Alexandre Kalimouttou, JAMA, 04/2025

Optimal Vasopressin Initiation in Septic Shock - The OVISS Reinforcement Learning Study

BACKGROUND

- Vasopressin has been proposed as a second-line treatment in patients with septic shock and poor response to norepinephrine.
- Optimal timing for initiation of vasopressin has not been well-determined.

RESEARCH AIM

- To identify the **optimal vasopressin initiation** strategy using a reinforcement machine learning (ML) model
- Compare ML suggestions with real life clinicians' actions

METHODS

Design:
- Retrospective, electronic health record data
  - Training cohort: 3608 patients from 5 Californian hospitals hospitalized between 2012 and 2023
  - Validation cohort: 628 patients from 5 Californian hospitals and 10217 patients from external datasets derived from 277 US hospitals

Population:
- Patients with their first episode of septic shock, according to Sepsis-3 criteria, in the emergency department or ICU

Exposure:
- Clinical, laboratory and treatment variables

Primary outcome:
- In-hospital mortality

Model training:
- ML algorithm with reinforcement learning was used to identify the optimal rule for vasopressin initiation

Statistical analysis:
- Weighted pooled logistic regression comparing patients in whom care was similar vs different to the ML rule

RESULTS

Patients in the validation cohort had a median age of 67 [IQR 57-76] years, 56% (5743/10217) were male and median SOFA at onset of septic shock was 6 [4-9]. The table shows the ML-suggested start of vasopressin compared to clinicians' action:

	Clinicians	ML rule	P value
Patients with vasopressin start	31 % (3´186/10´217)	87 % (8´884/10´217)	< 0.001
Norepinephrine dose	0.37 [0.17-0.69] µg/kg/min	0.2 [0.08-0.45] µg/kg/min	< 0.001
Time since onset shock	5 [1-14] h	4 [1-8] h	< 0.001
SOFA score	9 [6-12]	7 [5-10]	< 0.001
Lactate	3.6 [1.8-6.] mmol/l	2.5 [1.7-4.9] mmol/l	< 0.001

When comparing patients whose care aligned with the ML rule to those whose care differed, adherence to the rule was associated with:

- Lower odds of in-hospital mortality (OR 0.81, 95% CI 0.73–0.91)
- Lower odds in kidney replacement therapy (OR 0.47, 95% CI 0.46–0.49)

No association with mechanical ventilation was found.

CONCLUSION

The machine learning model recommended more frequent and earlier initiation of vasopressin compared to standard clinical practice, and this approach was associated with reduced in-hospital mortality.

SIS COMMENTS

The Optimal Vasopressin Initiation in Septic Shock study (OVISS) investigated the optimal timing for initiating vasopressin in patients with septic shock using reinforcement learning, a machine learning (ML) approach [1]. In this study, Kalimouttou and colleagues found that the ML algorithm recommended **more frequent and earlier vasopressin use** compared to standard clinical practice. Specifically, the algorithm suggested initiating vasopressin sooner after shock onset, at lower norepinephrine doses, lower lactate levels, and lower SOFA scores.
When comparing patients whose treatment closely aligned with the algorithm's recommendations to those who were treated differently, those in the concordant group demonstrated significantly improved survival and a reduced need for kidney replacement therapy.

The effect of vasopressin on outcomes in patients with septic shock has been the subject of extensive research over the past decades. However, the two largest RCTS, namely VASST and VANISH, did not demonstrate a survival benefit [2,3]. This finding was further supported by a meta-analysis conducted by Nagendran and colleagues, which found no evidence of a mortality reduction at 28 days associated with vasopressin use [3].

In the era of big data and high-resolution subgroup analyses, the question arises whether specific patient subgroups might indeed benefit from the addition of vasopressin to norepinephrine. In this context, Xu and colleagues published a retrospective analysis in 2023 using data from the MIMIC-III and MIMIC-IV databases. They found that initiating vasopressin at a norepinephrine dose of less than 0.25 µg/kg/min was associated with a lower 28-day mortality risk compared to initiation at higher norepinephrine doses (≥ 0.25 µg/kg/min) [4].

The here discussed OVISS study further supports the findings of Xu and colleagues by demonstrating, through a robust ML approach, that **earlier and individualized initiation of vasopressin may improve outcomes** in patients with septic shock.

This outstanding and well-designed study, featuring a robust methodology and comprehensive analysis, highlights current possibilities of ML in the early identification and risk stratification of patients who may benefit from targeted therapies. By demonstrating the potential superiority of algorithm-guided decision-making over conventional clinical judgment, the findings underscore the growing utility of ML in supporting individualised treatment strategies.

In recent years, artificial intelligence (AI) has significantly accelerated the pace of biomedical research, enabling the development of more precise and dynamic tools for diagnosis, prognostication, and therapy selection. Despite these advances, the translation of AI algorithms into everyday clinical practice remains exceedingly limited. This gap is largely due to the technical complexity and high costs associated with implementing real-time data acquisition, processing, and analysis systems required to support AI-driven clinical decision-making. While AI continues to reshape how we understand and investigate medicine, greater efforts will be necessary to convert these technologies into practical, evidence-based treatment tools that demonstrably improve patient care at the bedside.

1. Kalimouttou et al, JAMA, 2025
2. Russell et al, N Engl J Med, 2008
3. Gordon et al, JAMA, 2016
4. Nagendra et al, Intensive Care Med, 2019
5. Xu et al, BMC Infect Dis, 2023

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