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CLINICAL INVESTIGATION

Methylene Blue Administration in Septic Shock: A Retrospective Cohort Study

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OBJECTIVES: To describe the epidemiology of methylene blue (MB) use in septic shock and explore the association between MB dose and hospital outcomes.

DESIGN: Retrospective cohort study.

SETTING: United States.

PATIENTS: Eight hundred fifty-nine thousand eight hundred sixty-eight adult (≥ 18 yr) patients from 1100 centers with a diagnosis of septic shock (sepsis with vasopressor administration), discharged from Premier Healthcare Database hospitals in the United States from 2008 to 2021.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: We included patients who received MB at any point during hospitalization (to describe utilization), then separately focused on those who received MB within the first 3 hospital days (to examine association of dose with outcomes). The primary outcome was hospital mortality. We used mixed-effects multivariable regression models to evaluate the MB use and the association between MB dose (modeled as a five-knot restricted cubic spline) and outcomes. Among patients with septic shock, 4082 patients (0.5%) from 663 hospitals received at least one dose of MB. Patients receiving MB tended to be younger and received major surgery. Hospitals in which MB was administered were larger urban teaching hospitals. After multivariable adjustment, use of MB was lower in 2016–2020 than in 2008. Of 2507 patients (61.4%) who received MB within the first 3 days of hospitalization, 375 (15.0%) died in hospital. Our spline analysis suggests a nonlinear association between MB dosing and outcomes among patients receiving MB early in their hospitalization.

CONCLUSIONS: Use of MB in septic shock is rare in the United States, but with substantial inter-hospital variability and decreased use over time through 2020. Randomized evidence is required to evaluate the efficacy and safety of MB.

KEYWORDS: critical care medicine; methylene blue; septic shock

Sepsis and septic shock are caused by a dysregulated host response to infection, resulting in organ dysfunction and, in many patients, death (1). Septic shock remains one of the leading causes of death worldwide, particularly in low- and middle-income countries (2). Treatment of patients with septic shock focuses on early initiation of broad-spectrum antimicrobials, source control where possible, and supportive management through fluid resuscitation and vasopressor administration, with the goal of maintaining organ perfusion (3). However, prolonged and high doses of vasoactive medications can be harmful and have been associated with tachyarrhythmia, myocardial dysfunction, and peripheral ischemia (4, 5). Therefore, there is an urgent need for alternative therapeutic agents to assist the hemodynamic support of patients with profound septic shock.

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KEY POINTS

Question: What is the epidemiology of methylene blue (MB) use in adult septic shock, and how is MB dosing association with hospital outcomes in this population?

Findings: In this retrospective cohort of 859,868 ICU patients with septic shock from 1,100 centers, 4,082 (0.5%) received at least one dose of MB. MB use was more common in younger patients, those receiving major surgery, and those cared for in teaching hospitals and urban settings. Use of MB declined over time before 2021, but varied notably among hospitals. Finally, MB dosing was nonlinearly associated with outcomes among patients receiving it early in their hospitalization.

Meaning: MB use is uncommon in septic shock, with substantial variability across time, patient populations, and hospitals. This variability emphasizes the need for high-quality, randomized data on the efficacy and safety of MB in septic shock.

Methylene blue (MB) restores vascular tone through inhibition of endothelial and inducible nitric oxide synthase (NOS) and its downstream enzyme soluble guanylate cyclase (6). MB restores vasoregulation in conditions of nitrous oxide up-regulation, improving hemodynamics in patients with profound vasoplegia (7). While only a few randomized trials have been conducted examining the efficacy of MB in septic shock, the existing data suggest that MB may improve short-term mortality (8). However, the risk of MB-associated adverse effects is unclear, and existing trials were underpowered for harm (9). This is particularly important as trials investigating other nonselective NOS inhibitors (e.g., N^G-monomethyl-L-arginine, 546C88) in septic shock found that these agents reduced cardiac output and increased mortality (10, 11).

Little data exist describing the epidemiology of MB in septic shock, including variability in administration and association of dosing with hospital outcomes. To address this important knowledge gap, we conducted a large, multicenter retrospective cohort study to investigate the epidemiology (current use and temporal trends) of MB use, as well as outcomes associated with MB dosing in the United States.

METHODS

We performed a retrospective cohort study using data from the Premier Healthcare Database (PHD) from 2008 to 2021. PHD is an enhanced all-payer administrative dataset inclusive of greater than 172 million visits across greater than 1400 health systems representing ~25% of all U.S. inpatient admissions (12). We followed recommendations regarding control of confounding factors in causal inference and prognostic studies conducted in critical care medicine (13, 14). Results are reported using the STrengthening the Reporting of OBservational Studies in Epidemiology statement (15). Studies using the PHD are exempt from Institutional Review Board approval at the University of Miami due to the retrospective analysis of de-identified data. The license University of Miami holds allows PHD data use for any academic project during the contracted license period.

Cohorts

We included patients meeting the following eligibility criteria: 1) age 18 years old or older; 2) discharged (alive or deceased) from hospital January 1, 2008, to December 31, 2021; 3) diagnosed with sepsis at the time of hospital admission; and 4) receiving vasopressors during their first hospital day (the first calendar day of hospitalization). We identified sepsis using *International Classification of Diseases* (ICD) coding described by Angus et al (16), and used previously in the PHD (17). "Sepsis" was defined as "severe sepsis" from the SEP-1 criteria (18), which is now defined as "sepsis" by the Sepsis-3 criteria (1). The requirement for vasopressors on hospital day 1 was to focus on patients with early sepsis and hypotension (as a surrogate for early septic shock).

To investigate utilization of MB, we then excluded patients for the following conditions: 1) transferred in from another hospital (given unknown time of shock development) or 2) documented methemoglobinemia (defined by ICD, 9th Revision 289.7 or 10th Revision D74; as MB administration is indicated for treatment). To examine the clinical association of differing doses of MB use, we further restricted this cohort to patients receiving MB early in their hospital stay (by hospital day 3). Patients were excluded if they were discharged on hospital day 1 or 2 or they received a total of less

than 5 mg or greater than 1000 mg of MB (outliers) across hospital days 1, 2, and 3 (8).

Exposures

For the MB epidemiology analysis, we focused on two primary exposures. First, we assessed the individual discharge hospital for each patient. Second, to explore temporal trends in MB use, we assessed the quarter (3-mo period) of hospital discharge for each patient. For the clinical outcomes analysis, we assessed the exposure of cumulative MB dosing on hospital days 1–3.

Outcome

To describe the utilization patterns of MB administration we evaluated the outcome of MB receipt (of any dose) at any point during hospitalization. Because medication use is identified by daily charge codes (without time stamps), we could not differentiate between bolus or continuous dosing of MB. To examine clinical outcomes following MB, we examined the primary outcome of hospital mortality and the secondary outcome of vasopressor-free days (VFDs) to hospital day 30.

Statistical Analyses

We used standard summary statistics to describe cohort patients (stratified by MB use and by hospital mortality). Unadjusted comparisons were assessed using standardized mean differences (SMDs). We then quantified mean daily MB dose, timing of initiation, and cumulative days of receipt using numbers and percentages.

To evaluate patient and hospital factors associated with MB administration, we created a mixed-effects multivariable logistic regression model with hospital of discharge as a random effect. We selected variables a priori, as recommended (13), and included patient characteristics (age, sex, race [White, Black, other/unknown], primary insurer [private, Medicare, Medicaid, or other], number of Elixhauser comorbidities [19], receipt of major surgery during the index hospitalization "defined by Healthcare Cost and Utilization Project major procedures 3 and 4" [20]), any invasive mechanical ventilation in the first 3 d of hospitalization, year of discharge, and hospital characteristics [teaching vs. nonteaching hospital, urban vs. rural setting, number of hospital beds (stratified as: 0–99, 100–199, 200–299, 300–399, 400–499, ≥ 500)], and U.S. region [Midwest, Northeast, South, West]). To allow better assessment of variability over time and across hospitals, we then reconstructed the same model among a cohort restricted to patients discharged from hospitals who contributed at least one patient to the cohort in all 14 of the study years.

We used the median odds ratio (MOR) to quantify the association of individual hospital with MB use (21, 22). The MOR, which is always greater than 1, is interpreted as the median relative change in odds of MB use when comparing patients from two randomly selected hospitals that are ordered by risk. The magnitude of the MOR can be compared directly with the odds ratios (ORs) of other patient-level covariates to assess the impact of center-level variation.

To evaluate the association of MB dose and outcomes of hospital mortality and VFD, we followed recommendations for causal inference (13). We created a five-knot restricted cubic spline for the primary exposure of total MB dose by hospital day 3 and visually interpreted these plots to identify inflection points. The categorization defined by these splines was subsequently included in mixed-effects multivariable regression models (logistic for mortality, Poisson for VFD), using the same variables as described above. As per recommendations (13), the final model was included in the **Electronic Appendix** (https://links.lww.com/CCM/H833) only, so as to avoid Table 2 Fallacy. Finally, as sensitivity analyses, we modeled the exposure of total MB dose in categories: 1) binary (< 200 vs. ≥ 200 mg) and 2) three-category (< 100 vs. 100–199 vs. ≥ 200 mg).

RESULTS

Cohort Characteristics

From 2008 to 2021, a total of 2,193,331 adult inpatients from 1,125 centers had a diagnosis of sepsis on hospital admission and received vasopressors during their hospitalization. A flow diagram is shown in **Supplemental Figure 1** (https://links.lww.com/CCM/H833). Following exclusion of patients transferred from another hospital (n = 257,816, 11.8%), those not on vasopressors on hospital day 1 (n = 1,075,581; 49.0%), and those with methemoglobinemia (n = 66; 0.003%), we included 859,868 patients with septic

TABLE 1.
Baseline Characteristics of Sepsis Patients Receiving Methylene Blue and Those That Did Not (*n* = 859,868)

Variable	Did Not Receive Methylene Blue (*n* = 855,786)	Received Methylene Blue (*n* = 4,082)	Standardized Mean Difference
Age, yr, mean (SD)	66.8 (14.9)	61.8 (15.3)	0.33
Female, *n* (%)	426,088 (49.8)	1,963 (48.1)	0.03
Race, *n* (%)			0.02
White	631,422 (73.8)	3,002 (73.5)	
Black	110,774 (12.9)	514 (12.6)	
Other/unknown	113,590 (13.3)	566 (13.9)	
Payor, *n* (%)			0.26
Private	121,887 (14.2)	942 (23.1)	
Medicare	580,102 (67.8)	2,293 (56.2)	
Medicaid	101,594 (11.9)	554 (13.6)	
Other	52,203 (6.1)	293 (7.2)	
Number of Elixhauser comorbidities, mean (SD)	5.7 (2.5)	5.4 (2.7)	0.11
Major surgery, *n* (%)	235,090 (27.5)	3,413 (83.6)	1.37
Mechanical ventilation by hospital day 3, *n* (%)	426,656 (49.9)	2,365 (57.9)	0.16
Teaching hospital, *n* (%)	388,619 (45.4)	2,270 (55.6)	0.21
Urban environment, *n* (%)	760,792 (88.9)	3,768 (92.3)	0.12
Hospital size (number of beds), *n* (%)			0.21
500+	273,702 (32.0)	1,517 (37.2)	
400–499	112,787 (13.2)	733 (18.0)	
300–399	166,022 (19.4)	668 (16.4)	
200–299	158,217 (18.5)	621 (15.2)	
100–199	112,572 (13.2)	426 (10.4)	
0–99	32,486 (3.8)	117 (2.9)	
U.S. region, *n* (%)			0.10
Midwest	181,479 (21.2)	968 (23.7)	
Northeast	102,893 (12.0)	528 (12.9)	
South	417,220 (48.8)	1,789 (43.8)	
West	154,194 (18.0)	797 (19.5)	
Hospital mortality, *n* (%)	235,345 (27.5)	919 (22.5)	0.12
Vasopressor-free days, mean (SD)	21.1 (11.4)	22.2 (10.4)	0.09

shock from 1,100 hospitals. Of these, 4,082 patients (0.5%) from 663 hospitals received at least one dose of MB at any point during their hospitalization. Characteristics of patients who received MB and those who did not are shown in **Table 1**, with complete data included in **Supplemental Table 1** (https://links.lww.com/CCM/H833). Overall mortality among patients receiving MB was lower (22.5% vs. 27.5%; SMD = 0.12). Prevalence of MB use by ICU type is shown in **Supplemental Table 2** (https://links.lww.com/CCM/

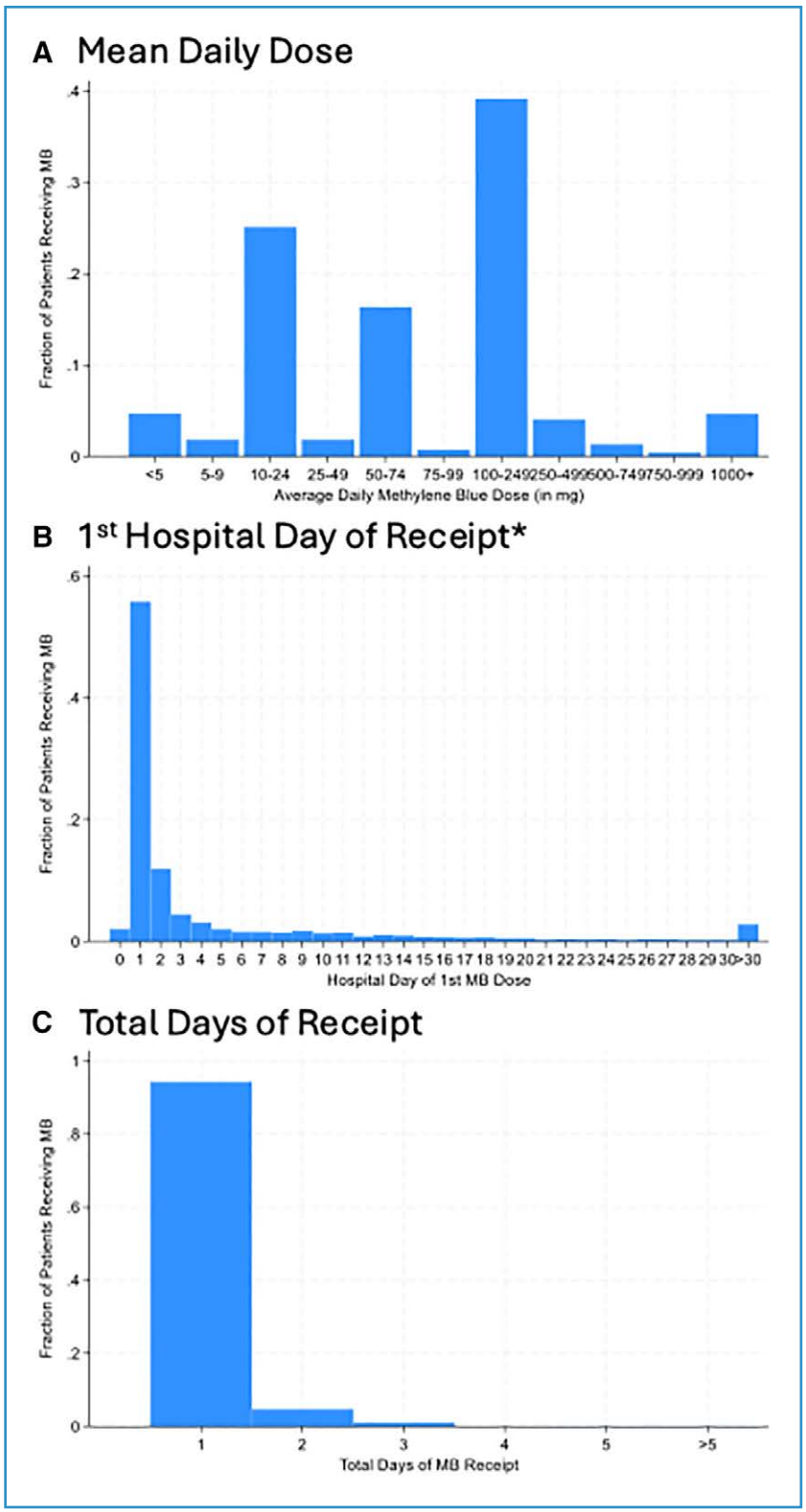

Figure 1. Variation in methylene blue (MB) administration among sepsis patients receiving at least one dose during their hospitalization ($n = 4082$). Data for these analyses are from the cohort investigate use of MB, before further exclusions for outlier (< 5 or > 1000 mg) total doses over the first 3 d of hospitalization.

H833), although data on ICU type could not be discerned in 63.2% of patients.

Variation in MB Dosing Strategies

Bar graphs depicting variation in MB administration are shown in **Figure 1**. There was tremendous variability in mean daily dosing. The most common mean daily dose of MB was 100–249 mg (39.2%), followed by 10–24 mg (25.1%) and 50–75 mg (16.3%); 100 mg was the single most common mean daily dose (73.9% of 100–249 mg doses, 28.9% of all doses). Cumulative dosing across the hospitalization is shown in **Supplemental Figure 2** (https://links.lww.com/CCM/H833). Most patients (55.7%) received MB on their first day of hospital admission, primarily (94.2%) for 1 day. Among decedents who received MB (n = 919), approximately half received their first dose on the day of death, or 1 day prior (**Supplemental Fig. 3**, https://links.lww.com/CCM/H833).

Patient and Hospital Factors Associated With MB Administration

Results of the multivariable regression model showing factors associated with MB administration are displayed in **Table 2**. Full model is shown in **Supplemental Table 3** (https://links.lww.com/CCM/H833). Patients receiving MB tended to be younger (adjusted OR [aOR], 0.99 per 1 yr old; 95% CI, 0.98–0.99). Administration of MB was much more likely among patients who had major surgery during their hospitalization (aOR, 12.5; 95% CI, 11.5–13.6), and received invasive mechanical ventilation by hospital day 3 (aOR, 1.42; 95% CI, 1.33–1.51). Hospital characteristics associated with MB administration included teaching sites (aOR, 1.26; 95% CI, 1.08–1.47) and urban settings (aOR, 1.31; 95%

CI, 1.06–1.60). The association of individual hospital with MB receipt was stronger than any patient factors evaluated other than major surgery (MOR, 1.97; 95% CI, 1.86–2.10).

Temporal Trends and Individual Hospital Variability

Temporal changes in unadjusted MB use are demonstrated graphically in **Figure 2**. The marginal probability of MB use after multivariable adjustment revealed the proportion of patients receiving MB declining over time through 2016, with similar use thereafter through 2020 (aOR [vs. 2008] range: 0.72 [in 2017]–0.79 [in 2019, 2020]; Wald test $p = 0.003$), but with use in 2021 rebounding (0.56%). Among the 145 hospitals contributing data during every study year, unadjusted MB use through 2020 was relatively stable, with a numerical peak in 2021 (**Supplemental Fig. 4**, https://links.lww.com/CCM/H833). We found substantial hospital level variation in MB use (MOR, 1.97; 95% CI, 1.86–2.10), with two hospitals using MB in over 16% of patients with septic shock, and nearly two-fifths of hospitals (437/1100, 39.7%) never using it.

Association of MB Dose With Outcomes

For this analysis, out of the 4082 patients who ever received MB, we excluded 302 patients (7.4%) discharged before hospital day 3, 1062 patients (26.0%) who did not receive MB before hospital day 3, 126 patients (3.1%) who received less than 5 mg of MB, and 85 patients (2.1%) who received greater than 1000 mg of MB. Thus, the analysis included 2507 patients with septic shock from 568 hospitals who received MB during the first 3 days of their hospital admission. Of these, 375 died (15.0%) in hospital. Comparison of MB patients who survived to discharge and those who died in hospital are shown in **Table 3**, with complete data included in **Supplemental Table 4** (https://links.lww.com/CCM/H833). Restricted cubic splines evaluating cumulative MB dose across the first 3 hospital days revealed five knots: 10, 20, 50, 100, and 300 mg. Multivariable regression models evaluating the association between MB dosing and hospital mortality and VFDs are shown in **Supplemental Table 5** (https://links.lww.com/CCM/H833), and graphical depiction of splines are shown in **Figure 3**. There was a significant (Wald test for all spline terms; $p < 0.001$) nonlinear (Wald test for higher order spline terms; $p < 0.001$ and $p = 0.009$, respectively) association of total MB dose with both mortality and VFDs: within lower dosage ranges (5–50 mg cumulative dose), increasing doses were associated with lower mortality and more VFDs; within moderate dosage ranges (50–200 mg cumulative dose), higher

TABLE 2.
Multivariable Logistic Regression Model Evaluating Factors Associated With Methylene Blue Administration Among Patients With Septic Shock ($n = 859,868$)

Variable	OR (95% CI)	p
Age (per 1 yr)	0.99 (0.98–0.99)	< 0.001
Race		
White	Reference	
Black	0.87 (0.79–0.96)	0.008
Other/unknown	0.96 (0.86–1.06)	0.38
Payor		
Private	Reference	
Medicare	0.86 (0.79–0.94)	0.001
Medicaid	0.77 (0.69–0.86)	< 0.001
Other	0.84 (0.73–0.96)	0.01
Major surgery	12.50 (11.49–13.60)	< 0.001
Mechanical ventilation by hospital day 3	1.42 (1.33–1.51)	< 0.001
Teaching hospital	1.26 (1.08–1.47)	0.003
Urban environment	1.31 (1.06–1.60)	0.01
Hospital size (number of beds)		
500+	Reference	
400–499	1.13 (0.90–1.43)	0.30
300–399	0.93 (0.75–1.15)	0.48
200–299	0.90 (0.73–1.11)	0.32
100–199	0.90 (0.72–1.12)	0.34
0–99	0.95 (0.71–1.29)	0.75
U.S. region		
Midwest	Reference	
Northeast	1.12 (0.90–1.40)	0.30
South	1.04 (0.88–1.24)	0.65
West	1.24 (1.01–1.52)	0.04
Individual hospital (median OR)	1.97 (1.86–2.10)	

OR = odds ratio.

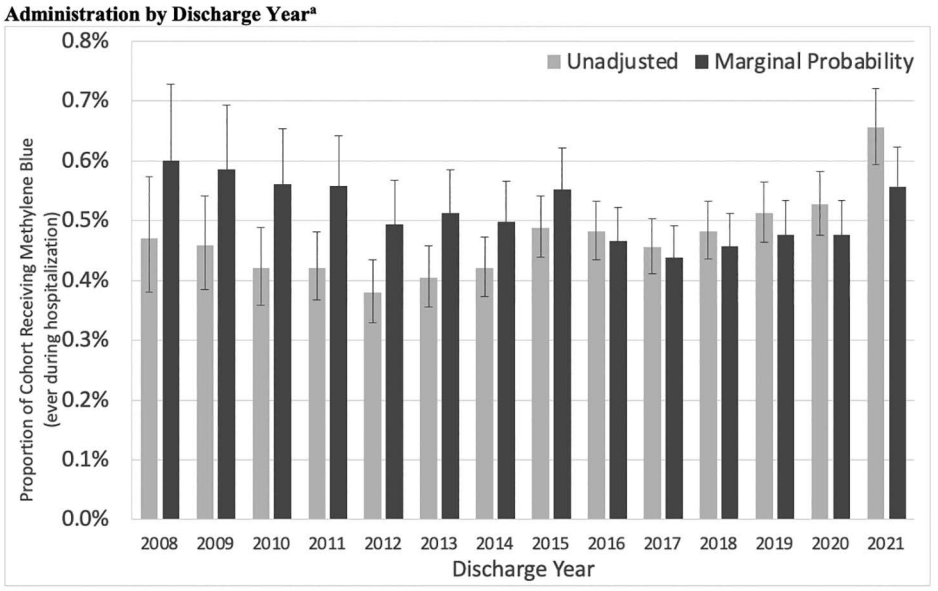

Figure 2. Temporal trends and individual hospital variability in methylene blue administration among patients with septic shock. [a]Error bars = 95% CIs. Unadjusted and adjusted (marginal probabilities from multivariable model) presented. Wald test for discharge year from multivariable model (p = 0.003). [b]*Black line* = median (0.21%), *light gray area* = 25th–75th percentile (0–0.57%). Median odds ratio (95% CI) from multivariable model = 1.97 (1.86–2.10).

doses (> 200 mg cumulative dose) were associated with higher mortality and fewer VFDs; and, within higher dosage ranges, no substantial association was observed. Sensitivity analyses categorizing MB dose into binary or three-category bins (**Supplemental Table 6**, https://links.lww.com/CCM/H833) were consistent with the findings of the moderate dosage ranges in the primary model; namely, that mortality was higher and VFDs were lower with higher cumulative MB doses over the first three hospital days (p < 0.001 for all associations).

DISCUSSION

We conducted a retrospective cohort study of 859,869 patients with septic shock early in their hospitalization from 1,100 hospitals to evaluate the utilization of MB administration in the United States over a 14-year period. Only one of every 200 patients with septic shock received MB during their hospitalization, and doses were variable. We found that MB use is more common in younger patients, those receiving major surgery, and those cared for in teaching hospitals and urban settings. Interestingly, use declined over time before 2021, but varied notably among hospitals. Finally, MB dosing was nonlinearly associated with outcomes among patients receiving it early in their hospitalization, and remaining in hospital for at least 3 days. Taken together, these data provide important insights into MB utilization, highlighting the need for further randomized trials.

MB has been considered a potentially useful treatment for patients with refractory septic shock, owing to its efficacy in other conditions of vasodilatory shock (6, 7). Despite this, randomized data examining the use of MB in septic shock remain sparse, and the current Surviving Sepsis Campaign clinical practice guidelines do not comment on its use (3). The existing randomized data show a potential signal of benefit, but with low certainty from a small number of trials (8). Similarly, adverse events from MB are largely unknown, and existing trials are underpowered to detect harm.

TABLE 3.
Baseline Characteristics of Sepsis Patients Receiving Methylene Blue, Stratified by Hospital Survival

Variable	Survivors (*n* = 2132)	Decedents (*n* = 375)	Standardized Mean Difference
Age, yr, mean (SD)	62.1 (15.3)	64.5 (15.2)	0.16
Female, *n* (%)	1081 (50.7)	161 (42.9)	0.16
Race, *n* (%)			0.04
White	1587 (74.4)	273 (72.8)	
Black	257 (12.1)	46 (12.3)	
Other/unknown	288 (13.5)	56 (14.9)	
Payor, *n* (%)			0.16
Private	507 (23.8)	67 (17.9)	
Medicare	1213 (56.9)	232 (61.9)	
Medicaid	270 (12.7)	44 (11.7)	
Other	142 (6.7)	32 (8.5)	
Number of Elixhauser comorbidities, mean (SD)	4.8 (2.6)	6.6 (2.7)	0.67
Major surgery, *n* (%)	1973 (92.5)	254 (67.7)	0.65
Mechanical ventilation by hospital day 3, *n* (%)	999 (46.9)	339 (90.4)	1.06
Teaching hospital, *n* (%)	1158 (54.3)	228 (60.8)	0.13
Urban environment, *n* (%)	1982 (93.0)	354 (94.4)	0.06
Hospital size (number of beds), *n* (%)			0.26
500+	815 (38.2)	143 (38.1)	
400–499	348 (16.3)	88 (23.5)	
300–399	337 (15.8)	60 (16.0)	
200–299	337 (15.8)	48 (12.8)	
100–199	223 (10.5)	33 (8.8)	
0–99	72 (3.4)	3 (0.8)	
U.S. region, *n* (%)			0.17
Midwest	491 (23.0)	72 (19.2)	
Northeast	252 (11.8)	61 (16.3)	
South	969 (45.5)	157 (41.9)	
West	420 (19.7)	85 (22.7)	

We found that certain patients more commonly received MB. Administration seems to be more frequent in younger patients. The reasoning behind this is unclear but may reflect a desire to consider alternative therapies in younger patients deteriorating with septic shock. Interestingly, it may be older patients with septic shock that are most likely to benefit from agents that reduce vasopressor exposure, however (23). We also found particularly high use in patients who received major surgery, which may in part be due to the high prevalence of systemic inflammation seen among post-surgical patients with septic shock (24).

Beyond major surgery, the three factors with the largest magnitude of association with MB receipt were hospital characteristics—urban setting, hospital size, and individual hospital. Although we cannot exclude the possibility of residual confounding, variability based on where a patient receives care is

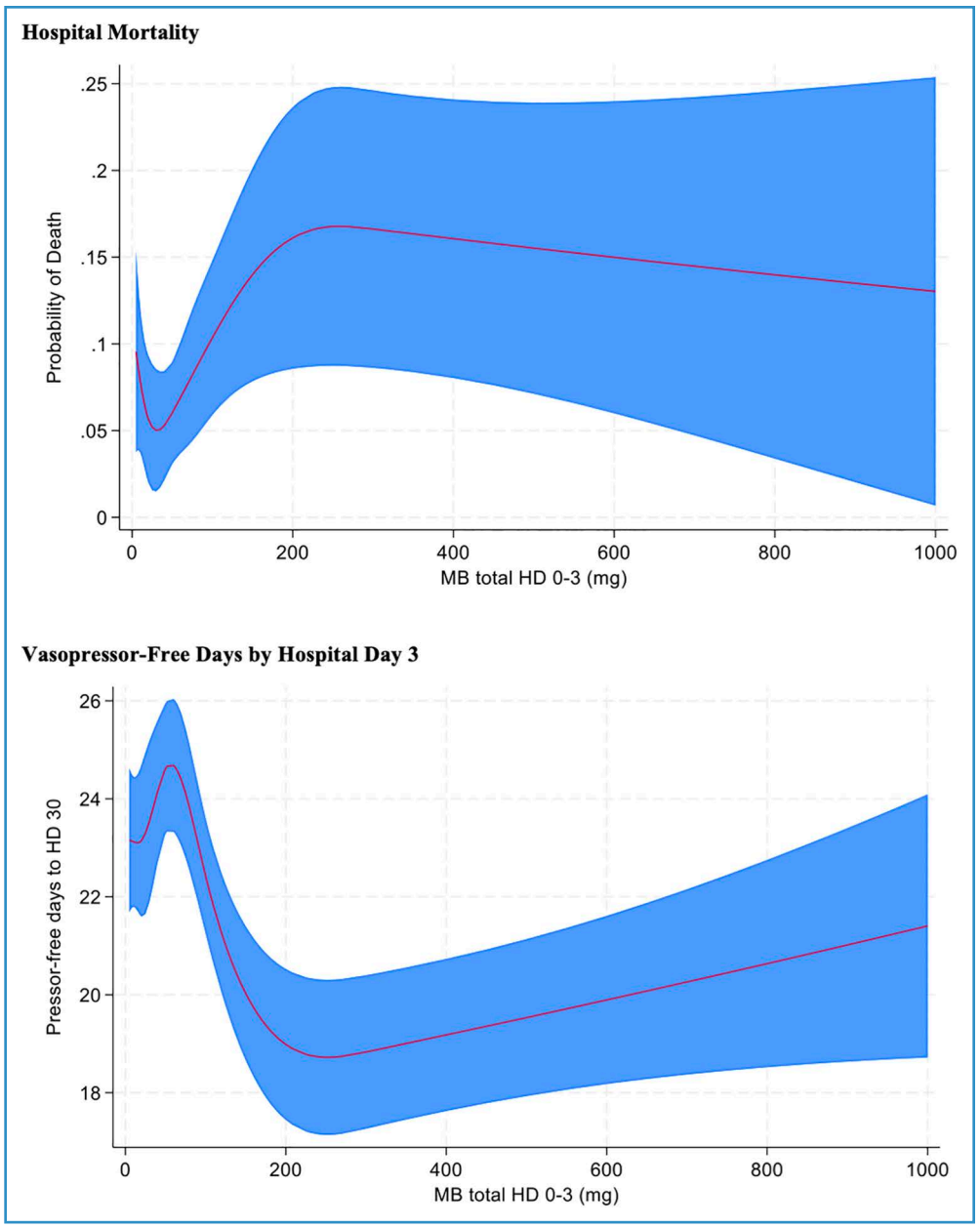

Figure 3. Five-knot restricted cubic spline analyses modeling the association between cumulative methylene blue (MB) dose by hospital day (HD) 3 and outcomes for a patient with population average characteristics (mean for continuous and mode for categorical model covariables) with septic shock. Five knots = 10, 20, 50, 100, and 300 mg.

unlikely to be patient-centric and likely driven by other factors. This profound variability emphasizes the need for robust randomized trial data to guide the use of MB in septic shock and reduce this jurisdictional variability. While we identified a slight reduction in MB use over the study period through 2020, use appeared to increase in 2021. Since the most recent trial of MB suggesting potential efficacy was published in 2023 (25), current utilization may be higher. Again, this finding underscores the need for further randomized trial data to evaluate the efficacy and safety of MB (9).

Dose variation was documented in this cohort; the most common mean daily dose was 100–250 mg, followed by 10–24 mg. Importantly, our results may show a nonlinear association between cumulative MB dose (over the first 3 hospital days) and outcome. Within lower dosage ranges (5–50 mg cumulative dose), increasing doses were associated with lower mortality and more VFDs; but within moderate dosage ranges (50–200 mg cumulative dose), higher doses were associated with higher mortality and fewer VFDs. At the highest doses (> 200 mg cumulative dose), we did not observe any association. This finding may represent a true dose-response relationship of MB in septic shock, or it may be due to residual confounding as patients still in profound shock on subsequent hospital days may be more likely to receive more MB. Identifying an optimal dose of MB would allow for maximal efficacy while limiting potential adverse events, although surgical data (where MB is used for localization of the parathyroid gland) report safe dosing as high as 7.5 mg/kg, with minimal adverse events (26). Clinical trials examining MB have not used a standardized dosing regimen (8). Some trials used only a bolus dose of 1–2 mg/kg daily (27), others used only an infusion of 0.50 mg/kg/hr for 6 hours once (28), and the most recent trial used an infusion of

100 mg over 6 hours daily, regardless of patient weight (25). Presently, the optimal dose of MB for septic shock remains unclear.

This study has important strengths, including investigation of a novel therapy for septic shock using a large database describing more than 800,000 patients from over 1,000 centers over 14 years.

This work also has important limitations, most notably the granularity of available data. We sought to capture patients with septic shock, and relied upon ICD coding rather than Sepsis-3 criteria, which were not captured in this dataset. Therefore, the indication for MB administration was presumed to be due to septic shock, but it is possible that patients might have received it for other causes. We did not have access to an acute illness severity scale, and illness severity likely confounds the association of MB administration with outcomes. In fact, we judged this limitation to be too great to allow comparison of use of MB to no use, and focused instead on dosing, which we felt was more likely driven by provider or institutional practice than illness severity. Data on individual ICUs (size, population) and providers (training, experience) were unreliable but represent an important avenue for future research. We captured data examining MB daily dosing but have no details about how MB was administered (i.e., bolus, infusion, timing of administration). We could not reliably assess important adverse events associated with MB, including induced methemoglobinemia, serotonin syndrome, reduced cardiac output, and pulmonary hypertension (7). Understanding such adverse events is critical in determining the risk-benefit profile of MB in septic shock, particularly given data suggesting harm from the use of other NOS inhibitors in this population (11). For all these reasons, our methods of causal inference were limited. Ultimately, randomized trial data are needed to determine the efficacy and safety of MB in septic shock. Finally, the results of this study were generated in a large database obtained from a single country (the United States); it is unclear whether these findings can be extended to other geographical regions.

CONCLUSIONS

In this retrospective cohort study of 859,869 patients with septic shock, we found that MB use was rare, with substantial variability in administration and a potential impact of the dose used on clinically relevant patient outcomes. In the context of the plausible mechanism of MB in septic shock, the minimal available randomized trial evidence, and lack of direction in clinical practice guidelines, this study emphasizes the need for high-quality, randomized trial data to inform providers on the efficacy and safety of this therapy among patients with septic shock.

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Drs. Fernando, Rochwerg, Adhikari, and Gershengorn conceived the study idea. Drs. Fernando, Rochwerg, and Gershengorn designed the study. Dr. Gershengorn had full access to the data, and performed statistical analyses. All authors interpreted the data analyses. All authors co-wrote and revised the article for intellectual content. All authors provided their final approval for the article submission. All authors agree to be accountable for all aspects of the work.

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REFERENCES

1. Singer M, Deutschman CS, Seymour CW, et al: The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016; 315:801–810
2. Rudd KE, Johnson SC, Agesa KM, et al: Global, regional, and national sepsis incidence and mortality, 1990-2017: Analysis for the Global Burden of Disease Study. *Lancet* 2020; 395:200–211
3. Evans L, Rhodes A, Alhazzani W, et al: Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. *Intensive Care Med* 2021; 47:1181–1247
4. McIntyre WF, Um KJ, Alhazzani W, et al: Association of vasopressin plus catecholamine vasopressors vs catecholamines alone with atrial fibrillation in patients with distributive shock: A systematic review and meta-analysis. *JAMA* 2018; 319:1889–1900
5. Sacha GL, Lam SW, Wang L, et al: Association of catecholamine dose, lactate, and shock duration at vasopressin initiation with mortality in patients with septic shock. *Crit Care Med* 2022; 50:614–623
6. Kwok ES, Howes D: Use of methylene blue in sepsis: A systematic review. *J Intensive Care Med* 2006; 21:359–363
7. Puntillo F, Giglio M, Pasqualucci A, et al: Vasopressor-sparing action of methylene blue in severe sepsis and shock: A narrative review. *Adv Ther* 2020; 37:3692–3706
8. Fernando SM, Tran A, Soliman K, et al: Methylene blue in septic shock: A systematic review and meta-analysis. *Crit Care Explor* 2024; 6:e1110
9. Arias-Ortiz J, Vincent JL: Administration of methylene blue in septic shock: Pros and cons. *Crit Care* 2024; 28:46
10. Petros A, Lamb G, Leone A, et al: Effects of a nitric oxide synthase inhibitor in humans with septic shock. *Cardiovasc Res* 1994; 28:34–39
11. López A, Lorente JA, Steingrub J, et al: Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: Effect on survival in patients with septic shock. *Crit Care Med* 2004; 32:21–30
12. Premier: Applied Research and Analytics. 2021. Available at: https://products.premierinc.com/applied-sciences/solutions/applied-research-and-analytics. Accessed May 2, 2025
13. Lederer DJ, Bell SC, Branson RD, et al: Control of confounding and reporting of results in causal inference studies. Guidance for authors from editors of respiratory, sleep, and critical care journals. *Ann Am Thorac Soc* 2019; 16:22–28
14. Leisman DE, Harhay MO, Lederer DJ, et al: Development and reporting of prediction models: Guidance for authors from editors of respiratory, sleep, and critical care journals. *Crit Care Med* 2020; 48:623–633
15. von EE, Altman DG, Egger M, et al: The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Lancet* 2007; 370:1453–1457
16. Angus DC, Linde-Zwirble WT, Lidicker J, et al: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; 29:1303–1310
17. Kohn R, Ashana DC, Vranas KC, et al: The association of pregnancy with outcomes among critically ill reproductive-aged women: A propensity score-matched retrospective cohort analysis. *Chest* 2024; 166:765–777
18. Bone RC, Balk RA, Cerra FB, et al: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992; 101:1644–1655
19. Elixhauser A, Steiner C, Harris DR, et al: Comorbidity measures for use with administrative data. *Med Care* 1998; 36:8–27
20. Healthcare Cost and Utilization Project: HCUP Procedure Classes. 2025. Available at: https://hcup-us.ahrq.gov/toolssoftware/procedure/procedure.jsp. Accessed August 12, 2025
21. Larsen K, Merlo J: Appropriate assessment of neighborhood effects on individual health: Integrating random and fixed effects in multilevel logistic regression. *Am J Epidemiol* 2005; 161:81–88
22. Wijeysundera DN, Austin PC, Beattie WS, et al: Variation in the practice of preoperative medical consultation for major elective noncardiac surgery: A population-based study. *Anesthesiology* 2012; 116:25–34
23. Lamontagne F, Day AG, Meade MO, et al: Pooled analysis of higher versus lower blood pressure targets for vasopressor therapy septic and vasodilatory shock. *Intensive Care Med* 2018; 44:12–21
24. Pittet D, Rangel-Frausto S, Li N, et al: Systemic inflammatory response syndrome, sepsis, severe sepsis and septic shock: Incidence, morbidities and outcomes in surgical ICU patients. *Intensive Care Med* 1995; 21:302–309
25. Ibarra-Estrada M, Kattan E, Aguilera-González P, et al: Early adjunctive methylene blue in patients with septic shock: A randomized controlled trial. *Crit Care* 2023; 27:110
26. Patel HP, Chadwick DR, Harrison BJ, et al: Systematic review of intravenous methylene blue in parathyroid surgery. *Br J Surg* 2012; 99:1345–1351
27. Kirov MY, Evgenov OV, Evgenov NV, et al: Infusion of methylene blue in human septic shock: A pilot, randomized, controlled study. *Crit Care Med* 2001; 29:1860–1867
28. Memis D, Karamanlioglu B, Yuksel M, et al: The influence of methylene blue infusion on cytokine levels during severe sepsis. *Anaesth Intensive Care* 2002; 30:755–762