Title: Early Norepinephrine for Patients with Septic Shock: An Updated Systematic Review and Meta-analysis with Trial Sequential Analysis

Journal: *Critical Care* (2025), Impact Factor ≈ 9.3
DOI: 10.1186/s13054-025-05400-z
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Date: 1404/04/29

Background

- Septic shock is a life-threatening condition and a major cause of ICU mortality.
- Norepinephrine (NE) is the first-line vasopressor recommended by international guidelines.
- Early NE may restore perfusion faster and reduce fluid overload, but it might also cause excessive vasoconstriction and increase catecholamine exposure.
- Current guidelines (e.g., Surviving Sepsis Campaign) do not define the optimal timing for NE initiation.
- Some evidence supports early NE, but concerns remain about safety and efficacy—hence this updated analysis.

Study Objective

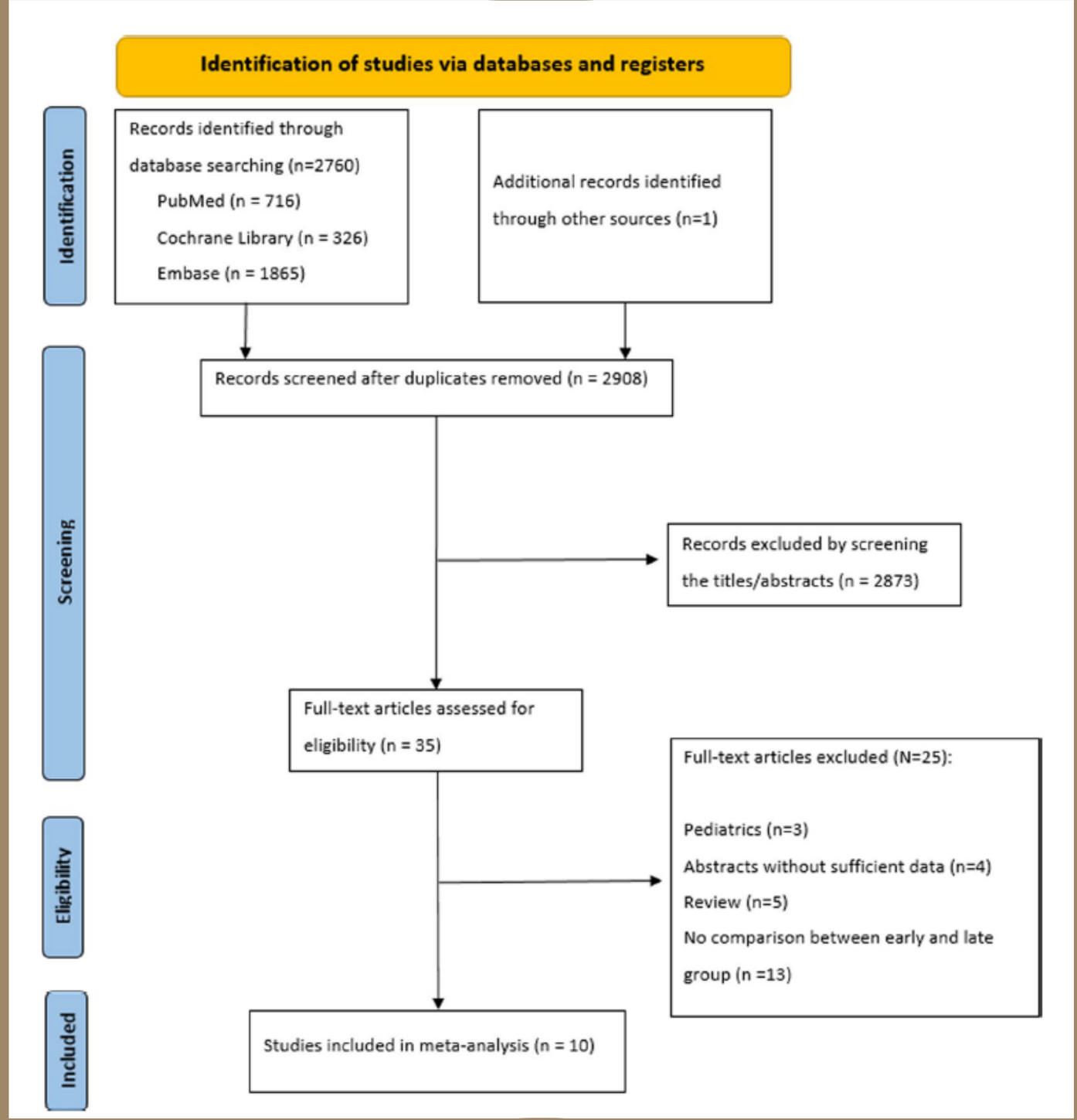
- To determine whether early norepinephrine initiation improves clinical outcomes in adults with septic shock compared to delayed initiation.
- Specifically evaluates impact on mortality and several secondary outcomes.
- Incorporates recent studies and uses trial sequential analysis (TSA) to assess the conclusiveness of findings.

Methods: Literature Search and Eligibility

- Databases: PubMed, Embase, Cochrane Library (up to September 2024).
- Registered on PROSPERO (CRD42023424058).
- Included studies:
  - Randomized Controlled Trials (RCTs),
  - Propensity Score Matching (PSM) studies,
  - Observational cohorts.
- Population: Adult patients with septic shock.
- Intervention: Early NE initiation (varied definitions: ≤1h, <3h, etc.)
- Comparator: Delayed/non-early NE initiation.
- Outcomes: Primary = Mortality; Secondary = Fluid volume, MAP time, MV-free days, RRT use, ICU length of stay.

Study Selection and Characteristics

- Total included studies: 10 (n = 4,767 patients).
  - 2 RCTs (n = 411),
  - 3 PSM studies (n = 3,346),
  - 5 observational studies (n = 1,010).
- Countries: USA, France, China, Thailand, Korea, Colombia, Egypt.
- "Early" NE generally ranged from ≤1h to ≤3h post-diagnosis or fluid initiation.
- Patient severity and timing varied widely.



Risk of Bias and Study Quality

- 1 RCT: Low risk of bias.
- 1 RCT: Some concern (randomization issues).
- Observational studies: Moderate risk (NOS assessment).
- Funnel plots and Egger's test: No strong publication bias detected.
- Overall, moderate-to-low certainty of evidence (GRADE).

Primary Outcome: Mortality

RCTs only (n = 411):

- OR = 0.49 (95% CI: 0.25 to 0.96), I^2 = 45%, p = 0.04

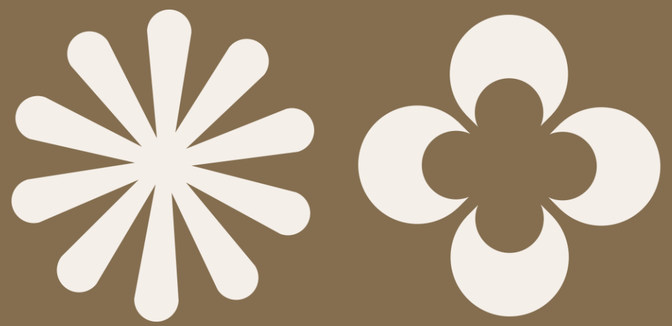
RCT + PSM (n = 3,757):

- OR = 0.65 (95% CI: 0.42 to 0.89), I^2 = 74%, p = 0.05

Observational (n = 1,010):

- OR = 0.71 (95% CI: 0.54 to 0.94), I^2 = 66%, p = 0.02

→ Suggests a significant reduction in mortality with early NE across all designs.



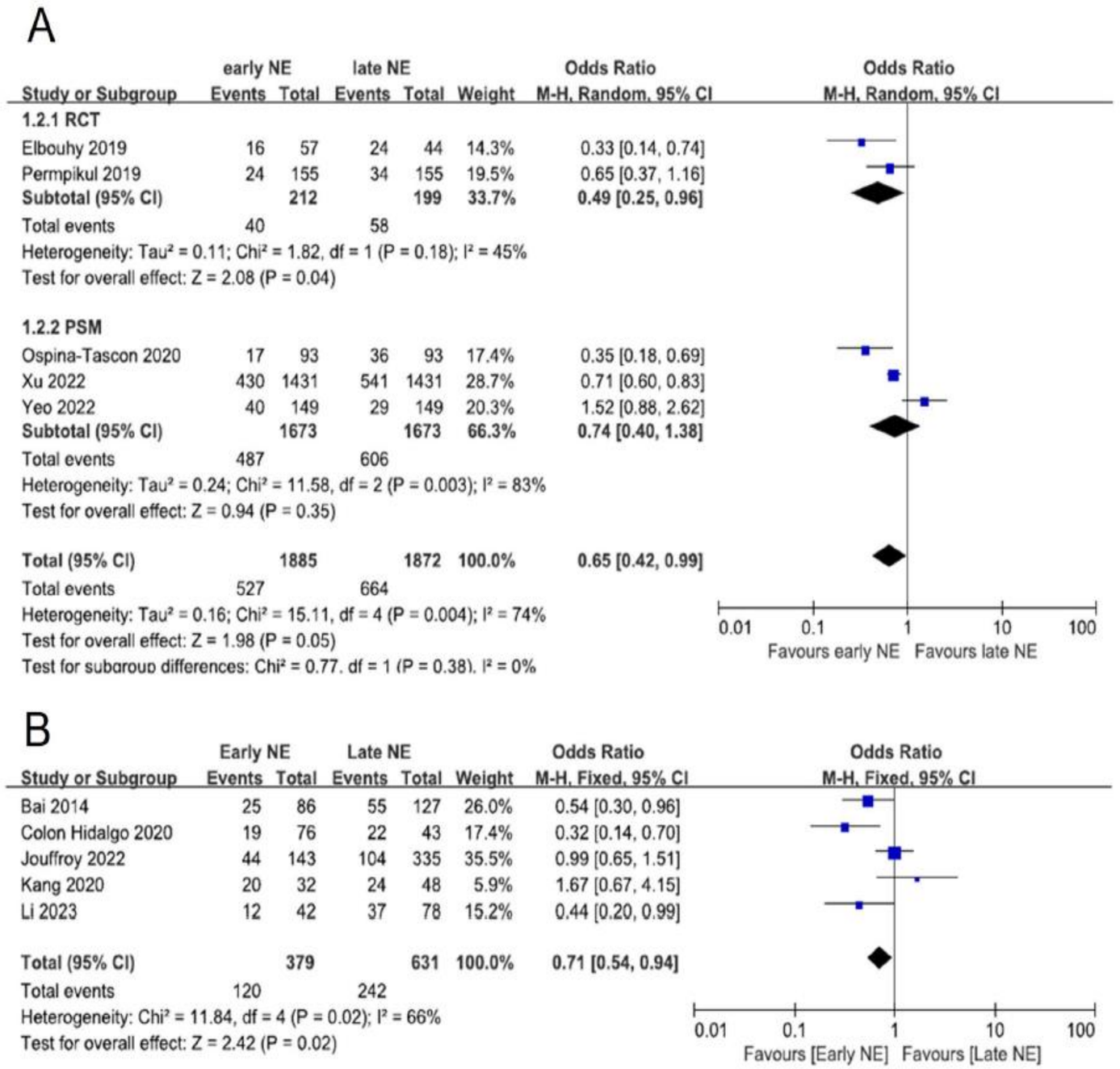


Fig. 2 Forest plot for mortality in (**A**) RCT and PSM studies, or in (**B**) observational studies. NE: Norepinephrine; PSM: propensity score matched; RCT: randomized control trial

Trial Sequential Analysis (TSA)

- TSA used to determine whether data are conclusive.
- Required information size (RIS): 8,251 patients.
- Current pooled data (n = 3,757 for RCT + PSM) fell short.
- Z-curve did not cross benefit or futility boundaries.

→ Result: Evidence still inconclusive—more RCTs needed.

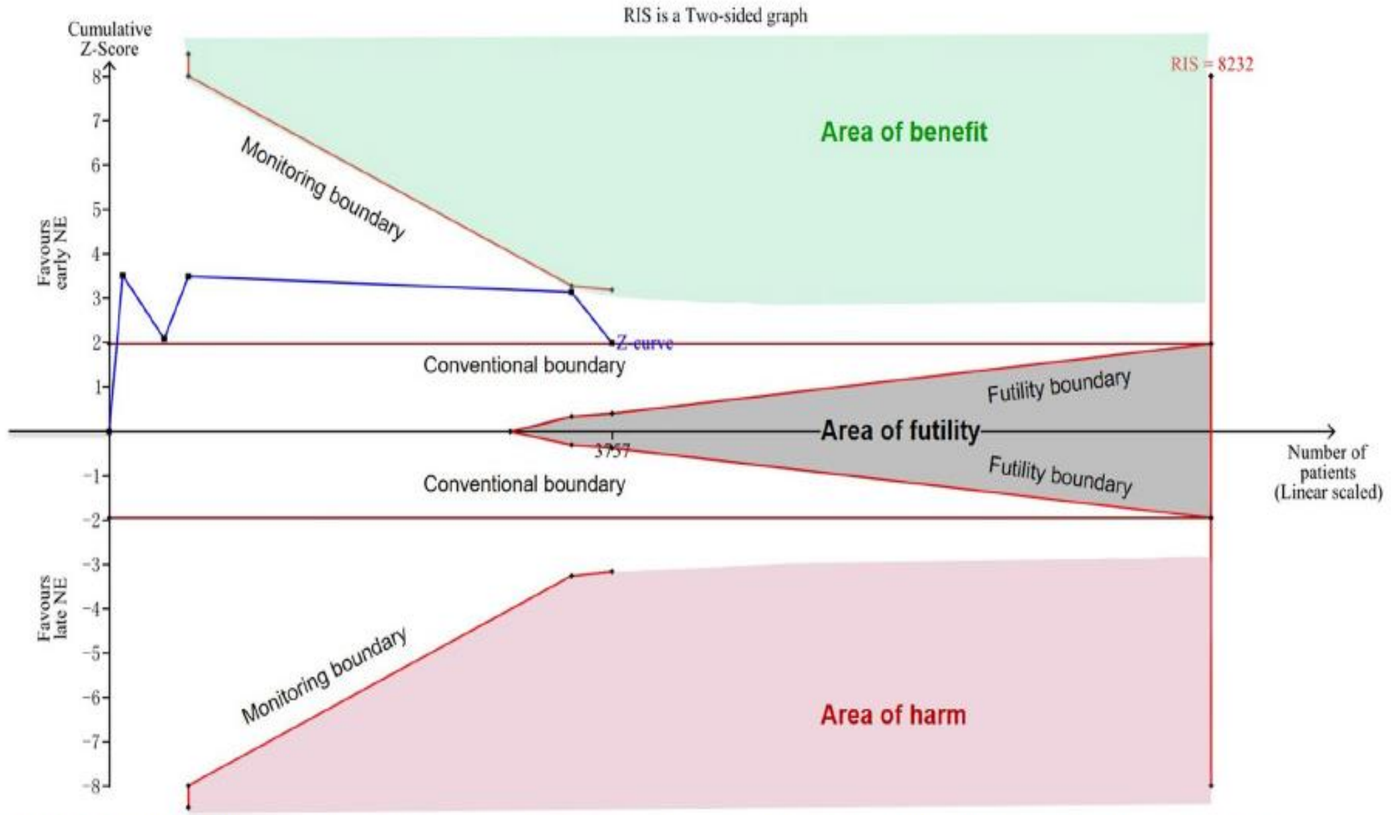


Fig. 3 Trial sequential analysis for mortality. The cumulative Z-curve neither crossed the futility boundary nor reached the required information size, suggesting insufficient evidence and inconclusive result. A diversity-adjusted required information size of 8 251 patients was calculated. NE: norepinephrine; RIS: required information size

Subgroup Analysis: Lactate and Timing

Lactate ≤3 mmol/L:
OR = 0.61 (95% CI: 0.43 to 0.86), I^2 = 49%, p = 0.006
Lactate >3 mmol/L:
No significant benefit.
NE initiation >1 hour after onset:
OR = 0.70 (95% CI: 0.6 to 0.82)
NE ≤1 hour:
No significant mortality benefit
→ Early NE seems more effective in **moderate cases**, not severe.

Sensitivity Analyses

- Excluding Bai et al. or studies with non-Sepsis-3 definitions:
  - Mortality benefit disappeared

Sensitivity to individual studies (e.g., Yeo et al.)
Significant heterogeneity due to:
- Definitions of "early",
- Shock severity,
- Fluid strategies

→ Need for more standardized protocols.

Secondary Outcome

Time to MAP Target
Pooled data from 2 RCTs:

Mean Difference = −1.30 hours (95% CI: −1.75 to −0.85), I^2 = 0%

→ Early NE leads to **faster hemodynamic stabilization**.

Fluid Volume at 6 Hours
RCT + PSM data:

Mean Difference = −502.6 mL (95% CI: −899.2 to −106.0), I^2 = 91%

→ Early NE reduces fluid requirements during early resuscitation.

Mechanical Ventilation-Free Days
1 RCT + 2 PSM studies:

Mean Difference = +3.99 days (95% CI: 2.42 to 5.57), I^2 = 32%

→ Early NE associated with **longer ventilator-free survival**.

Other Secondary Outcomes

ICU Length of Stay:
No significant difference

Renal Replacement Therapy:
OR = 1.03 (95% CI: 0.87 to 1.22), I^2 = 0%

Cumulative NE Dose:
Mean Difference = −3.44 µg/kg (95% CI: −6.13 to −0.76), I^2 = 0%

→ No harm, and possibly **reduced NE exposure**.

Discussion

Potential Mechanisms of Benefit:

Early NE improves preload and MAP faster, limits fluid overload.
May enhance perfusion before organ injury occurs.

Nuances of Benefit:

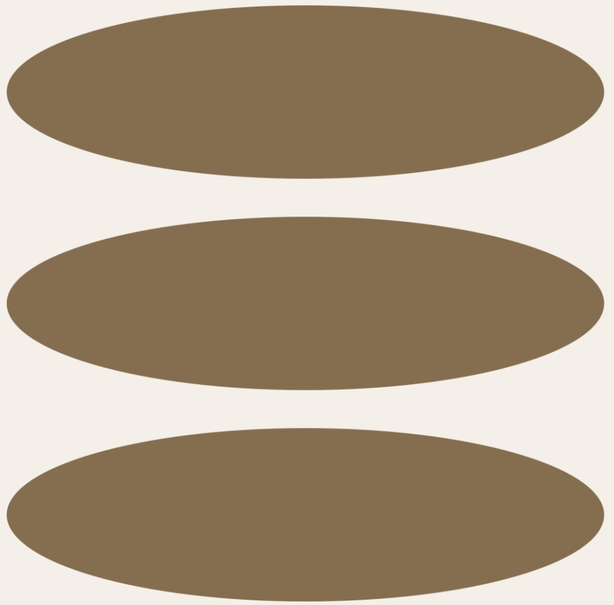
Mortality reduction **not evident** when NE given **within 1 hour** → ultra-early NE might not help and may reflect severe illness.
Lactate <3 mmol/L group benefited most → may represent patients with reversible hypoperfusion.

Limitations:

Substantial heterogeneity (definitions, timing, fluid protocols).
Most evidence from **non-RCTs** or PSM studies — potential confounding and selection bias.
TSA confirms current data insufficient to draw definitive conclusions on mortality.

Clinical Implication:

While promising, early NE should be considered case-by-case.
Aggressive, unmeasured early use may not benefit sicker patients.
Need for **well-powered, homogeneous RCTs** with Sepsis-3 criteria and protocolized interventions.



Conclusions

- Early norepinephrine **may** improve clinical outcomes in septic shock.
- Appears safe and reasonable to consider in clinical practice.
- However, evidence is still **not conclusive**.
- **High-quality RCTs** are needed to confirm benefits and define ideal candidates.

Key Take-Home Points

Summary of critical findings from the meta-analysis on norepinephrine use

✅ Early NE:
↓ Mortality
↓ Fluid overload
↑ Ventilator-free days
↑ Hemodynamic control

⚠️ Limitations:
Evidence still inconclusive (TSA)
Benefits vary by severity and timing
Ongoing trials (e.g., NCT05931601) will clarify optimal approach.

➡️ Until then, individualize NE initiation based on patient context.

Feel free to reach out for more insights

Thank you for your attention

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