Narrative Review

Treatment of Delirium in Septic Shock Patients: A Focused Evidence Review

Delirium in Septic Shock Patients

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ABSTRACT

Objective: To review pharmacological and non-pharmacological strategies for established delirium in adults with septic shock.

Place and Duration of Study: This review was conducted Intensive Care Medicine, Department of Adult Intensive Care Medicine, King Abdullah Specialized Hospital, Ministry of National Guards Health Affairs, Qassim, KSA.from January to March 2026.

Methods: PubMed/MEDLINE was searched for studies published between 2021 and 2026 on septic shock, delirium, sepsis-associated encephalopathy, dexmedetomidine, antipsychotics, the ABCDEF bundle, early mobilization, and melatonin.

Results: Dexmedetomidine may improve some organ-related outcomes but increases hypotension and has no consistent mortality or delirium benefit. Quetiapine and haloperidol show comparable efficacy for hyperactive delirium. ABCDEF bundle implementation improves long-term functional outcomes. Early mobilization appears feasible in hemodynamically stable patients, while melatonin improves sleep but has not consistently reduced delirium.

Conclusion: No pharmacological therapy has demonstrated a clear mortality or delirium-resolution benefit in septic shock.

Key Words: Septic shock; Delirium; Sepsis-associated encephalopathy

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INTRODUCTION

The reason is biological, not just statistical. Sepsis-associated encephalopathy (SAE) is increasingly recognized as a distinct clinical entity rather than a generic label for "ICU confusion."[1,2] Systemic cytokine release, blood-brain barrier disruption, microglial activation, and impaired neurovascular coupling combine to injure the frontal cortex, hippocampus, and brainstem in ways that differ mechanistically from postoperative or trauma-related delirium.[3–5]

This matters clinically because guidelines built around pooled ICU populations, most visibly the Society of Critical Care Medicine's Pain, Agitation, Delirium, Immobility, and Sleep (PADIS) recommendations delivered through the ABCDEF bundle, offer blanket advice that was never designed to answer a sepsis-specific question: does treating delirium in a hemodynamically unstable, cytokine-driven illness require a different approach than treating it after elective surgery?[3,5]

This review asks that question directly. We focus on adult patients with septic shock, examine both pharmacological agents (dexmedetomidine, antipsychotics, and corticosteroids as an unavoidable confounder) and non-pharmacological strategies (the ABCDEF bundle, early mobilization under vasopressor support, and sleep optimization), and close by identifying where the evidence base still falls short.

METHODS

We searched PubMed/MEDLINE for studies published between 2021 and 2026, combining the terms septic shock, sepsis, delirium, sepsis-associated encephalopathy, dexmedetomidine, antipsychotic,

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ABCDEF bundle, ICU Liberation, early mobilization, and melatonin from January 2026 to March 2026. Because several of the systematic reviews and meta-analyses retrieved through this strategy had themselves searched Embase, Cochrane CENTRAL, Scopus, Web of Science, and CINAHL, evidence from those databases is represented indirectly within this synthesis even though each platform was not independently queried. Randomized controlled trials, meta-analyses, and large cohort or registry studies enrolling adult patients with sepsis or septic shock were prioritized.

PATHOPHYSIOLOGY

Why Septic Shock Delirium Is Not Generic ICU Delirium

Sepsis-associated encephalopathy begins with a systemic inflammatory cascade rather than a focal insult. Circulating cytokines including IL-1β, IL-6, and TNF-α activate cerebral endothelium and disrupt tight-junction proteins such as claudin-5, allowing peripheral immune signaling to cross into the CNS.(3,4,6)microglial activation follows, and recent work using pharmacological CDK9 inhibition in a caecal ligation and puncture model showed that blocking this inflammatory kinase reduced both microglial activation and blood-brain barrier breakdown, evidence that the pathway is druggable in principle even though no such agent is yet in clinical use.[6]

Beyond inflammation, cerebral perfusion itself is deranged. Systemic inflammation impairs the brain's glymphatic clearance system, and in an experimental model, restoring cerebral blood flow with levosimendan normalized glymphatic flux and reduced neuroinflammation, pointing to hypoperfusion, not inflammation alone, as an independent contributor to SAE.[7] Consistent with this, ascorbate depletion, common in sepsis and disproportionately affecting the metabolically demanding frontal cortex, has been proposed as a modifiable contributor to microvascular dysfunction and encephalopathy, an area currently more mechanistic than clinical.[8] Endothelial phenotyping adds a further layer: a specific circulating endothelial subset (CD32b-positive cells) independently predicted 28-day delirium in a prospective cohort of postoperative septic and non-septic ICU patients, with an adjusted area under the curve of 0.89, suggesting endothelial injury tracks with brain dysfunction risk beyond what organ-failure scores alone capture.[9] Recent reviews now describe SAE not as a single syndrome but as a family of mechanism-based subphenotypes, ischemic-hypoxic, inflammatory-dominant, and metabolic-degenerative, each with a distinct clinical trajectory.[10] Blood-based biomarkers including neurofilament light chain, glial fibrillary acidic protein (GFAP), UCH-L1, and Tau correlate with both delirium and structural brain injury on imaging, and GFAP in particular improved prediction of unfavorable neurological outcome and 90-day mortality beyond age, SOFA, and APACHE II alone in a recent exploratory analysis.[11]

PHARMACOLOGICAL INTERVENTIONS

Sedation Strategy and Dexmedetomidine

Sedation is unavoidable in ventilated septic shock, and current sedation reviews recommend an analgesia-first approach, adding sedatives only as needed, with propofol and dexmedetomidine preferred over benzodiazepines.[12] The trial-level picture is more mixed than the mechanistic rationale suggests. A 2026 meta-analysis of eight RCTs (702 patients) found that dexmedetomidine significantly reduced day-2 SOFA score and acute kidney injury incidence, but it also significantly increased hospital length of stay and the incidence of hypotension, with no significant difference in 28-day mortality, mechanical ventilation duration, ICU length of stay, or delirium incidence.[13] A separate meta-analysis of a similar trial set (eight RCTs, 662 patients) reached the same conclusion on mortality, no significant difference across in-hospital, ICU, or long-term endpoints, and again found dexmedetomidine significantly increased hospital length of stay, with the authors grading certainty of evidence as low throughout.[14] The model, incorporating age, BMI, sepsis status, SOFA score, and cumulative opioid, propofol, and benzodiazepine dosing, achieved an area under the receiver-operating curve of 0.83 on derivation and 0.70 on external validation, reasonable discrimination for a bedside tool once prospectively tested.[15] A separate retrospective cohort reinforces the same point from the opposite direction: a system-wide shift from benzodiazepines toward dexmedetomidine did not change annual delirium incidence, while septic shock, vasopressor use, corticosteroid use, and antipsychotic use all remained independent correlates of delirium on multivariate analysis.[16]

ANTIPSYCHOTICS

Neither of the two agents in routine use, haloperidol and quetiapine, has demonstrated superiority for treating established delirium, and the newest evidence continues that pattern. A 2026 meta-analysis with trial sequential analysis pooling four RCTs (292 hospitalized adults) found no significant difference in delirium severity reduction (DRS-R-98), ICU or hospital length of stay, or mortality between quetiapine and haloperidol; quetiapine showed a non-significant trend toward fewer extrapyramidal symptoms and more sleep, but GRADE certainty was very low across all outcomes and the trial sequential analysis confirmed the evidence base remains underpowered.[17] A dedicated RCT in 100 patients with hyperactive delirium found an essentially identical response rate between the two drugs (92% overall, no significant between-group difference), though the quetiapine group had a modestly

shorter ICU stay (10.1 versus 11.7 days) and more sleep per night.[18]

CORTICOSTEROIDS

An Unavoidable Confounder

Low-dose corticosteroids are frequently used in refractory septic shock for hemodynamic support, and this creates a direct tension with delirium management that is easy to overlook. A comprehensive narrative review of corticosteroid use across critical illness, including septic shock, documents agitation and delirium among the recognized adverse effects, alongside genuine benefits in shock reversal and reduced mechanical ventilation duration.[19] Yet the relationship is not uniformly harmful. In a retrospective cohort of 583 patients undergoing emergency surgery for gastrointestinal obstruction or perforation, in which septic shock was among the strongest independent risk factors for postoperative delirium (adjusted odds ratio 8.57), low-dose dexamethasone was independently protective (adjusted odds ratio 0.41).[20]

Table No. 1: Key trials and meta-analyses of dexmedetomidine in septic shock

Study	Design / N	Key findings
Wolfkind et al. (2026)(13)	Meta-analysis, 8 RCTs, n=702	↓ Day-2 SOFA, ↓ AKI; ↑ hospital LOS, ↑ hypotension; no significant difference in mortality, delirium, or MV duration
Alsagban et al. (2025)(14)	Meta-analysis, 8 RCTs, n=662	No difference in-hospital, ICU, or long-term mortality; ↑ hospital LOS; low certainty of evidence throughout
Prendergast et al. (2025)(15)	Derivation n=836; external validation n=340	Prediction model for sedative-associated delirium (age, BMI, sepsis, SOFA, drug doses); AUROC 0.83 derivation, 0.70 external validation

Table No. 2: Antipsychotic trials for ICU and hospital delirium

Study	Design / N / Comparator	Key findings
de Oliveira et al. (2026)(17)	Meta-analysis with TSA, 4 RCTs, n=292; quetiapine vs haloperidol	No significant difference in DRS-R-98 reduction, LOS, or mortality; GRADE very low certainty; TSA confirms evidence is inconclusive
Zakhary et al. (2024)(18)	RCT, n=100, hyperactive delirium; quetiapine vs haloperidol	Equal response rate (92%); quetiapine associated with shorter ICU stay and more sleep; no mortality difference

THE ABCDEF / ICU LIBERATION BUNDLE

The ABCDEF bundle, translating the PADIS guidelines into a daily checklist covering pain assessment, spontaneous awakening and breathing trials, choice of sedation, delirium assessment, early mobility, and family engagement, remains the backbone of non-pharmacological delirium management.[21] Its long-term value was tested in a secondary analysis of the MIND-USA trial cohort, in which median proportional bundle compliance was high (97%), and greater compliance was associated with better twelve-month functional independence and health-related quality of life, though not with better long-term cognition, mental health, or survival.[22] That distinction matters: the bundle appears to protect physical and functional recovery more reliably than it protects the brain itself, at least on the outcomes measured so far.

In clinical practice, adherence to the individual components of the bundle remains inconsistent. A retrospective cohort study from Chile reported that early mobilization, represented by element E, had the highest compliance rate at 67%, whereas spontaneous awakening trials (B1) and family engagement (F) were rarely implemented.[23] The same concerns were found in a study conducted by the Society of Critical Care Medicine in 2026 that questioned 456 clinicians and healthcare leaders. The survey revealed an even greater drop in compliance with the bundles after the onset of COVID-19. The chief problems were lack of support from leadership, lack of communication within healthcare teams, and lack of staffing. Standardized order sets, checklists and incorporation into EHRs were perceived as helpful tools to facilitate adherence, in contrast[24] Although efforts are being made to standardize the documentation of bundle components and link them with common data models for more consistent auditing, these approaches have not yet become part of routine clinical practice.[25]

EARLY MOBILIZATION IN VASOPRESSOR-DEPENDENT PATIENTS

Recent evidence does not support the traditional fear that mobilizing patients on vasopressors is unsafe. In the 64% of patients that were mobilized on low-dose vasoactive medications, and in the 30% of patients that were mobilized on moderate-dose vasoactive drugs, and even 7% of patients that were mobilized on high-dose vasoactive drugs, the overall rate of adverse events was 2%.[26] A large retrospective cohort of over 12,000 ICU patients receiving more than 59,000 mobilization sessions identified specific, actionable norepinephrine dose thresholds: safe mobilization out of bed up to approximately 0.20 mcg/kg/min, and in-bed mobilization up to 0.33 mcg/kg/min, without a significant increase in adverse events within these limits.[27] Nurse-led quality improvement work in a cardiovascular ICU replicated this safety signal for

post-cardiac surgery patients on vasoactive medication, with mobility scores improving significantly after a structured educational intervention.[28] A prospective multicenter protocol currently underway in Colombia should further clarify adverse event rates and dose-response relationships.[29]

Whether this translates into less delirium specifically, rather than just less ICU-acquired weakness, is now better supported than it once was. A large 2025 meta-analysis of 59 RCTs (8,462 patients) found that enhanced mobilization activities reduced ICU-acquired weakness (moderate certainty), reduced delirium duration by just over a day on average (low certainty), and shortened mechanical ventilation duration, with little to no increase in adverse events.[30]

Table No. 3: Priority research gaps in delirium management for septic shock

Gap	Description
Subgroup reporting gap	Septic shock is rarely a prespecified primary population in delirium treatment trials
Phenotyping deficit	Hyperactive/hypoactive and SAE mechanistic subphenotypes are not used to stratify treatment trials
Biomarker-treatment integration	NfL, GFAP, endothelial CD32b$^+$ subsets, and mNUTRIC associate with delirium but remain untested as treatment-response markers
Corticosteroid paradox	Protective against delirium in one septic-surgical cohort, listed as a risk factor in general critical illness

CONCLUSION

No pharmacological agent reviewed here, dexmedetomidine, quetiapine, haloperidol, or melatonin, has shown a clear delirium-resolution or mortality advantage over its comparator, and most of that evidence still comes from mixed ICU cohorts rather than septic shock specifically. Non-pharmacological bundle care, paired with hemodynamically informed early mobilization and basic sleep hygiene, currently carries the more consistent signal, primarily for functional and quality-of-life recovery rather than a proven cognitive or mortality effect.

Conflict of Interest: The study has no conflict of interest to declare by any author.

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REFERENCES

1. Qu J, Lv C, Zhang X, Ren X, Li Y, Wu C. The S-shaped association between mNUTRIC score and delirium in septic patients in the intensive care unit: a retrospective cohort study using the MIMIC-IV database. Shock 2025;64(2):161-8.
2. Shankar-Hari M, Benghanem S, Bourhy L, Cunningham C, Ehler J, Girard TD, et al. Current knowledge and challenges of sepsis-associated encephalopathy. Intensive Care Med 2026.
3. Payal N, Saxena J, Srivatsava VK, Kaushik S, Siddiqui AJ, Chauhan K, et al. Sepsis-associated brain dysfunction: mechanisms, clinical insights, and therapeutic strategies. Curr Drug Targets 2025;26(14):992-1009.
4. Zhang X, Huang K, Wu Z, Ding R, Han J, Zhang Y, et al. Sepsis-associated encephalopathy: unraveling molecular mechanisms, emerging therapeutics, and translational frontiers. Pharmacol Ther 2025;278:108971.
5. Yan R, Ma G, Huang H, Mei J, Yang Q, Gong Y, et al. Pathophysiology-driven neuroimaging: decoding brain injury in sepsis. Front Mol Neurosci 2026;19:1840888.
6. Marzani E, Alves GF, Zemer A, Rubeo C, Aimaretti E, Porchietto E, et al. Pharmacological inhibition of CDK9 counteracts neuroinflammatory impairments in sepsis-associated encephalopathy. Biomed Pharmacother 2026;198:119274.
7. Zhao R, Sun B, Wei P, Sun Y, He Q, Zhang K, et al. Potentiating cerebral perfusion normalizes glymphatic dynamics in systemic inflammation. Adv Sci (Weinh) 2025;12(47).
8. Bishop MS, Lane DJR, Ayton S, May C, Plummer MP, Lankadeva YR. Sodium ascorbate versus ascorbic acid in sepsis: a narrative review of emerging cardiovascular and neurological benefits. Crit Care 2026;30(1):54.
9. Prieto-Utrera RD, García-Concejo A, Gómez-Sánchez E, Bardají-Carrillo M, Cobo-Zubia R, Rebollo-Mato I, et al. Circulating endothelial signature: a biomarker of delirium risk and severity in postoperative patients. Anesthesiol 2026.
10. Qin S, Song B. Decoding sepsis-associated encephalopathy: from blood-brain barrier injury to mechanism-based subphenotypes. Brain Res Bull 2025;233:111660.
11. Ruhlmann M, Xu L, Bauer M, Lehmann T, Panagiotou G, Neugebauer S, et al. Correlation of brain injury biomarkers with brain dysfunction, brain injury, and outcomes in critically ill patients: a post hoc exploratory analysis. Infection 2026;54(3):1501-17.
12. Marra A, Smith RJ, Pandharipande PP, Hayhurst CJ. Optimal sedation in ventilated patients with sepsis and septic shock. Crit Care Clin 2025; 41(4):775-90.
13. Wolfkind IB, Geftos LT, Mitchell WK, McOsker RJ, Puglisi JL, Gill BS. Dexmedetomidine versus usual care in adult patients with septic shock receiving vasopressors. Eur J Anaesthesiol Intensive Care 2026;5(3).

14. Al-Sagban A, Saab O, Al-Obaidi H, Algodi M, Koenig M, Patel B. The effect of dexmedetomidine on clinical and management outcomes in patients with septic shock: a systematic review and meta-analysis of randomized trials. J Crit Care 2025;91:155251.
15. Prendergast N, Onyemekwu CA, Toth KM, Franz CA, Kitsios GD, McVerry BJ, et al. Derivation and validation of a prediction rule for sedative-associated delirium during acute respiratory failure requiring mechanical ventilation. J Crit Care 2025; 92:155407.
16. Franz ND, Alaniz C, Miller J, Farina N. Association between sedative medication administration and delirium development in a medical intensive care unit. J Pharm Pract 2023;36(5):1164-9.
17. Oliveira LGAM de, Squizzato FAT, Matos HS da S, Maia AS, Lima-Araújo I, Cintra ACG, et al. Quetiapine versus haloperidol for the treatment of delirium in hospitalized adults: a meta-analysis of randomized controlled trials with trial sequential analysis. Gen Hosp Psychiatr 2026;101:159-65.
18. Zakhary T, Ahmed I, Luttfi I, Montasser M. Quetiapine versus haloperidol in the management of hyperactive delirium: randomized controlled trial. Neurocrit Care 2024;41(2):550-7.
19. Haan BJ, Blackmon SN, Cobb A, Cohen HE, DeVier M, Perez MM, et al. Corticosteroids in critically ill patients: a narrative review. Pharmacotherapy 2024;44(7):581-602.
20. Lyu W, Wang Z, Yang C, Wang X, Feng H, Jiao Y, et al. Delirium after emergency surgery in patients with gastrointestinal obstruction or perforation: a retrospective cohort study for 5 years. J Gastrointest Surg 2025;29(9):102083.
21. Bhadade R, Harde M, Nadkar M, Tiwasker M, Vora A, Saraf A, et al. Clinical practice guidelines for management of pain, agitation, delirium, immobility, and sleep disturbance in the intensive care unit: the ABCDEF bundle. J Assoc Physicians Ind 2023;71(7):11-2.
22. Boehm LM, Mart MF, LaNoue M, Siao SF, Pun BT, Bowton DL, et al. Association between ABCDE bundle compliance and long-term outcomes: a secondary longitudinal analysis. Intensive Care Med 2026;52(3):466-75.
23. Muñoz-Muñoz F, Leppe J, González-Seguel F, Castro-Ávila AC. Daily compliance of the ABCDEF liberation bundle for patients in the intensive care unit: a retrospective descriptive study. Medwave 2024;24(4).
24. Gurnani PK, Setliff EL, Abu-Sultaneh S, Kordik C, Fistler C, Guo L, et al. Barriers and facilitators to ICU Liberation Bundle implementation and compliance. Crit Care Explor 2026;8(6).
25. Islam MF, Douglas MR, Mosier J, Subbian V. Standardizing data elements for implementation of ICU Liberation Bundle. Appl Clin Inform 2026;17(1):52-9.
26. Parada-Gereda HM, Pardo-Cocuy LF, Vanegas JMA, Molano-Franco D, Masclans JR. Early mobilisation in patients with shock and receiving vasoactive drugs in the intensive care unit: a systematic review and meta-analysis of observational studies. Med Intensiva (Engl Ed) 2025;49(4):193-204.
27. Lindholz M, Schellenberg CM, Grunow JJ, Kagerbauer SM, Milnik A, Zickler D, et al. Mobilisation of critically ill patients receiving norepinephrine: a retrospective cohort study. Crit Care 2022;26(1):362.
28. AlSaeed S, Alohali A, Alohali A, Almojel AA, Bagazi AA, AlJohi AA. Early mobility for post-cardiac surgery patients on vasoactive medication: a nurse-led quality improvement project. Nurs Crit Care 2025;30(5).
29. Parada-Gereda HM, Merchán-Chaverra RA, Medina-Parra J, Benavides-Cruz J, Gaitán-Duarte H. Safety of early mobilisation in the intensive care unit: a prospective and multicentre cohort study protocol. BMJ Open 2025;15(8).
30. Carayannopoulos KL, Chaudhuri D, McNett M, Balas MC, Kho ME, Stollings JL, et al. Effect of enhanced versus usual mobilization activities in critically ill adults: a systematic review and meta-analysis of randomized controlled trials. Crit Care Med 2025;53(11).