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Perspective

The potential role of methylene blue as an adjunctive therapy in septic shock

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Methylene blue (MB) has attracted renewed interest in septic shock because it targets a clear biological mechanism. In vasoplegic shock, excessive nitric oxide (NO) signaling activates soluble guanylate cyclase (sGC) and cyclic guanosine monophosphate (cGMP), leading to profound vasodilation and loss of vascular tone. By blocking this pathway, MB may help restore vascular tone and reduce the need for conventional vasopressors.[1] However, MB should not be viewed simply as another vasopressor. The more important question is not whether MB works in all patients with septic shock but which patients are most likely to benefit and when it should be used.

The current evidence suggests that the most consistent effect of MB is vasopressor sparing. A systematic review and meta-analysis reported that MB shortened the duration of vasoactive support by approximately 31.49 h compared with standard therapy alone.[2] Earlier clinical studies also reported reductions in norepinephrine, epinephrine, and dopamine requirements in selected patients.[1,3] However, whether these vasopressor-sparing effects translate into lower mortality, shorter intensive care unit stay, shorter mechanical ventilation, or other patient-centered benefits remains uncertain. This distinction is important. MB may help reduce vasopressor dependence, but it has not yet been proven to improve major clinical outcomes.

This uncertainty is not surprising. Septic shock is not only a problem of low blood pressure, but it also involves microcirculatory failure, endothelial injury, mitochondrial dysfunction, metabolic stress, and organ failure. A recent randomized trial showed that MB improved sublingual microcirculatory parameters, including microvascular flow index, total vessel density, and perfused vessel density, while reducing flow heterogeneity.[4] However, this small trial did not establish whether these microcirculatory improvements translate into improved organ function or survival.[4] Therefore, the current evidence supports MB as a drug with measurable effects on hemodynamics and microcirculation, but not yet as a treatment that clearly changes patient-centered outcomes.

One reason for the inconsistent evidence may be that MB has often been tested in heterogeneous septic shock populations.[5] Septic shock changes over time. In the early phase, excessive NO–sGC–cGMP signaling can be a major driver of vasoplegia.[6] At this stage, MB has a strong biological rationale. As shock progresses, however, endothelial injury, oxidative stress, mitochondrial dysfunction, microvascular collapse, and multiorgan failure become more dominant.[7] In this later phase, low blood pressure may no longer be mainly driven by NO signaling. Blocking the NO–sGC pathway may then improve arterial pressure only temporarily, without reversing the underlying organ injury[6,7] (Figure 1).

This time-dependent model helps explain why early use may be more promising than late rescue therapy. In one placebo-controlled randomized trial, MB given within 24 h after starting norepinephrine shortened the time to vasopressor discontinuation and reduced intensive care unit length of stay.[8] In patients with cancer and septic shock, early adjunctive MB reduced the time to vasopressor discontinuation and increased vasopressor-free days, although larger multicenter validation is still needed.[9] These findings suggest that MB may work best as an early adjunct, before prolonged exposure to high-dose catecholamines and before irreversible microcirculatory and metabolic injuries become dominant. In contrast, late use may only produce a short-lived increase in blood pressure.

This perspective should change how future trials are designed. Trials should no longer ask only whether MB is effective in unselected septic shock. Instead, they should ask a more

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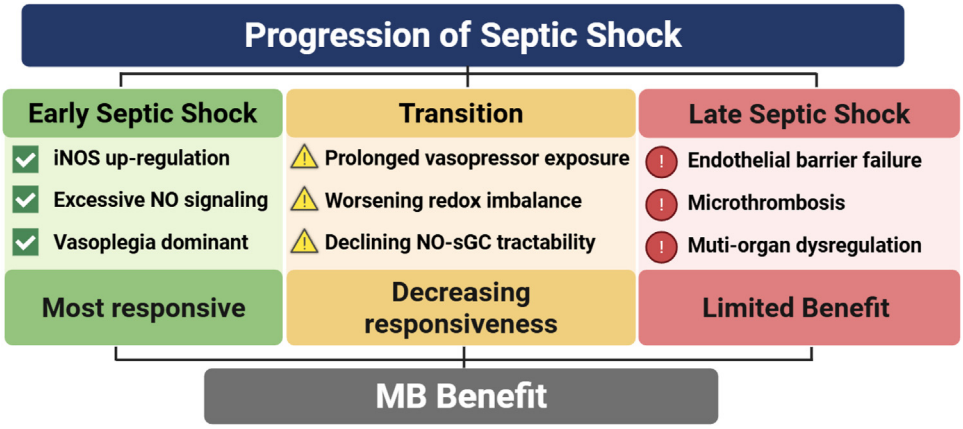


Figure 1. Therapeutic window of methylene blue in septic shock. MB is most likely to be effective in early septic shock, when vasoplegia is still largely driven by the NO–sGC–cGMP pathway. As shock progresses, oxidative stress, endothelial injury, mitochondrial dysfunction, and multiorgan dysregulation increasingly shape the hemodynamic phenotype, reducing the fraction of hypotension that remains responsive to MB. This stage-dependent transition supports earlier use of MB, ideally before prolonged high-dose vasopressor exposure and advanced organ failure.
cGMP, Cyclic guanosine monophosphate; MB, Methylene blue; NO, Nitric oxide; sGC, Soluble guanylate cyclase; iNOS, Inducible nitric oxide synthase.

precise question: in which vasoplegic phenotype, at what time point, and under which treatment framework does MB provide benefit? Future studies should enrich enrollment for patients with early distributive shock who still require high-dose vasopressors and whose hypotension is likely to be driven by NO-related vasodilation. Trial protocols should also standardize background care, including vasopressor escalation, corticosteroid use, fluid strategy, antibiotics, and source control.[10] Outcomes should include not only blood pressure or vasopressor dose, but also lactate clearance, microcirculatory indices, organ support-free days, and safety events. Without this alignment, any true treatment signal may remain diluted by the biological heterogeneity of septic shock.

In septic shock, intravenous administration remains the only route evaluated in interventional clinical studies. Available trials have used heterogeneous regimens, including bolus-plus-infusion protocols, fixed-dose prolonged infusion, and microcirculation-oriented strategies.[4,8,9,11] Because these studies differed in patient population, timing, co-interventions, and endpoints, no regimen can currently be considered clearly superior. Dosing should therefore be evaluated within phenotype- and timing-selected protocols, rather than treated as an isolated pharmacological issue.

Consistent with the 2026 Surviving Sepsis Campaign guidelines, current evidence remains insufficient to recommend intravenous injection MB as routine rescue therapy in refractory septic shock.[12] MB should be considered only as a selective adjunct to guideline-based septic shock care, rather than a replacement for standard therapies such as antibiotics, source control, fluids, vasopressors, or corticosteroids when indicated.[8,12] Its potential benefit should be interpreted as an incremental effect within integrated shock management.

Safety considerations further support a precision-use strategy. At commonly used intravenous doses, MB is generally well tolerated, and common effects such as blue-green discoloration of urine or secretions and mild gastrointestinal symptoms are usually reversible.[8,13] However, important risks must be considered. Glucose-6-phosphate dehydrogenase (G6PD) deficiency should be regarded as a major safety concern because MB may increase the risk of oxidative hemolysis and related complications in susceptible patients.[13,14] MB also inhibits monoamine oxidase A and may trigger serotonin syndrome when combined with selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), or other serotonergic drugs.[15,16] In addition, an abrupt fall in pulse oxygen saturation after MB administration often reflects optical interference with pulse oximetry rather than true hypoxemia.[17] Oxygenation should therefore be checked with arterial blood gas analysis and, when available, co-oximetry.

Special populations require particular caution. At excessive cumulative doses or under conditions of impaired clearance or reduced antioxidant capacity, MB may paradoxically contribute to oxidative hemolysis and, rarely, methemoglobinemia, even in patients without known G6PD deficiency.[13,18] In patients receiving extracorporeal blood purification or hemoadsorption, drug exposure may be difficult to predict. Similarly, pediatric and neonatal data remain limited, and adult septic shock evidence should not be directly extrapolated to these populations.[19–21]

Overall, MB should neither be promoted as a proven mortality-reducing therapy nor dismissed as an outdated drug with inconsistent evidence. The most reasonable position is that MB may be useful as an early, mechanism-guided adjunct in selected patients with NO–sGC–cGMP-driven vasoplegia. Future research should move beyond the broad question of whether MB works in septic shock. The field should instead define the right patient, the right timing, the right dose, and the right monitoring strategy. Only then can MB move from occasional rescue use to rational precision therapy.

Conclusions

MB should be reframed as an early, phenotype-guided adjunct for selected patients with NO–sGC–cGMP-driven vasoplegia. It is not a universal rescue vasopressor. Future trials should identify the patients, timing, dosing strategy, and safety framework most likely to produce meaningful clinical benefit.

CRediT Authorship Contribution Statement

Xinxin Cui: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis. **Jian Song:** Writing – review & editing. **Xiaohui Shi:** Writing – review & editing. **Xiaoxiao Sun:** Writing – review & editing. **Ding Zhang:** Writing – review & editing. **Linhao Ma:** Writing – review & editing. **Hui Chen:** Writing – review & editing. **Yu**

Li: Writing – review & editing, Writing – original draft, Supervision, Data curation, Conceptualization. **Zongping Fang:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

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Ethics Statement

Not applicable.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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