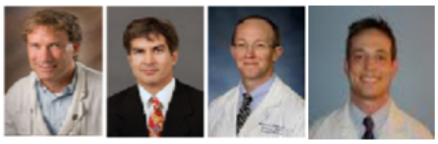
critical care perspectives in emergency medicine



Timing of Vasopressin Administration in Septic Shock

Key Article

- *Kalimouttou A, Kennedy JN, Feng J, et al. Optimal vasopressin initiation in septic shock. The OVISS reinforcement learning study. JAMA. 2025. Published online March 18, 2025.*

Background

- Sepsis accounts for more than 270,000 deaths each year in the US.
- Resuscitation of the patient with sepsis centers on timely recognition, appropriate antibiotic administration, fluid resuscitation, source control, and vasopressor administration for those with evidence of persistent hypoperfusion.
- Current international guidelines for the resuscitation of sepsis recommend norepinephrine as the first-line vasopressor agent. Furthermore, they suggest adding vasopressin as a second-line agent when the MAP remains low despite norepinephrine.
- While vasopressin use has increased, there is little literature to guide the optimal timing of its administration.
- Reinforcement learning is a branch of machine learning where a virtual agent learns from trial and error an optimized set of treatment rules to maximize the probability of a good outcome.
- The current Optimal Vasopressin Initiation in Septic Shock (OVISS) study used reinforcement learning…

Objective

- To derive, validate, and measure the treatment implications of a vasopressin initiation rule optimized to improve both short- and long-term outcomes among critically ill adult patient with septic shock receiving norepinephrine.

Methods

- Derivation and Validation Cohorts
  - Training, testing, and internal validation of the model used data from the UCSF De-Identified Clinical Data Warehouse.
    - Contained data on > 120,000 critically ill admissions from 2012-2023
  - Patients
    - First episode of community- or hospital-onset septic shock
    - In the ED or ICU
    - Already receiving NE
  - External validation of the reinforcement learning model
    - Used 3 datasets: MIMIC-IV, eICU-CRD, EHR dataset from UPMC
    - Datasets had > 250,000 admissions from 227 US hospitals from 2018-2020.
- Data Preparation for Reinforcement Learning Models
  - UCSF data split into derivation and internal validation sets using a 70/15/15 random splitting procedure.
  - Validation cohort consisted of UCSF internal validation and the 3 external datasets

    - Each patient described by age, sex, height, weight, race, ethnicity, SOFA score, MAP, lactate, NE dose, fluid before inclusion, mechanical ventilation, CRRT, Charlson Comorbidity Index score.
    - Source of infection, microbiology, or time to source control were note captured.
- Model Training
    - Reinforcement learning model is a specific type of machine learning algorithm where an agent learns how to make decisions by interacting with an environment.
    - Agent aims to maximize rewards over time by choosing actions based on the current state, with the decision-making process guided by likelihood of future outcomes.
    - Investigators defined the action as a binary decision – start vasopressin or do not start vasopressin.
    - The reward was a weighted combination of in-hospital mortality and changes in lactate, MAP, SOFA, and NE dose.
- Evaluation and Treatment Implications of the Reinforcement Learning Rule
    - Evaluated the treatment implications of the rule recommended by the reinforcement learning model in the 3 external databases.
    - Described the % of patients who would receive vasopressin, timing of initiation relative to shock onset, dose of NE, SOFA score, and serum lactate at vasopressin initiation under the clinician-observed action and under the optimal reinforcement learning rule.
    - Used weighted pooled logistic regression to estimate the adjusted odds of in-hospital mortality, comparing patients in whom care was similar vs different to the reinforcement learning rule in each time block.
    - Defined concordance in each time block as present if the clinician-observed action matched the action recommended by the reinforcement learning algorithm.
- Primary outcome
    - In-hospital mortality
- Secondary outcomes
    - Use of mechanical ventilation
    - Use of RRT

Results

- A total of 14,453 patients with septic shock were included
    - Derivation cohort: 3,608 patients
    - Validation cohort: 10,845 patients
        - 6,251 from UPMC dataset
        - 3,056 from MIMIC-IV dataset
        - 910 from eICU-CRD dataset
        - 628 from UCSF dataset
- Clinician Initiated Vasopressin
    - In the 3 external datasets…
    - Vasopressin initiated in 31% of patients
        - Median SOFA score of 9
        - Median of 5 hours after shock
        - NE dose of 0.37 mcg/kg/min
        - Lactate of 3.6
    - In-hospital mortality: 28-43%
- Reinforcement Learning Rule

    - 2,362 patients in whom vasopressin was recommended by the rule and initiated by clinicians
    - 14% had vasopressin initiated in the same hour as the reinforcement rule recommended
    - Compared to clinician-observed action, the reinforcement learning model suggested vasopressin initiation…
        - In more patients
        - Lower median SOFA score (7)
        - Earlier onset after shock (4 hrs)
        - Lower NE dose (0.20 mcg/kg/min)
        - Lower serum lactate (2.5)
    - Results consistent across each of the 3 validation sets
- Primary Outcome
    - The reinforcement learning model outperformed the clinician-observed action.
    - Concordance with the rule in each time block was associated with reduced odds of in-hospital mortality.
- Secondary Outcomes
    - Concordance with the rule was also associated with a reduced odds of requiring RRT at each time point but not with the odds of requiring mechanical ventilation.

Limitations Identified by Authors

- Did not prospectively test the reinforcement learning rule – used existing databases
- May have limited generalizability to patients underrepresented in the derivation data
- Clinician subjectivity cannot be fully captured by the model
- Did not capture infectious source or source control. There likely exist other unmeasured variables.
- The rule recommended the initiation of vasopressin but did not recommend dosing strategy.

Take Home Point

- A reinforcement learning model recommended more frequent and earlier use of vasopressin for adult patients with septic shock receiving norepinephrine.