



Original Research Article

EFFICACY OF EARLY ADJUNCTIVE METHYLENE BLUE IN PATIENTS WITH SEPTIC SHOCK: AN AMBISPECTIVE OBSERVATIONAL STUDY IN A TERTIARY CARE HOSPITAL IN COIMBATORE

Naveenraj P.¹, Dhilipan K.², Gowtham V.³

¹Post Graduate Resident, Department of Emergency Medicine, Kovai Medical Center and Hospital, Coimbatore, Tamil Nadu, India.

²Associate Professor, Department of Emergency Medicine, KMCH Institute of Health Sciences and Research, Coimbatore, Tamil Nadu, India.

³Senior Resident, Department of Emergency Medicine, Kovai Medical Center and Hospital, Coimbatore, Tamil Nadu, India.

Received : 15/01/2026
Received in revised form : 04/03/2026
Accepted : 20/03/2026

Corresponding Author:

Dr. Naveenraj P.,
Post Graduate Resident, Department of
Emergency Medicine, Kovai Medical
Center and Hospital, Coimbatore, Tamil
Nadu, India.
Email: rajnaveen.dr@gmail.com

DOI: 10.70034/ijmedph.2026.1.581

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2026; 16 (1); 3392-3397

ABSTRACT

Background: Septic shock is characterised by profound vasodilation, refractory hypotension, and high mortality despite standard therapy. Methylene blue (MB) has emerged as a potential adjunct to restore vascular tone and improve haemodynamic stability by inhibiting the nitric oxide–cGMP pathway. This study aimed to evaluate the efficacy of early adjunctive MB in patients with septic shock.

Materials and Methods: An ambispective observational study was conducted on 66 patients at Kovai Medical Centre and Hospital from January 2023 to January 2026. Patients were divided into two groups: those receiving methylene blue in addition to standard sepsis care and those receiving standard care. Baseline characteristics and haemodynamic parameters were recorded at baseline and 6–72 h. Outcomes included vasopressor duration, lactate clearance, ICU stay, and haemodynamic stabilisation.

Results: A total of 66 patients were included (33 patients per group). MAP was significantly higher in the MB group from 6 h onwards ($p = 0.016$ at 6 h; $p < 0.001$ at 12 and 24 h), with significant time, group, and interaction effects (all $p < 0.001$). Norepinephrine requirement was similar at baseline ($p = 0.608$) but significantly lower in the MB group at 12 and 24 h (both $p = 0.001$), with significant overall group and interaction effects ($p = 0.024$ and $p < 0.001$). Lactate levels differed significantly at 48 h ($p = 0.037$), and lactate clearance was higher in the MB group at 24, 48, and 72 h ($p = 0.026$, $p < 0.001$, and $p = 0.022$, respectively). The MB group showed significantly earlier vasopressor discontinuation ($p = 0.004$) and higher methemoglobin levels ($p < 0.001$) than the control group.

Conclusion: Early methylene blue administration was well tolerated and was associated with faster haemodynamic stabilisation and improved metabolic response in patients with septic shock.

Keywords: Shock, Septic; Methylene Blue; Vasoplegia; Vasoconstrictor Agents; Hemodynamics.

INTRODUCTION

Septic shock represents the most severe subset of sepsis, characterised by profound circulatory and cellular/metabolic abnormalities, leading to hypotension and tissue hypoperfusion. It remains a leading cause of death in critically ill patients.^[1] Despite early recognition and standard treatment

(fluids, antibiotics, and vasopressors), mortality remains high.^[2] Despite adequate fluid resuscitation, a subset of patients develops vasoplegia with persistent hypotension, creating a major therapeutic challenge.^[3]

Excess nitric oxide (NO) production contributes to profound vasodilation and loss of vascular tone in patients with septic shock. Inducible nitric oxide

synthase (iNOS) produces high levels of NO that enter vascular smooth muscle, activate soluble guanylate cyclase, increase cGMP, and cause vasodilation.^[4] In septic shock, loss of vascular tone leads to arterial hypotension and impaired tissue perfusion. Vasopressor therapy with norepinephrine is typically required to restore mean arterial pressure (MAP) and improve organ perfusion.^[5]

Non-adrenergic vasopressors, such as vasopressin and angiotensin II, have been used as adjuncts to manage vasodilation in patients with septic shock. However, the response may be variable, and adverse effects, such as arrhythmias or ischaemic complications, may limit their use in selected patients.^[6] Methylene Blue (MB) counteracts NO-mediated vasodilation by inhibiting soluble guanylate cyclase and limiting downstream cGMP signalling. It has been investigated as an adjunct to catecholamine-resistant or refractory septic shock. By targeting the NO–cGMP pathway, MB may restore vascular tone and improve response to vasopressors.^[7]

The use of MB in sepsis dates back to the late 1990s. Early clinical studies have shown that short infusions of norepinephrine can raise systemic vascular resistance and MAP in patients with septic shock, without much change in cardiac output.^[8] A few reports have mentioned possible effects on pulmonary pressures and oxygenation, which have led to safety concerns. Over the past two decades, growing clinical experience has clarified dose-related effects and supported an acceptable safety profile when administered as a controlled infusion rather than a bolus.^[7]

Recent trials and systematic reviews suggest the potential haemodynamic benefits of MB as an adjunct in septic shock, particularly reduced vasopressor duration and earlier MAP improvement. A meta-analysis of randomised controlled trials demonstrated that MB significantly reduced the total duration of vasopressor therapy and hospital stay, and improved MAP within the first six hours, indicating an early haemodynamic benefit, without an associated increase in adverse events.^[9] Another systematic review similarly reported shorter ICU stay, fewer days on mechanical ventilation, and earlier vasopressor tapering among patients receiving MB compared to those on standard therapy alone.^[10] This mechanism suggests the greatest benefit when MB is administered early in septic shock, when vasoplegia is predominantly nitric oxide-driven. A prospective randomised trial found that MB given within 24 hours of septic shock was associated with earlier vasopressor discontinuation, shorter ICU and hospital stay, and no major adverse effects.^[11] An Indian randomised controlled trial comparing early MB with vasopressin showed both agents effectively improved MAP, with MB demonstrating comparable safety and no excess renal dysfunction.^[12]

Additional pilot trials and observational studies have shown that continuous MB infusion reduces vasopressor requirements, improves perfusion

indices, and may exert immunomodulatory effects.^[13,14] A recent multicentre protocol proposed standardised MB dosing to further evaluate its impact on vasopressor dependence, organ dysfunction, and survival.^[15] However, MB is not yet included in standard sepsis guidelines because of limited sample sizes, heterogeneous dosing regimens, and uncertainty regarding optimal timing. Some reports have mentioned that very late or high-dose use of MB may temporarily worsen pulmonary haemodynamics or cause mild hypoxia, although these changes are usually dose-related and reversible.^[16] However, evidence remains limited in real-world emergency department settings, particularly regarding early initiation and haemodynamic response over the first 72 hours. Therefore, local observational data are required to evaluate the efficacy and safety of early adjunctive MB in conjunction with standard sepsis care.

Aim

This study aimed to evaluate the efficacy of early adjunctive MB in patients with septic shock in the emergency department.

MATERIALS AND METHODS

An ambispective observational study was conducted on 66 patients at the Emergency Department of Kovai Medical Centre and Hospital (KMCH), Coimbatore, between January 2023 and January 2026. Ethical approval was obtained from the Institutional Ethics Committee, KMCH. Written informed consent was obtained from the patients or their legally authorised representatives.

Inclusion Criteria

Patients aged ≥ 18 years, with a confirmed diagnosis of septic shock per the Sepsis-3 criteria, and initiation of vasopressors following adequate fluid resuscitation were included. Septic shock was defined according to the Sepsis-3 criteria: the requirement of vasopressors to maintain MAP ≥ 65 mmHg and serum lactate >2 mmol/L despite adequate fluid resuscitation.

Exclusion Criteria

Patients with pre-existing severe organ dysfunction (e.g. advanced chronic kidney disease), prior MB administration before arrival at the KMCH Emergency Department, and with haemorrhagic, obstructive, or hypovolemic shock were excluded from the study.

Methods

Patients were categorised into two groups: MB group: Patients receiving MB along with standard sepsis management. Control group: Patients receiving standard sepsis management.

Baseline demographic variables, clinical characteristics, comorbidities, and illness severity (APACHE II and SOFA scores) were also recorded. Haemodynamic parameters, including MAP and vasopressor requirements (converted to norepinephrine equivalents), were documented at

baseline and 6, 12, 24, 48, and 72 h after treatment initiation. The metabolic response was assessed using serial lactate values and lactate clearance. Additional outcomes included the time to vasopressor discontinuation and length of ICU and hospital stay. All clinical and laboratory data were extracted from the documented case records maintained in the Medical Records Department (MRD).

Statistical Analysis

Data were summarised using the mean and standard deviation for continuous variables and frequency with percentage for categorical variables. Continuous variables were compared using independent sample t-tests. Repeated measures comparisons over time were performed using a mixed-model ANOVA. Categorical variables were analysed using Pearson's

chi-square test. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using IBM SPSS version 29.0.

RESULTS

A total of 66 patients were included in the study (33 per group). The baseline demographic characteristics were comparable between the MB and control groups, with no significant differences in age distribution ($p = 0.685$) and sex ($p = 0.215$). Pulmonary infection was the most common source of sepsis in both groups (42.4% vs. 54.5%; $p = 0.086$). [Table 1]

Table 1: Baseline demographic characteristics and source of infection

Variable	Category	MB group	Control group	P-value
Age group (years)	<30	2 (6.1%)	2 (6.1%)	0.685
	31-40	5 (15.2%)	3 (9.1%)	
	41-50	13 (39.4%)	10 (30.3%)	
	51-60	9 (27.3%)	10 (30.3%)	
	>61	4 (12.1%)	8 (24.2%)	
Sex	Female	12 (36.4%)	17 (51.5%)	0.215
	Male	21 (63.6%)	16 (48.5%)	
Infection source	Intra-abdominal	9 (27.3%)	13 (39.4%)	0.086
	Pulmonary	14 (42.4%)	18 (54.5%)	
	Urinary	4 (12.1%)	1 (3.0%)	
	Other	6 (18.2%)	1 (3.0%)	

Baseline severity measures were similar between the groups. The mean APACHE II score was 22.61 ± 4.70 in the MB group and 23.76 ± 3.10 in the control group ($p = 0.244$). The mean SOFA score was 10.67

± 2.87 in the MB group and 10.39 ± 3.51 in the control group ($p = 0.731$). Shock-to-intervention time did not differ significantly between the groups (7.85 ± 2.31 vs. 7.28 ± 1.55 hours; $p = 0.247$) (Table 2).

Table 2: Comparison of baseline disease severity and shock characteristics between the groups

Parameter	MB group	Control group	P-value
APACHE II score	22.61 ± 4.70	23.76 ± 3.10	0.244
SOFA score	10.67 ± 2.87	10.39 ± 3.51	0.731
Shock to intervention time (hours)	7.85 ± 2.31	7.28 ± 1.55	0.247

MAP at baseline was comparable between the groups (67.17 ± 4.28 vs. 67.22 ± 4.41 mmHg; $p = 0.964$). MAP was significantly higher in the MB group at 6 h ($p = 0.016$) and remained significantly higher at 12 and 24 h (both $p < 0.001$) (Figure 1). Mixed-model ANOVA demonstrated significant effects of time, group, and time \times group interaction (all $p < 0.001$), indicating a faster MAP response in the MB group. [Table 3]

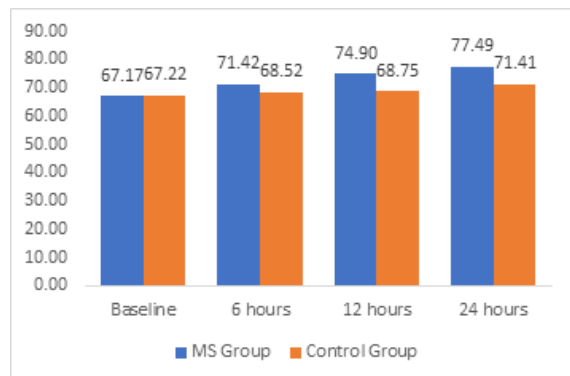


Figure 1: MAP between groups across time intervals

Table 3: Summary of mixed-model ANOVA results for MAP between groups

Effect	F (df)	P-value	Partial η^2
Time Effect	120.84 (2.23, 142.58)	<0.001	0.654
Group Effect	11.09 (1, 64)	0.001	0.148
Time \times Group Interaction	28.33 (2.23, 142.58)	<0.001	0.307
Estimated Mean MAP	MB: 72.74 mmHg; Control: 68.97 mmHg	-	-
Pairwise Comparison	Mean Diff = 3.77 mmHg	0.001	-

The baseline norepinephrine requirement was similar between the groups ($p = 0.608$). At 12 and 24 h, norepinephrine requirements were significantly lower in the MB group (both $p = 0.001$) (Figure 2). Mixed-model ANOVA revealed significant time, group, and time \times group interaction effects ($p < 0.001$). [Table 4]

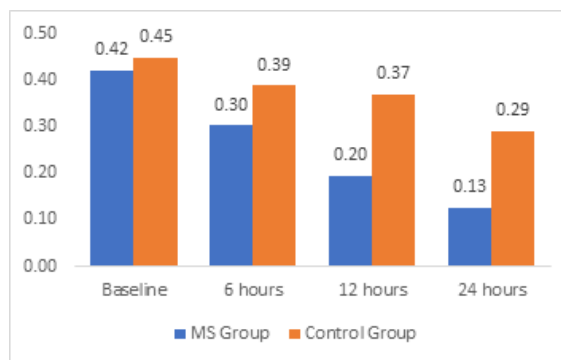


Figure 2: Norepinephrine requirement between groups across time intervals

Table 4: Summary of mixed-model ANOVA results for norepinephrine requirement between groups

Effect	F (df)	P-value	Partial η^2
Time Effect	188.25 (2.37, 151.62)	<0.001	0.746
Group Effect	5.35 (1, 64)	0.024	0.077
Time \times Group Interaction	24.82 (2.37, 151.62)	<0.001	0.279
Estimated Mean NE	MB: 0.261; Control: 0.374	-	-
Pairwise Comparison	Mean Diff = -0.113 $\mu\text{g/kg/min}$	0.024	-

Baseline lactate values were comparable between the MB and control groups (5.12 ± 2.16 vs. 5.33 ± 2.13 mmol/L; $p = 0.687$). Lactate levels declined over time in both groups, with significantly lower lactate levels observed in the MB group at 48 h ($p = 0.037$). Lactate clearance was significantly higher in the MB group at 24, 48, and 72 h ($p = 0.026$, $p < 0.001$, and $p = 0.022$, respectively).

Time to vasopressor discontinuation was significantly shorter in the MB group (48.95 ± 20.63

vs 63.72 ± 15.32 hours; $p = 0.004$). The ICU and total hospital stays were shorter in the MB group, but the differences were not statistically significant.

Regarding safety, maximum methaemoglobin levels were significantly higher in the MB group ($2.73 \pm 0.67\%$ vs $0.66 \pm 0.21\%$; $p < 0.001$). Urine discoloration was observed in 12 patients (18.2%) in the MB group, without serious adverse events. [Table 5]

Table 5: Comparison of metabolic response, clinical outcomes, and adverse effects between the groups

Parameter	Category	MB group (mmol/L)	Control group (mmol/L)	P-value
Lactate levels (mmol/L)	Baseline	5.12 ± 2.16	5.33 ± 2.13	0.687
	24 hours	3.39 ± 2.26	4.16 ± 2.41	0.187
	48 hours	2.25 ± 2.20	3.40 ± 2.16	0.037
	72 hours	1.76 ± 1.86	2.68 ± 2.31	0.079
Lactate clearance (%)	24 hours	39.58 ± 23.92	26.42 ± 22.93	0.026
	48 hours	63.24 ± 23.56	40.82 ± 20.18	<0.001
	72 hours	71.39 ± 24.51	56.15 ± 28.14	0.022
Clinical outcomes	Time to vasopressor discontinuation (hours)	48.95 ± 20.63	63.72 ± 15.32	0.004
	ICU stay (days)	3.09 ± 1.96	3.64 ± 1.88	0.253
	Hospital stay (days)	9.27 ± 3.44	10.70 ± 3.42	0.097
Safety profile	Maximum methaemoglobin (%)	2.73 ± 0.67	0.66 ± 0.21	<0.001
	Urine discoloration	12 (18.2%)	-	-

DISCUSSION

In the present study, the majority of patients were middle-aged, with no significant differences in age distribution, sex, or the source of infection. The APACHE II and SOFA scores were similar between the groups. Kirov et al. reported comparable baseline profiles, with a mean age of 55.3 ± 20.9 years in the MB group and 59.4 ± 14.5 years in controls, and equal sex distribution. Baseline SOFA scores were also similar (10.1 ± 2.1 vs. 10.5 ± 3.7).^[17] Memiş et al. likewise demonstrated comparable baseline illness severity, with APACHE II scores of 13.3 ± 5.3 versus 14.4 ± 5.2 and SOFA scores of 6.2 ± 3.3 versus 7.06

$\pm 5.17.18$ Donati et al. and Sari-Yavuz et al. enrolled more severely ill populations, reporting APACHE II scores of 22 and 25.8 ± 6.4 , and SOFA scores of 14 and 11.3 ± 3.0 , respectively.^{19,20} Ibarra-Estrada et al. also found balanced baseline characteristics, with APACHE II scores of 22.9 ± 4.4 versus 22.4 ± 4.4 and identical median SOFA scores of 10 (IQR 8–12).^[11]

In our study, the haemodynamic improvement was greater in the MB group. While baseline MAP and vasopressor doses were similar, the MB group demonstrated a faster and more sustained rise in MAP, along with earlier and greater reductions in norepinephrine requirements over time. These

findings align closely with Schneider et al., who described rapid MAP increases following MB administration, with one patient's MAP rising from 59 mmHg to 79 mmHg within 15 minutes after a 1 mg/kg dose, remaining between 78–89 mmHg after escalation to 2 mg/kg, and norepinephrine being discontinued within 12 hours in both reported cases.²¹ Gachot et al. similarly observed MAP rising from 69.7 ± 4.5 mmHg to 83.7 ± 5.1 mmHg within approximately 20 minutes of MB infusion ($p = 0.028$).²² Kirov et al. demonstrated significant MAP improvement compared with both baseline ($p = 0.018$) and controls ($p = 0.017$), persisting at 24 hours ($p = 0.04$), along with marked reductions in norepinephrine (87%), epinephrine (81%), and dopamine (40%) requirements.¹⁷⁷ Memiş et al. reported MAP increasing from 74.1 ± 10.2 mmHg to 85 ± 14 mmHg ($p < 0.001$), remaining significantly higher than controls after infusion.¹⁸¹

Donati et al. observed significant MAP elevations within 20 minutes ($p < 0.001$), sustained at one hour.¹⁹¹ Huang et al. found that MB increased MAP more than placebo, with a mean difference of 6.48 mmHg (95% CI 2.65–10.27; $p = 0.01$).²³ Zhao et al. reported a pooled MAP increase of 4.76 mmHg (95% CI 2.99–6.54; $p < 0.001$).²⁴¹ Fernando et al. demonstrated a MAP rise of 10.2 mmHg (95% CI 6.1–14.2) at six hours, along with a significant reduction in vasopressor duration of approximately 31 hours.⁹¹

In the present study, metabolic recovery was favoured by the MB group. Although the baseline lactate levels were similar, lactate levels declined more rapidly, and lactate clearance was consistently greater with MB. Evidence from previous studies supports this observation, although with some variability. Donati et al. reported a transient reduction in lactate at 20 minutes after MB administration ($p < 0.05$), but no sustained difference at later time points.¹⁹ In contrast, Huang et al. demonstrated a significant pooled reduction in lactate of -0.72 mmol/L (95% CI -1.33 to -0.12 ; $p = 0.02$).²³ Zhao et al. reported a stronger pooled reduction of -0.97 mmol/L (95% CI -1.34 to -0.59 ; $p < 0.001$).²⁴ Porizka et al. observed that MB responders had significantly lower lactate levels at 9 hours (4.2 ± 3.3 vs. 10.2 ± 1.5 mmol/L; $p = 0.007$) and 12 hours (3.4 ± 2.7 vs. 9.9 ± 2.2 mmol/L; $p = 0.002$) compared with non-responders.²⁵¹

In our study, patients who received MB achieved earlier vasopressor independence. The ICU stay and total hospital stay were not significantly different between the groups. Schneider et al. observed rapid vasopressor withdrawal, although both patients ultimately died, highlighting that haemodynamic improvement does not necessarily equate to survival benefit.²¹¹ Kirov et al. reported faster shock resolution, but no significant differences in ICU stay, hospital stay, or 28-day survival.¹⁷¹ Memiş et al. also found no significant differences in mortality, ventilation duration, or ICU stay, with identical mortality of 26.6% in both groups.¹⁸¹

Ballarin et al. demonstrated reductions in ICU stay ($p = 0.03$), mechanical ventilation duration ($p = 0.010$), and vasopressor duration ($p < 0.001$).¹⁰ Porizka et al. observed striking outcome differences between responders and non-responders, with early mortality of 0% versus 45.5% and 30-day mortality of 44.4% versus 100% ($p < 0.001$).²⁵¹ These mixed results suggest that MB may not confer a uniform survival benefit, but its ability to shorten the duration of circulatory failure is clinically meaningful and may influence outcomes in selected patients.

In our study, MB demonstrated an acceptable safety profile. Methemoglobin levels increased as expected but remained clinically manageable, and urine discoloration was the most frequent benign adverse effect. Kirov et al. reported a significant increase in methaemoglobin at 1, 2, and 6 hours ($p < 0.05$) compared with controls, along with transient blue-grey skin discoloration and blue urine lasting 2–4 days.¹⁷¹ Memiş et al. observed a mild rise in methaemoglobin from $0.88 \pm 0.06\%$ to $1.06 \pm 0.22\%$, normalising within 24 hours.¹⁸ Porizka et al., Zhao et al., and Ibarra-Estrada et al. reported no serious adverse effects, with only temporary blue discoloration.^{25,24,111} Maheshwari et al. similarly concluded that MB is generally well tolerated, with rare serious complications.²⁶¹ These data support the overall safety of MB when used judiciously in septic shock.

A key strength of this study is the evaluation of MB in terms of haemodynamics, metabolic response, and outcomes in both groups at baseline. Assessments allowed for tracking changes over time. Future research should be conducted as larger multicentre trials to confirm the benefits, define the dose and timing, and identify responders. Longer follow-up and biomarkers, including endothelial or pharmacogenomic data, may further clarify MB's role and support personalised treatment.

Limitations

This study has limitations, including a small sample size and single-centre design, which may affect generalisability. Follow-up included only short-term outcomes, and MB timing was not standardised. The study was not blinded, so bias may exist, and mechanistic biomarkers were not measured. Larger multicentre randomised trials are needed to validate these results.

CONCLUSION

Methylene blue use was associated with faster and more sustained haemodynamic stabilisation, as evidenced by higher MAP, reduced norepinephrine requirement, better lactate clearance, and earlier vasopressor discontinuation compared with standard therapy alone. The ICU and hospital stays were slightly shorter in the MB group, although the difference was not significant. The treatment was well tolerated, with expected transient effects, such as mild methaemoglobinaemia and urine

discolouration, and no serious adverse events. Overall, early MB administration may be a safe and potentially beneficial adjunctive therapy in the management of septic shock. However, larger multicentre randomised trials are needed to confirm these findings and define the optimal dosing and timing.

REFERENCES

- Astiz ME, Rackow EC. Septic shock. *The Lancet* 1998;351:1501–5. [https://doi.org/10.1016/S0140-6736\(98\)01134-9](https://doi.org/10.1016/S0140-6736(98)01134-9).
- Scheeren TWL, Bakker J, De Backer D, Annane D, Asfar P, Boerma EC, et al. Current use of vasopressors in septic shock. *Ann Intensive Care* 2019;9:20. <https://doi.org/10.1186/s13613-019-0498-7>.
- Levy B, Fritz C, Tahon E, Jacquot A, Auchet T, Kimmoun A. Vasoplegia treatments: the past, the present, and the future. *Crit Care* 2018;22:52. <https://doi.org/10.1186/s13054-018-1967-3>.
- Symeonides S, Balk RA. Nitric oxide in the pathogenesis of sepsis. *Infect Dis Clin North Am* 1999;13:449–63. [https://doi.org/10.1016/S0891-5520\(05\)70085-4](https://doi.org/10.1016/S0891-5520(05)70085-4).
- Thooft A, Favory R, Salgado DR, Taccone FS, Donadello K, De Backer D, et al. Effects of changes in arterial pressure on organ perfusion during septic shock. *Crit Care* 2011;15:R222. <https://doi.org/10.1186/cc10462>.
- Russell JA. Vasopressor therapy in critically ill patients with shock. *Intensive Care Med* 2019;45:1503–17. <https://doi.org/10.1007/s00134-019-05801-z>.
- Puntillo F, Giglio M, Pasqualucci A, Brienza N, Paladini A, Varrassi G. Vasopressor-Sparing Action of Methylene Blue in Severe Sepsis and Shock: A Narrative Review. *Adv Ther* 2020;37:3692–706. <https://doi.org/10.1007/s12325-020-01422-x>.
- Lo JCY, Darracq MA, Clark RF. A Review of Methylene Blue Treatment for Cardiovascular Collapse. *J Emerg Med* 2014; 46:670–9. <https://doi.org/10.1016/j.jemermed.2013.08.102>.
- Fernando S, Tran A, Soliman K, Flynn B, Oommen T, Li W, et al. Methylene Blue in Septic Shock: A Systematic Review and Meta-Analysis. *Crit Care Explor* 2024; 6. <https://doi.org/10.1097/cce.0000000000001110>.
- Ballarin RS, Lazzarin T, Zornoff LAM, Azevedo P, Pereira FWL, Tanni SE, et al. Methylene blue in sepsis and septic shock: a systematic review and meta-analysis. *Front Med* 2024;11. <https://doi.org/10.3389/fmed.2024.1366062>.
- Ibarra-Estrada M, Kattan E, Aguilera-González PE, Sandoval-Plascencia L, Rico-Jauregui U, Gómez-Partida CA, et al. Early adjunctive methylene blue in patients with septic shock: a randomized controlled trial. *Crit Care* 2023;27. <https://doi.org/10.1186/s13054-023-04397-7>.
- Kuri HR, Sharma A, Meshram TM, Kothari N, Goyal S, Paliwal B, et al. Effects of Early Use of Methylene Blue and Vasopressin on Noradrenaline Dose in Septic Shock: A Randomized Controlled Trial. *Indian J Crit Care Med Peer-Rev Off Publ Indian Soc Crit Care Med* 2025; 29:108–12. <https://doi.org/10.5005/jp-journals-10071-24905>.
- Luis-Silva F, Meneguetti MG, Peres LM, Sepeda C dos R, Jordani MC, Mestriner F, et al. Methylene blue therapy in addition to standard treatment for acute-phase septic shock: a pilot randomized controlled trial. *Front Med* 2024;11. <https://doi.org/10.3389/fmed.2024.1431321>.
- Rajbanshi L, Bajracharya A, Arjyal B, Devkota D. Can Use of Intravenous Methylene Blue Improve the Hemodynamics and Outcome of the Patients with Refractory Septic Shock? An Observational Study. *Indian J Crit Care Med Peer-Rev Off Publ Indian Soc Crit Care Med* 2023; 27:669–74. <https://doi.org/10.5005/jp-journals-10071-24535>.
- Jia J, Ji J, Liu Z. Efficacy of methylene blue in refractory septic shock: study protocol for a multicenter, randomized, placebo-controlled trial. *Trials* 2024;25. <https://doi.org/10.1186/s13063-024-08439-5>.
- Arias-Ortiz J, Vincent J. Administration of methylene blue in septic shock: pros and cons. *Crit Care* 2024;28. <https://doi.org/10.1186/s13054-024-04839-w>.
- Kirov MY, Evgenov OV, Evgenov NV, Egorina EM, Sovershaev MA, Sveinbjörnsson B, et al. Infusion of methylene blue in human septic shock: a pilot, randomized, controlled study. *Crit Care Med*. 2001;29(10):1860–7. <https://pubmed.ncbi.nlm.nih.gov/11588440/>
- Memis D, Karamanlioglu B, Yuksel M, Gemlik I, Pamukcu Z. The influence of methylene blue infusion on cytokine levels during severe sepsis. *Anaesth Intensive Care*. 2002; 30:755–62. <https://pubmed.ncbi.nlm.nih.gov/12500513/>
- Donati A, Conti G, Loggi S, Münch C, Coltrinari R, Pelaia P, et al. Does methylene blue administration to septic shock patients affect vascular permeability and blood volume? *Crit Care Med*. 2002;30(10):2271–7. <https://pubmed.ncbi.nlm.nih.gov/12394955/>
- Sari-Yavuz S, Heck-Swain K-L, Keller M, Magunia H, Feng Y-S, Haerberle HA, et al. Methylene blue dosing strategies in critically ill adults with shock-A retrospective cohort study. *Front Med (Lausanne)* 2022; 9:1014276. <https://doi.org/10.3389/fmed.2022.1014276>.
- Schneider F, Lutun P, Hasselmann M, Stoclet JC, Tempé JD. Methylene blue increases systemic vascular resistance in human septic shock: Preliminary observations. *Intensive Care Med* 1992; 18:309–11. <https://doi.org/10.1007/bf01706481>.
- Gachot B, Bédos JP, Veber B, Wolff M, Régnier B. Short-term effects of methylene blue on hemodynamics and gas exchange in humans with septic shock. *Intensive Care Med* 1995; 21:1027–31. <https://doi.org/10.1007/bf01700666>.
- Huang X, Yan W, Chen Z, Qian Y. Effect of methylene blue on outcomes in patients with distributive shock: a meta-analysis of randomised controlled trials. *BMJ Open* 2024;14:e080065. <https://doi.org/10.1136/bmjopen-2023-080065>.
- Zhao C-C, Zhai Y-J, Hu Z-J, Huo Y, Li Z-Q, Zhu G-J. Efficacy and safety of methylene blue in patients with vasodilatory shock: A systematic review and meta-analysis. *Front Med (Lausanne)* 2022; 9:950596. <https://doi.org/10.3389/fmed.2022.950596>.
- Porizka M, Kopecky P, Dvorakova H, Kunstyr J, Lips M, Michalek P, et al. Methylene blue administration in patients with refractory distributive shock - a retrospective study. *Sci Rep* 2020; 10:1828. <https://doi.org/10.1038/s41598-020-58828-4>.
- Maheshwari N, Malkania B, Mudiyansele R. Methylene blue in septic shock: Emerging evidence, clinical applications, and future directions. *Cureus* 2025;17: e86701. <https://doi.org/10.7759/cureus.86701>.