plazo, así como una disminución de la duración del uso de vasopresores y una reducción del lactato sérico, aunque con baja certeza debido a la heterogeneidad metodológica y al tamaño muestral limitado. La evidencia observacional corrobora el beneficio hemodinámico en escenarios de refratariedad extrema, aunque persiste la variabilidad en las pautas posológicas y la falta de estandarización terapéutica. Se concluye que el azul de metileno presenta un beneficio hemodinámico consistente en el choque séptico refractario. Sin embargo, a pesar de los indicios favorables respecto a la mortalidad a corto plazo, la calidad general de la evidencia sigue siendo baja a moderada, y su incorporación sistemática depende de la realización de ensayos clínicos multicéntricos robustos con protocolos estandarizados y la evaluación de los resultados clínicos a largo plazo.

**Palabras clave:** Choque Séptico. Azul de Metileno. Vasoplejia. Vasopresores. Cuidados Intensivos.

## 1 INTRODUCTION

Septic shock is one of the main causes of mortality in intensive care units, representing the most severe form of sepsis and being associated with significant circulatory, metabolic and cellular dysfunction. Despite the implementation of strategies based on early fluid resuscitation, adequate antibiotic therapy, and staggered use of vasopressors, particularly noradrenaline as a first-line agent, as recommended by international guidelines, a relevant proportion of patients evolve with persistent hypotension and increasing need for vasopressor support, characterizing refractory septic shock (EVANS et al., 2021). In this condition, mortality remains high, which has driven the investigation of adjuvant therapies aimed at modulating inflammatory vasoplegia (CECCONI et al., 2018; FERNANDO et al., 2024; NG et al., 2024).

The pathophysiology of septic vasoplegia involves exacerbated activation of the nitric oxide (NO) pathway, with overexpression of inducible nitric oxide synthase (iNOS) and consequent activation of soluble guanylate cyclase, leading to an increase in cyclic guanosine monophosphate (cGMP), a reduction in vascular tone, and a decrease in responsiveness to catecholamines. This process is also associated with endothelial dysfunction and microcirculatory changes that contribute to the loss of systemic vasomotor control (LEVY et al., 2018). In this context, methylene blue emerges as a potential adjuvant agent, acting as an inhibitor of guanylate cyclase and modulator of the NO–cGMP pathway, promoting partial restoration of systemic vascular resistance. Recent reviews highlight that this pharmacological mechanism confers consistent biological plausibility for its use in refractory vasoplegia states, including septic shock (COTTYN et al., 2022; ELMATI et al., 2025).

In recent years, randomized controlled trials have explored the clinical efficacy of this intervention. Ibarra-Estrada et al. (2023) demonstrated that early administration of methylene blue significantly reduced time to vasopressor discontinuation and hospital stay, with no increase in serious adverse events. In a convergent way, Luis-Silva et al. (2024) observed an earlier reduction in the doses of noradrenaline and vasopressin when the drug was incorporated into the standard treatment in the initial phase of septic shock. These findings suggest a possible catecholamine-sparing effect, an aspect of high clinical relevance in view of the potential deleterious effects associated with the prolonged use of high doses of vasopressors.

Recent quantitative syntheses reinforce these results. Meta-analyses published in 2024 identified an increase in mean arterial pressure, a reduction in serum lactate levels, a decrease in the duration of vasopressor support, and a possible reduction in short-term

mortality in patients treated with methylene blue, although with a degree of certainty considered low, due to the methodological heterogeneity and limited sample size of the available studies (NG et al., 2024; FERNANDO et al., 2024). These data point to a consistent hemodynamic benefit, but it is still insufficient to support definitive recommendations in international sepsis management guidelines.

Despite pathophysiological plausibility and promising preliminary clinical results, substantial gaps persist regarding dose standardization, optimal timing of administration, and the actual impact on robust clinical outcomes such as mortality and organ dysfunction. Multicenter protocols currently under development seek to clarify these issues and establish more solid therapeutic parameters (JIA et al., 2024). In this context, the present study aims to critically analyze the evidence published in the last decade about the efficacy, safety, and protocols for the use of methylene blue as an adjuvant therapy in refractory septic shock, with emphasis on hemodynamic and clinical outcomes.

## 2 METHODOLOGY

The present study is characterized as an integrative review of the literature, conducted in a systematic way and based on the methodological framework proposed by Whitemore and Knafl (2005), which comprises five structured stages: identification of the problem, systematic search of the literature, critical evaluation of the selected studies, analysis and synthesis of data and presentation of results. The choice of this design is justified by the methodological heterogeneity of the publications on the use of methylene blue in refractory septic shock, including randomized clinical trials, observational studies, systematic reviews, and clinical trial protocols. The integrative review enables the incorporation and critical analysis of different levels of evidence, favoring a comprehensive understanding of hemodynamic effects, therapeutic safety, and administration strategies described in the recent literature.

The guiding question was defined as: what scientific evidence published in the last decade supports the efficacy, safety, and protocols for the use of methylene blue as an adjunctive therapy in refractory septic shock? The formulation of the question was based on the PICO strategy, contemplating the population of interest (adult patients with refractory septic shock), the phenomenon of interest (use of methylene blue) and the context (intensive care units), ensuring clear conceptual delimitation and alignment with the study objective.

The bibliographic search was carried out in the PubMed/MEDLINE, SciELO and ScienceDirect databases, from January 2014 to December 2024. Controlled descriptors from Medical Subject Headings (MeSH) and free terms combined by Boolean operators

(AND/OR) were used, structured to increase the sensitivity and specificity of the search. The strategy included the following combinations: "Septic Shock" AND "Methylene Blue"; "Refractory Septic Shock" AND "Methylene Blue"; "Vasoplegic Shock" AND "Methylene Blue"; "Nitric Oxide" AND "Septic Shock"; "Vasopressors" AND "Methylene Blue". Studies published in English, Portuguese or Spanish were included. In addition, a manual search was carried out in the reference lists of the selected articles.

The identified records were exported to bibliographic management software, with automated removal and subsequent manual duplicate checking. The selection of studies occurred in three stages: reading of titles, analysis of abstracts and full reading of potentially eligible texts. The process was conducted by two independent reviewers, with resolution of disagreements by consensus.

We included randomised controlled trials involving adult patients diagnosed with septic shock, systematic reviews and meta-analyses related to the use of methylene blue in this setting, observational studies with a specific focus on refractory septic shock, and multicentre clinical trial protocols. Experimental studies in animal models, duplicate publications, studies without access to full text, and investigations whose focus was not directly related to the use of methylene blue in septic shock were excluded.

The critical evaluation of the studies considered the methodological design, the sample size, the diagnostic criteria used, the definition of the outcomes, the internal consistency of the results, and the limitations recognized by the authors. The interpretation respected the hierarchy of evidence, attributing greater analytical weight to randomized controlled trials and systematic reviews.

Data extraction was carried out using a standardized instrument, including: authorship, year and country of publication; design; sample characteristics; methylene blue administration protocol (dose, route and duration); hemodynamic outcomes; clinical outcomes; and adverse events. The information was organized in a comparative table to support critical analysis.

The synthesis of the results was conducted in a qualitative and interpretative way. Considering the clinical and methodological heterogeneity among the included studies, no additional meta-analysis was performed, and a structured narrative approach was adopted to integrate the findings.

### **3 RESULTS**

The integrated analysis of the included studies showed consistency regarding the hemodynamic effect of methylene blue as an adjuvant therapy in refractory septic shock,

particularly in reducing vasopressor dependence and increasing mean arterial pressure. Randomized controlled trials, recent meta-analyses, and observational studies were included, totaling approximately 300 patients in the available quantitative syntheses. Although the magnitude of the effects varies between the designs, convergence in the improvement of hemodynamic stability is observed as the predominant intermediate outcome.

Among randomized controlled trials, early administration of methylene blue was associated with significantly reduced time to discontinuation of vasopressors and decreased length of hospital stay, with no statistically significant increase in serious adverse events (Ibarra-Estrada et al., 2023). Similarly, a clinical trial conducted in Brazil demonstrated that continuous infusion of the drug, associated with standard treatment, promoted earlier reduction in the doses of noradrenaline and vasopressin, reinforcing the potential catecholamine-sparing effect (Luis-Silva et al., 2024). In both studies, no significant differences were observed in the incidence of major adverse events, although statistical power for safety was limited.

Meta-analyses published in 2024 broadened the interpretation of these findings by aggregating data from multiple clinical trials. A systematic review involving six randomized trials ( $n = 302$  patients) identified a reduction in short-term mortality (RR 0.66; 95% CI 0.47–0.94), decreased duration of vasopressor use (mean difference of  $-31.1$  hours), and reduced length of hospital stay, although with evidence classified as low-certain, due to imprecision and reduced number of events (Fernando et al., 2024). Convergently, another meta-analysis observed a significant increase in mean arterial pressure, a reduction in serum lactate levels, and a possible reduction in mortality (OR 0.49; 95% CI 0.27–0.88), highlighting, however, relevant methodological heterogeneity among the included studies (Ng et al., 2024). The directional consistency of the results strengthens the hypothesis of clinical benefit, although statistical robustness remains limited.

Observational studies and clinical reports complement the evidence by describing hemodynamic improvement in scenarios of shock refractory to multiple vasopressors. A report involving prolonged continuous infusion documented reversal of vasoplegia even in a patient on advanced support, including ECMO (Jaiswal et al., 2020). Similar findings have been described in catecholamine-resistant shock, with increased blood pressure and reduced need for vasopressor agents (Pluta et al., 2023). Despite the lower hierarchical level of evidence, these studies reinforce the clinical coherence of the findings observed in the controlled trials.

Regarding administration protocols, relevant heterogeneity was observed in therapeutic strategies, including intravenous boluses between 1 and 3 mg/kg, followed or not by continuous infusion of approximately 0.5 mg/kg/h for up to 48 hours (Luis-Silva et al., 2024). A recent multicenter protocol proposes an initial bolus of 2 mg/kg followed by continuous infusion for 48 hours, with a primary endpoint focused on reducing the need for vasopressors (Jia et al., 2024), which may contribute to future standardization.

Overall, the findings point to a consistent hemodynamic benefit of methylene blue in refractory septic shock, especially in intermediate outcomes. However, despite favorable signs regarding short-term mortality and length of hospital stay, the overall quality of the evidence remains classified as low to moderate, due to the limited number of clinical trials, small sample size, and methodological heterogeneity among the included studies (Fernando et al., 2024; Ng et al., 2024).

#### 4 DISCUSSION

The present integrative review demonstrates that methylene blue exerts a consistent hemodynamic effect as an adjunctive therapy in refractory septic shock, particularly in reducing the duration of vasopressor support and elevating mean arterial pressure. These findings should be interpreted in light of the contemporary definition of septic shock established by the Sepsis-3 consensus, characterized by the need for vasopressors to maintain mean arterial pressure  $\geq 65$  mmHg and serum lactate levels  $> 2$  mmol/L in the absence of hypovolemia (SINGER et al., 2016). In this clinical context of high severity and prognostic risk, interventions capable of modulating refractory vasoplegia assume potential therapeutic relevance.

The convergence between randomized controlled trials, recent meta-analyses, and observational evidence confers external coherence to the findings and supports the clinical plausibility of methylene blue as a modulator of sepsis-associated vasoplegia. The pathophysiological rationale is based on the inhibition of guanylate cyclase and the modulation of the nitric oxide-cGMP pathway, a central mechanism in the loss of systemic vascular tone described in severe sepsis. This process involves endothelial dysfunction, systemic inflammatory activation, and dysregulation of nitric oxide-dependent vascular signaling, components widely described in the pathophysiology of septic vasoplegia (LEVY et al., 2018; COTTYN et al., 2022; ELMATI et al., 2025).

The available randomized controlled trials demonstrate measurable hemodynamic benefit, especially in reducing the time to discontinuation of vasopressors (IBARRA-ESTRADA et al., 2023) and in the early decrease of noradrenaline and vasopressin doses

(LUIS-SILVA et al., 2024). These results suggest a potential catecholamine-sparing effect, which may be clinically relevant in view of the adverse effects associated with the prolonged use of high doses of vasopressors. In comparison, vasopressin is currently used as an adjunctive agent for reducing the dose of noradrenaline in septic shock, although its impact on mortality remains limited (RUSSELL, 2019). In this scenario, methylene blue represents a pathophysiologically distinct strategy, still in the process of consolidating clinical evidence.

Recent meta-analyses expand this interpretation by suggesting a possible impact on more robust clinical outcomes as well, including short-term mortality (FERNANDO et al., 2024; NG et al., 2024). However, although statistically significant, these estimates are accompanied by relatively large confidence intervals and classified as low-certainty evidence, reflecting a limited number of events, small sample sizes, and methodological heterogeneity among the included trials. The possibility of overestimation of the effect cannot be ruled out, especially in emerging interventions with predominantly small studies.

It is important to emphasize that hemodynamic benefit is an intermediate outcome. The translation of this effect to sustained reduction in mortality or persistent organ dysfunction remains uncertain. Most studies focus on short-term outcomes, with a paucity of data from prolonged follow-up. In addition, there are no robust subgroup analyses capable of identifying profiles of patients potentially more responsive to the intervention, such as those with predominant vasoplegia compared to patients with a significant component of associated myocardial dysfunction.

Observational studies and clinical reports reinforce the applicability of methylene blue in extreme refractoriness scenarios, including in patients under advanced circulatory support, such as ECMO (JAISWAL et al., 2020; PLUTA et al., 2023). However, the lower hierarchical level of this evidence prevents definitive causal inferences, and such findings should be interpreted as exploratory support.

Another relevant aspect refers to the absence of therapeutic standardization. Significant variation is observed in dose, time of administration, and duration of infusion (LUIS-SILVA et al., 2024; JIA et al., 2024), which makes it difficult to compare studies and define an ideal clinical protocol. The conclusion of ongoing multicenter trials may contribute to reducing this uncertainty and establishing more uniform parameters of use.

Finally, it is noteworthy that current international guidelines prioritize noradrenaline as a first-line vasopressor and do not include methylene blue as a formal recommendation in the management of septic shock (EVANS et al., 2021). This gap shows that, although promising, the intervention still lacks evidence of greater methodological robustness for routine incorporation into clinical practice.

In summary, methylene blue has a consistent and pathophysiologically plausible hemodynamic benefit in the context of refractory septic shock. However, the available evidence remains limited by small sample sizes, methodological heterogeneity, and the absence of large, multicenter trials assessing long-term clinical outcomes. Thus, its use should be carefully considered, in light of the patient's clinical profile and the absence of specific contraindications, until additional studies confirm a sustained prognostic impact.

## 5 CONCLUSION

The present integrative review demonstrates that methylene blue has consistent hemodynamic benefit as an adjunctive therapy in refractory septic shock, particularly in reducing the duration of vasopressor support and improving mean arterial pressure. The available evidence also suggests possible reduction in short-term mortality and improvement of hemodynamic markers; However, the overall quality of the evidence remains classified as low to moderate, mainly due to the limited number of trials, small sample size, and methodological heterogeneity among the included studies. The most robust benefits are found to be concentrated in intermediate outcomes, while the definitive impact on harsh clinical outcomes, especially long-term mortality, has yet to be confirmed. From the pathophysiological point of view, the therapeutic rationale of methylene blue is based on the modulation of the nitric oxide–cGMP pathway, a central mechanism in septic vasoplegia; However, the lack of standardization regarding the time of administration, ideal dose, and duration of infusion constitutes a relevant obstacle to the consolidation of formal clinical recommendations. Thus, methylene blue is a promising intervention in the management of refractory septic shock, but its routine incorporation into clinical practice depends on robust multicenter randomized clinical trials, with standardized protocols and evaluation of long-term clinical outcomes capable of confirming sustained prognostic benefit.

## REFERENCES

- Cottin, J., et al. (2022). The role of methylene blue in the management of vasoplegic shock. *Journal of Critical Care*, 69, 154–161. <https://doi.org/10.1016/j.jcrc.2022.02.003>
- Elmati, A., et al. (2025). Methylene blue in the critical care setting: Current evidence and future perspectives. *Critical Care Medicine*, 53(1), e12–e20.
- Evans, L., et al. (2021). Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock 2021. *Intensive Care Medicine*, 47, 1181–1247. <https://doi.org/10.1007/s00134-021-06506-y>
- Fernando, S. M., et al. (2024). Methylene blue in septic shock: A systematic review and meta-analysis. *Critical Care*, 28(1), Article 45. <https://doi.org/10.1186/s13054-024-04875-4>

- Ibarra-Estrada, M. Á., et al. (2023). Early adjunctive methylene blue in patients with septic shock: A randomized controlled trial. *Intensive Care Medicine*, 49(5), 593–602. <https://doi.org/10.1007/s00134-023-07024-1>
- Jaiswal, S., et al. (2020). Extended continuous infusion of methylene blue for refractory septic shock: A case report. *Journal of Critical Care*, 58, 230–233. <https://doi.org/10.1016/j.jcrc.2020.04.012>
- Jia, Y., et al. (2024). Efficacy of methylene blue in refractory septic shock: Protocol for a multicenter randomized controlled trial. *Trials*, 25(1), Article 102. <https://doi.org/10.1186/s13063-024-07941-2>
- Levy, B., et al. (2018). Vasoplegia in septic shock: Pathophysiology and management. *Intensive Care Medicine*, 44, 202–214. <https://doi.org/10.1007/s00134-018-5216-9>
- Luis-Silva, M., et al. (2024). Methylene blue therapy in addition to standard treatment in septic shock: Randomized clinical trial. *Revista Brasileira de Terapia Intensiva*, 36(1), 45–53. <https://doi.org/10.5935/0103-507X.20240005>
- Ng, K., et al. (2024). The use of methylene blue in adult patients with septic shock: A meta-analysis. *Journal of Intensive Care*, 12(1), Article 18. <https://doi.org/10.1186/s40560-024-00695-8>
- Russell, J. A. (2019). Vasopressin in septic shock. *Intensive Care Medicine*, 45, 1070–1072. <https://doi.org/10.1007/s00134-019-05548-x>
- Singer, M., et al. (2016). The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*, 315(8), 801–810. <https://doi.org/10.1001/jama.2016.0287>
- Whittemore, R., & Knafl, K. (2005). The integrative review: Updated methodology. *Journal of Advanced Nursing*, 52(5), 546–553. <https://doi.org/10.1111/j.1365-2648.2005.03621.x>