**Introduction:**

Vasoactive medications are commonly used in sepsis treatment but may correlate with peripheral ischemia and the well-publicized complication of limb and digit loss. Yet, the association between limb and digit threat and the intensity, duration, and pattern of vasopressor exposure are unknown.

**Methods:**

We studied adults (2010-2014) at 12 hospitals in an integrated health system who met criteria for Sepsis-3. We identified the time to clinically apparent limb or digit threat using clinical adjudication among those with vasopressor-dependent sepsis (i.e. >1 hour of vasopressors at sepsis onset) who had a surgical evaluation within 28-days of sepsis onset. We defined daily vasopressor intensity as 0 to 4 vasopressors administered. Then, we created a time-dependent model for threat with mortality as a competing risk with a weight function to estimates the varying contribution of vasopressors over time. We determined the sub-distribution hazard (SH) ratio of threat for various patterns of vasopressor exposure and intensity, adjusted for age, baseline risk factors, and sequential organ failure assessment (SOFA) score at sepsis onset.

**Results:**

Of 110,621 adults with sepsis, 13,147 (12%) were vasopressor-dependent (age, 66 [IQR, 56-77]; 7,040 [54%] males; max SOFA score, 8 [SD 5]). Of these, 3,664 (28%) died and 117 (0.9%) had evaluations for limb or digit threat 4 [IQR, 1-8] days after sepsis onset. The model-based weight function showed the contribution of vasopressors to threat was stable over time (Fig 1A). Overall, a 1 unit increase in cumulative vasopressor exposure was associated with risk of threat (SH ratio, 2.60 [95%CI, 1.60-4.23], p<.001). For various patterns of vasopressor exposure, greater intensity associated with increased risk of threat (Fig 1B). Compared to constant exposure, an increasing and peak pattern associated with the greatest SH (Fig 1C).

**Conclusion:**

Cumulative vasopressor exposure was associated with an increased risk-adjusted hazard of limb or digit threat following sepsis.

Image:
Figure 1. Relationship between vasopressor exposure and limb or digit threat following vasopressor-dependent sepsis. Panel A demonstrates the estimated contribution of daily vasopressor intensity prior to surgical evaluation for limb or digit threat, with mortality as a competing risk. Panel B and C explore the relationship between threat and both cumulative vasopressor exposure and the pattern of exposure following sepsis onset. (B) The maximum cumulative vasopressor exposure was associated with the highest risk of limb or digit threat (SHR 17.5) when compared to reference exposure pattern (SHR 1.0, reference). (C) Increasing (SHR 1.2) and peak (SHR 1.2) patterns of cumulative exposure were associate with an increased SH of limb threat, while a decreasing pattern was associated with a lower risk (SHR 0.8) when compared to constant intensity (SHR 1.0, reference). Abbreviations: SHR: Sub-distribution hazard ratio.