

**Background:** Vasopressors are a mainstay of therapy for the support of failing organs in patients with septic shock. Current treatment guidelines recommend norepinephrine as the first-line vasopressor in septic shock followed by addition of vasopressin to achieve a goal mean arterial pressure (MAP). However, recommendations regarding when vasopressin should be added to norepinephrine are lacking. Limited evidence exists evaluating whether the timing of vasopressin initiation affects clinical outcomes in patients with septic shock. **Objective:** To determine whether the addition of vasopressin with respect to norepinephrine dose and infusion duration affects resolution of shock. **Methods:** This was a multi-site, retrospective cohort study including adult patients who were diagnosed with septic shock and received norepinephrine and vasopressin. The primary outcomes were time to shock resolution with respect to norepinephrine dose at vasopressin initiation, and time to shock resolution with respect to time between norepinephrine initiation and addition of vasopressin. Secondary outcomes included norepinephrine dose at 3 hours after vasopressin initiation, in-hospital mortality, and ICU length of stay. A multivariable Cox proportional hazard regression incorporating confounding treatment variables was performed. **Results:** A total of 243 patients were included in the analysis. There was no statistically significant difference in time to shock resolution between any of the 4 patient cohorts stratified according to norepinephrine dose at vasopressin initiation ( $p=0.677$ ). A statistically significant decrease in time to shock resolution was observed in the cohort of patients who had vasopressin added within 3 hours of norepinephrine initiation compared to those who had vasopressin added more than 3 hours after norepinephrine initiation (37.56 hours vs 60.73 hours; HR 2.02; 95% CI, 1.42-2.86;  $P<0.001$ ). **Conclusion:** Among adults with septic shock requiring vasopressor support, norepinephrine dose at vasopressin initiation did not affect time to shock resolution. However, addition of vasopressin to norepinephrine within 3 hours exhibited faster time to shock resolution than later addition of vasopressin. These findings support the early addition of vasopressin to norepinephrine in the treatment of patients with septic shock.