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ORIGINAL RESERACH

Dexmedetomidine vs. Other Sedatives in Mechanically Ventilated Sepsis Patients: Updated Meta-analysis

Rizky Eka Putera ✉*, Rafael Bagus Yudhistira**, Livilia Abigail Onggowasito*, Nathania Ella Sudiono*

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Authors' affiliations :
*Undergraduate Program, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia
**Departement of Anesthesiology and Intensive Care, Faculty of Medicine, Sebelas Maret Uniersity, Surakarta, Indonesia
✉ Correspondence:
rizky.eka12@student.uns.ac.id

ABSTRACT

Background: Globally, the incidence of sepsis is estimated at over 400 cases per 100,000 population annually, making it a major public health concern. . In this setting, sedation is essential to ensure patient-ventilator synchrony and reduce physiological stress. Dexmedetomidine is a selective α_2-agonist often used instead of traditional sedatives because it provides light sedation, lowers the risk of delirium, and may reduce inflammation. However, clinical outcomes remain inconsistent across studies. To assess the clinical effects of dexmedetomidine compared to other sedatives in mechanically ventilated sepsis patients.

Methods: A comprehensive literature search of Pubmed, Scopus, Cochrane Central, Scilit, and Epistemonikos was performed to identify studies published from 2020 to 2025. Inclusion criteria included Randomized Controlled Trial (RCT) studies that directly compared dexamethomidine as sedation and involving sepsis patients with mechanical ventilation. Risk of Bias was estimated using RoB2.0 and meta analysis was using Revman 5.4.

Results: Eight randomized control trials (n = 1119) were included. Compared to other sedatives, dexmedetomidine prolonged hospital LOS significantly (MD = 1.47; 95% CI: 0.59 to 2.34; p = 0.001), reduced ICU LOS significantly (MD = -0.91; 95%CI = -1.51 to -0.29; p = 0.004), not improving the event of mortality insignificantly (OR = 0.99; 95% CI: 0.71–1.37; p = 0.95), reduced ventilator-free days insignificantly (MD = –0.85; 95% CI = –1.94 to 0.25; p = 0.13), and improved lactate clearance insignificantly (MD = 0.54; 95%CI = -0.41 to 1.49; p = 0.21)

Conclusion: Dexmedetomidine reduces ICU length of stay and may offer early mortality benefits at 28 days in mechanically ventilated sepsis patients. However, its effects on hospital stay, lactate clearance, and ventilator-free days remain uncertain, and further standardized trials are needed.

Keywords: Dexmedetomidine; Mechanical Ventilation; Sedation; Sepsis.

INTRODUCTION

Sepsis represents a significant clinical challenge due to its high morbidity and mortality, and is regarded as the most severe complication of infection. Globally, sepsis remains a major public health concern. The prevalence of sepsis has been reported to reach 61.25%, with septic shock (SS) accounting for approximately 38.75% of cases[1]. In 2019, the global incidence of sepsis was estimated at 422 cases per 100,000 population[2]. Furthermore, the age-standardized sepsis-related mortality rate was reported at 148.1 deaths per 100,000 population. Both incidence and mortality increase with age, with the highest burden observed among individuals aged 65 years and older[3]. As a life-threatening medical emergency, sepsis results from the body's extreme response to infection, rapidly causing tissue damage, organ failure, and death. Its progression is driven by an excessive immune response and impaired repair mechanisms[4].

Patients with sepsis, particularly those progressing to septic shock (SS), often develop respiratory failure requiring mechanical ventilation. A recent study found that patients with SS had a significantly higher risk of intubation, with biomarkers such as serum lactate, albumin, and the lactate-to-albumin (L/A) ratio, especially the L/A ratio (AUC = 0.948), serving as strong predictors of ventilatory need. Elevated APACHE scores and hypoalbuminemia were also independently associated with increased risk[5]. In this context, sedation is essential to ensure ventilator synchrony, reduce distress, and optimize oxygenation. Current guidelines recommend light sedation (RASS –2 to 0), using agents such as propofol or dexmedetomidine. Deep sedation is avoided due to its association with prolonged ventilation and worse outcomes[6,7].

Dexmedetomidine exerts its pharmacologic effects by selectively binding to α_2-adrenergic receptors. This binding leads to reduce sympathetic nervous system activity. This also lowers intracellular cAMP levels and calcium influx in neurons, which limits excitatory neurotransmitter release and contributes to its sedative and analgesic effects[8]. Compared to conventional Gamma-Aminobutyric Acid (GABA) adrenergic agents like propofol and benzodiazepines, dexmedetomidine provides lighter, cooperative sedation with lower risk of delirium[9,10]. Furthermore, its ability to lower pro-inflammatory cytokines such as IL-6 and TNF-α, combined with antibacterial effects, provides added value, especially for patients with sepsis[11]

Several randomized controlled

trials (RCTs) have reported that dexmedetomidine significantly reduced mortality and ICU length of stay (LOS) compared to other sedative agents[12–14]. Not only that, some studies demonstrated its effectiveness in increasing 28-day mechanical ventilation-free days and improving lactate clearance [12,15,16]. However, other studies found no significant differences or even gave opposite effects in these outcomes, suggesting that the clinical efficacy of dexmedetomidine in this population remains controversial [7,17,18]. Therefore, this study aims to evaluate the effect of dexmedetomidine on patients sepsis requiring mechanical ventilation compared to other sedative agents.

METHODS

Study Design

This systematic review and meta-analysis was prepared according to the Cochrane Handbook for Systematic Reviews of Interventions 6.2 and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[1,2]. This review was not registered in the PROSPERO database or any other systematic review registry, but the methodology strictly adhered to PRISMA and Cochrane standards.

Study Eligibility Criteria

This study evaluated dexmedetomidine as sedation in sepsis patients requiring mechanical ventilation with comparison to other treatments. Studies that fit our research objectives, as detailed in the patient, intervention, comparator, and outcome (PICO) framework. The PICOs of this study are: patient (P): sepsis patients requiring mechanical ventilation; intervention (I): Dexmedetomidine as sedation and analgesic; comparator (C): other treatment; outcome (O): (a) mortality; (b) hospital LOS; (c) ICU LOS; (d) mechanical free days; and (e) lactate clearance. Studies that met the following criteria were included: (1) randomized controlled trial (RCT) studies that directly compared dexmedetomidine as sedation; and (2) sepsis patients requiring mechanical ventilation. In contrast, the exclusion criteria were as follows: (1) observational studies, review articles, case reports, and case series; (2) inaccessible full-text publications; or (3) articles not published in English.

Search Strategy

A systematic literature search was conducted as of 15 July 2025 using five electronic databases, such as Pubmed, Scopus, Cochrane Central, Scilit, and Epistemonikos. The search strategy was designed to identify relevant studies on dexmedetomidine for sepsis patients requiring mechanical ventilation. Search

terms included combinations of relevant keywords and Medical Subject Headings (MeSH), where applicable. The following search terms were used: (sepsis) OR ("Sepsis") OR (systemic inflammatory response syndrome) OR ("systemic inflammatory response syndrome") OR (SIRS) OR ("SIRS") OR (Septic Shock) OR (Shock Sepsis) AND (dexmedetomidine)

Data Extraction

Studies identified from the literature search and reference list check were imported into the Rayyan website to eliminate duplicates. Three researchers (REP, LAO, NES) independently reviewed study titles and abstracts then discussed inconsistent decisions until consensus was obtained. Researchers independently screened the fulltext for inclusion. In case of disagreement, consensus on inclusion or exclusion decisions was reached through discussion. We then extracted data from the included studies. From each eligible study, the following data were systematically extracted: (1) first author; (2) study design and geographic location; (3) year of publication; (4) total number of participants and mean age for each treatment group; (5) dosage and type of intervention for each group;
(6) APACHE II or SAPS II ad SOFA score; (7) focus of infection; and (8) study outcomes.

Outcomes

In this study, the effect of dexmedetomidine use was assessed on five outcomes. Mortality was assessed at 30-day follow-up, hospital and ICU LOS, mechanical free days, and lactate clearance.

Quality Assessment

The Revised Tool for Risk of Bias in Randomized Trials (ROB 2.0) was used to assess the risk of bias of each included study and the results were visualized using RoBVIS.

Statistical Analysis

Quantitative analysis was performed through the Review Manager 5.4 application (The Nordic Cochrane Center, The Cochrane Collaboration, Denmark) with inverse variance, fixed-effect model. The synthesized results were events and 95% confidence intervals (CI). Statistical heterogeneity was evaluated through Cochrane's Q test and I2 statistic with cutoff values of 0%, 25%, 50%, 75% for almost no, low, moderate or high heterogeneity, respectively.

RESULTS

Study Election Process

A total of 1207 studies from 5 databases were obtained in this study. Before screening, 264 studies were excluded due to duplicates. During title and abstract screening, 932 studies were

excluded, leaving 11 studies. In addition, 1 study was excluded because the article was not accessible, 1 study was excluded because it was not written in English. Furthermore, 1 study was from a year below 2020, thus 8 studies were used for qualitative and quantitative analysis. The screening and selection process by assessing eligibility criteria is presented in Figure 1.

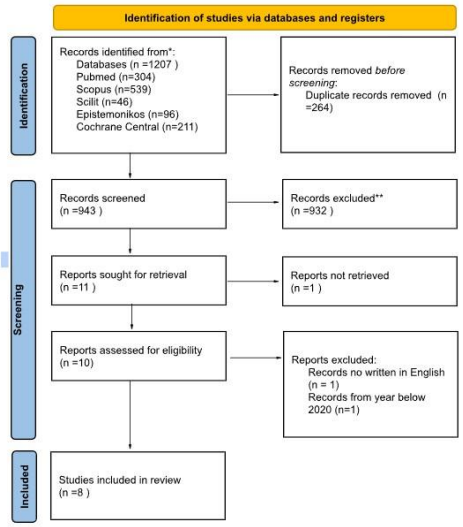

Figure 1. PRISMA flowchart of the study selection process.

Characteristic of Included Studies

A total population of 1,119 sepsis patients requiring mechanical ventilation received dexmedetomidine intervention with another treatment control group[12,13,15–20]. The study included articles published from 2020 to 2025 with study centers in Australia, China, Egypt, France, Japan, USA, and Switzerland in all nine studies. Study inclusion included a population aged at least 18 years with a diagnosis of sepsis requiring mechanical ventilation. Dexmedetomidine administered ranged from 0.2-1 mcg/kg with comparison other treatments given to patients included propofol, midazolam, placebo, or usual care with different doses. Study Characteristics can be seen in Table 1.

Quality Assessment

An evaluation of quality across five principal domains revealed that none of the studies showed any concerns or high risk in any area, indicating a consistently low risk of bias. This reflects a strong level of methodological rigor among the included trials. A comprehensive summary of the quality assessment for each study is provided in Figure 2.

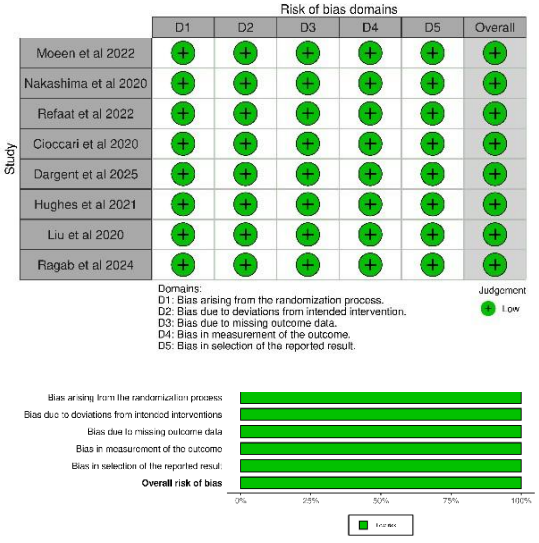

Figure 2. Risk of bias assessment

Hospital Length of Stay

Dexmedetomidine is used as sedation in sepsis patients who require mechanical ventilation. Out of 8 studies included in this review, 2 reported hospital LOS as an outcome. Cioccari et al. (2020) reported a longer hospital stay in the

dexmedetomidine group (16.2 ± 3.75 days) compared to the control group (13.78 ± 3.33 days), but this difference was not significant (p = 0.3). Similarly, Ragab et al. (2024) reported a longer hospital LOS in the dexmedetomidine group (6.0 ± 3.33 vs 5.0 ± 1.48 days), also with a non-significant result (p = 0.322). A meta-analysis was then conducted and showed that dexmedetomidine was associated with a significant increase in hospital LOS (MD = 1.47; 95% CI: 0.59 to 2.34; p = 0.001). The heterogeneity test indicated moderate heterogeneity (Chi^2 = 2.24, df = 1, p = 0.13; I^2 = 55%) (Figure 3).

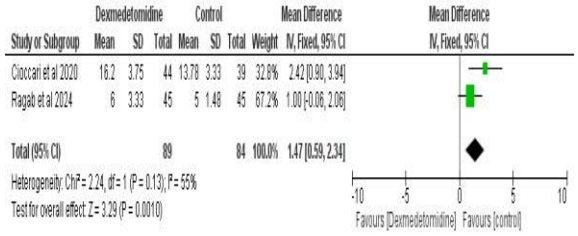

Figure 3. Forrest plot hospital LOS

ICU Length of Stay

ICU LOS was reported in 4 studies. There was only one study by Liu et al. reported a significantly shorter ICU LOS in the intervention group compared to the control group (13.5 ± 3.5 vs 17.0 ± 5.0; p < 0.05). Cioccari et al. reported no significant difference (p = 0.67). Meanwhile, Ragab et al. (6.5 ± 8.15 vs 5.33 ± 5.93; p = 0.145) and Refaat et al. (11.20 ± 4.69 vs 9.85 ± 3.26; p = 0.061) reported longer ICU LOS in the intervention group unsignificantly [13–15]. Meta-analysis was conducted and the result showed that dexmedetomidine had a highly significant effect in reducing ICU LOS (MD = -0.91; 95%CI = -1.51 to -0.29; p = 0.004). Heterogeneity test with Chi^2 = 30.48, df = 4, (P<0.00001); I^2 = 90%, showed high heterogeneity (Figure 4).

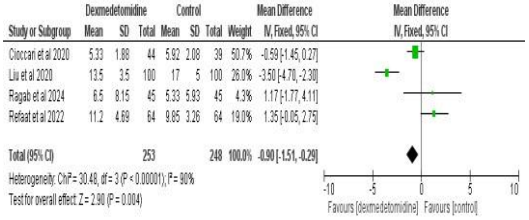

Figure 4. Forrest plot ICU LOS

Mortality

Mortality was reported in 5 out of the 8 studies, with varying follow-up durations. Dargent et al. (p = 0.108) and Hughes et al. (p = 0.127) reported 30-day mortality, both showing no significant difference between the dexmedetomidine and control groups. Meanwhile, three studies by Nakashima et al. (p = 0.03), Ragab et al. (p = 0.205), and Refaat et al. (p = 0.042) reported 28-day mortality. Among these, Nakashima et al. and Refaat et al. observed a significant reduction in mortality in the dexmedetomidine group, while Ragab reported no significant difference[12,13,15]. A meta-analysis of all five studies showed that dexmedetomidine did not significantly reduce overall mortality compared to control (OR = 0.99; 95% CI: 0.71–1.37; p = 0.95). However, subgroup analysis based on follow-up

duration revealed different trends: studies with 28-day follow-up showed a significant benefit (OR = 0.43; 95% CI: 0.25–0.76; p = 0.003), whereas those with 30-day follow-up did not (OR = 1.50; 95% CI: 1.01–2.24; p = 0.05). The heterogeneity test indicated high overall heterogeneity (Chi^2 = 14.20, df = 4, p = 0.003; I^2 = 79%), and the test for subgroup differences was also significant (Chi^2 = 12.58, df = 1, p = 0.0004; I^2 = 92.1%), suggesting that differences in follow-up duration may influence mortality outcomes (Figure 5).

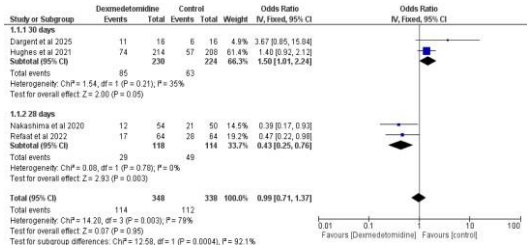

Figure 5. Forrest plot of mortality in 28 and 30 days.

Mechanical Ventilation Free Days

Mechanical ventilation-free days were defined as the number of days alive without invasive ventilation within 28 days. Out of 8 studies analyzed, 4 studies reported this outcome. Nakashima et al. reported mechanical ventilation free days were higher in the intervention compared to the control group significantly (18 ± 17.0 vs 5 ± 14.8; p = 0.009)[12]. In contrast, Dargent et al. (0.00 ± 12.9 vs 10.03 ± 16.3; p = 0.208) and Hughes et al. (17.0 ± 6.5 vs 18.2 ± 5.2; p > 0.05) reported non-significantly higher values in the control group[7,17]. A meta-analysis was then conducted to assess this outcome, showing that patients in the dexmedetomidine group had fewer ventilator-free days compared to control (MD = –0.85; 95% CI = –1.94 to 0.25; p = 0.13). The heterogeneity was high (I^2 = 91%), indicating substantial variation among the studies (Figure 6).

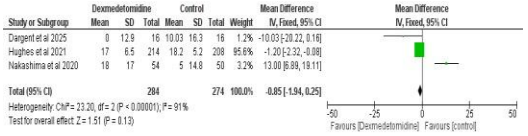

Figure 6. Forrest plot of mechanical free days

Lactate Clearance

From 8 studies analyzed, 3 studies reported lactate clearance that was identified as the reduction of lactate levels from baseline to outcome. Instead of showing lactate clearance, Dargent et al. reported a greater increase in lactate levels in the intervention group compared to the control group at 6 hours (–2.04 ± 10.19 vs –0.91 ± 6.09; p = 0.21) and 12 hours follow up (–0.69 ± 10.95 vs –0.09 ± 6.67; p = 0.40)[17]. In 24 hours follow up, Moeen et al. reported lactate clearance significantly higher in the use of dexmedetomidine than propofol (1.4 ± 2.6 vs 1.0 ± 2.8; p = 0.003) and midazolam (1.4 ± 2.6 vs 0.7 ± 2.6; p = 0.003), whereas Ragab et al. found no significant

difference (1.52 ± 3.34 vs 1.0 ± 4.58; p = 0.656)[15,16]. Meta-analysis was then conducted and the result showed that dexmedetomidine improved lactate clearance unsignificantly (MD = 0.54; 95%CI = -0.41 to 1.49; p = 0.21) with almost no heterogenity (I^2 = 0%). Thus, dexmedetomidine tended to improve lactate clearance, although not significantly (Figure 7).

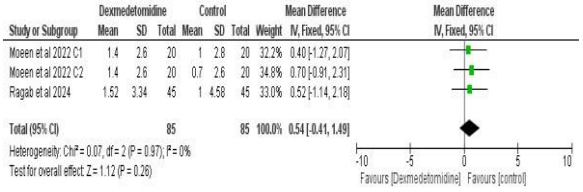

Figure 7. Forrest plot of lactate clearance

DISCUSSION

In patients with sepsis, mechanical ventilation is often required due to progressive respiratory failure caused by systemic inflammation, pulmonary edema, and metabolic acidosis. Sedation plays an important role in improving ventilator synchrony, reducing anxiety, enhancing oxygenation, and lowering risk of complications[21]. Dexmedetomidine is a sedative agent used in mechanically ventilated sepsis patients in ICU. This agent selectively binds to α_2-adrenergic receptors, particularly in locus coeruleus, to reduce norepinephrine release and decrease the fight or flight nervous system activity. The effectiveness of dexmedetomidine for this population is still controversial [8], therefore this study aimed to evaluate the clinical effects of dexmedetomidine compared to other sedatives in mechanically ventilated sepsis patients, focusing on five outcomes: hospital LOS, ICU LOS, mortality, mechanical ventilation-free days, and lactate clearance.

This systematic review and meta-analysis included 8 studies published in the last 5 years, so the findings reflect up- to-date evidence regarding the clinical effects of dexmedetomidine compared to other sedatives in mechanically ventilated sepsis patients. This study finds that dexmedetomidine slightly lowering ICU LOS significantly compared to other agents. This finding offers updated insight compared to the previous systematic review by Zhang et al. that reported the opposite finding[11].

This review confirms that although dexmedetomidine was associated with a significant reduction in ICU length of stay (LOS), it paradoxically showed a significant increase in hospital LOS[15,18]. This unexpected finding contrasts with previous assumptions that early stabilization in the ICU would shorten the overall duration of hospitalization. It also contradicts the results of a meta-analysis conducted by Wang et al., which found that dexmedetomidine not only reduced ICU LOS and duration of mechanical ventilation but also significantly

decreased hospital LOS[22].

Furthermore, the increased hospital LOS observed in the included studies may be influenced by differences in discharge criteria, care transition delays, or institutional variability, rather than a direct pharmacological effect of the drug.

With respect to mortality, the pooled analysis found no significant reduction in overall mortality with dexmedetomidine use compared to other sedatives. However, subgroup analysis by follow-up duration revealed a notable trend. The 28-day mortality outcomes showed a significant reduction, while 30-day mortality did not[7,12,13,15,17]. This suggests that dexmedetomidine's clinical benefits may manifest in the early phase of recovery, potentially related to its immunomodulatory and anti-inflammatory effects[23]. Mortality timing has been observed in prior meta-analyses, reinforcing the need for standardized follow-up periods in future trials.

There was no previous systematic review and meta-analysis in the previous last 5 years that assessed lactate clearance[11,14,24]. This study finds that dexmedetomidine promotes higher 24 hour lactate clearance in patients unsignificantly. Contrary, one individual RCT by Dargent et al. showed increased lactate levels in 6 and 12 hours follow up. This time-dependent pattern may reflect the biphasic physiological effects of dexmedetomidine. Initially, its sympatholytic action suppresses norepinephrine release, leading to transient reductions in cardiac output and systemic oxygen delivery. As a result, tissue hypoperfusion may temporarily elevate lactate levels in the early hours[25,26]. However, over time, dexmedetomidine exerts anti-inflammatory and endothelium-stabilizing effects that improve microcirculation and oxygen utilization at the cellular level, which may explain the improvement in lactate clearance observed at 24 hours[14,27].

The findings of this study have relevant implications for critical care practice. Dexmedetomidine may be considered as a preferred sedative agent for mechanically ventilated sepsis patients because it significantly reduces ICU length of stay, which could lead to decreased ICU resource utilization and improved patient turnover. Its potential early-phase mortality benefit at 28 days supports its use during the acute stage of sepsis management, possibly through attenuation of the sympathetic response and modulation of inflammatory pathways. However, the prolonged hospital stay observed suggests that improvements in ICU outcomes do not

necessarily translate into earlier discharge, emphasizing the importance of integrated post-ICU care. Clinicians should carefully consider individual hemodynamic profiles and sedation targets when initiating dexmedetomidine in septic patients.

This review has several limitations. First, the number of studies per outcome was limited, with small sample sizes in some trials. Specifically, hospital LOS was reported in only 2 studies, ICU LOS in 4 studies, mortality in 5 studies, mechanical ventilation-free days in 4 studies, and lactate clearance in 3 studies. Second, there was variation in follow-up duration for mortality (28-day vs. 30-day), which may affect comparability. Third, high heterogeneity was observed in several outcomes, especially mechanical ventilation-free days and hospital LOS. Additionally, the included studies used different sedation targets, and the control groups varied widely, including agents such as propofol, midazolam, placebo, or usual care, further complicating interpretation and reducing the internal consistency of comparisons.

CONCLUSION

This systematic review and meta-analysis found that dexmedetomidine, when used for sedation in mechanically ventilated sepsis patients, was associated with a significant reduction in ICU length of stay but a paradoxical increase in hospital length of stay. While overall mortality was not significantly reduced, a subgroup analysis indicated potential early-phase mortality benefits at 28 days. No definitive conclusions can be drawn regarding lactate clearance and ventilator-free days, as the findings were not statistically significant. The clinical efficacy of dexmedetomidine remains nuanced, with outcome variability influenced by study design, sedation targets, and follow-up durations. Further high-quality, standardized trials are warranted to clarify its role in the critical care management of sepsis.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest related to the research, authorship, or publication of this article. This declaration is made in accordance with journal policy, and the information will remain confidential during the peer review process and will not influence editorial decisions.

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