PGY-2

**Critical Review Form**

 **Prognosis**

[Alegría L, Vera M, Dreyse J, et al. A hypoperfusion context may aid to interpret hyperlactatemia in sepsis-3 septic shock patients: a proof-of-concept study. Ann Intensive Care. 2017 Dec;7(1):29.](http://pmid.us/28281216)

**Objectives: To test the hypothesis “that two different clinical patterns can be recognized in septic shock as defined by sepsis-3 consensus, according to the presence of a hypoperfusion context.” (p. 2)**

**Methods: This retrospective, observational study used a prospectively collected database from the intensive care unit (ICU) at the University Hospital of the Pontificia Universidad Catolica de Chile between July 2013 and December 2014. Adult patients (18 years or older) presenting with septic shock (requiring vasopressors to maintain MAP ≥ 65 with a lactate ≥ 2 mmol/L after initial fluid resuscitation) with complete dataset in the medical chart were eligible for inclusion. The authors defined a “hypoperfusion context” as an ScvO2 < 70%, a central venous-arterial PCO2 gradient (P(cv-a)CO2) ≥ 6 mmHg, or a capillary refill time (CRT) ≥ 4 seconds with an elevated lactate following fluid resuscitation. Patients who did not meet these criteria were defined as “non-hypoperfusion context.”**

**All patients were managed according to a local algorithm. Fluid challenges were administered until perfusion targets (ScvO2, P(cv-a)CO2, CRT) were achieved or there was an increase in central venous pressure ≥ 5 mmHg.**

**Out of 116 septic shock patients presenting during the study period, 90 met inclusion criteria. The mean age was 66 and 57% were female. The infectious source was intra-abdominal in 46 cases, pulmonary in 21 cases, urinary in 15 cases, and “other” in the remaining 8 cases. There were 70 patients with a hypoperfusion context and 20 without.**

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| **Critical Review Form: Prognosis** |
| Guide | Comments |
| **Are the results valid?** |
| **Was the sample of patients representative?** *In other words, how were subjects selected and did they pass through some sort of “filtering” system which could bias your results based on a non-representative sample. Also, were objective criteria used to diagnose the patients with the disorder?* | Mostly yes. The authors chose to only include patients with septic shock who had both an elevated lactate AND required vasopressors to maintain a MAP ≥ 65 mmHg. Twenty-six patients were excluded due to normal lactate levels at admission to the ICU (7), lack of data (10), lack of commitment for full resuscitation (4), or transfer to other hospitals (5). Despite these exclusions, this should correctly represent a set of patients with severe septic shock. |
| **Were the patients sufficiently homogeneous with respect to prognostic risk?** *In other words, did all patients share a similar risk from during the study period or was one group expected to begin with a higher morbidity or mortality risk?* | Yes. All patients had severe septic shock with both an elevated lactate level and a need for vasopressors. The high percentage of patients with an intra-abdominal source of infection (51%) suggest a large number of post-operative patients, which may have a different course toward recovery than those with non-operative sources of infection. The authors did not look at this group separately, so it is unclear if these patients had higher or lower morbidity or mortality compared to the rest of the cohort. |
| **Was follow-up sufficiently complete?** *In other words, were the investigators able to follow-up on subjects as planned or were a significant number lost to follow-up?* | Yes. As all outcomes were measured in-hospital, and none were measured after discharge, outcome data was available for all patients included in the study. |
| **Were objective and unbiased outcome criteria used?** Investigators should clearly specify and define their target outcomes before the study and whenever possible they should base their criteria on objective measures. | Somewhat. The outcomes were fairly objective (including mortality, norepinephrine dose, duration of mechanical ventilation, need for high volume hemofiltration (HVHF), and ICU and hospital length of stay), but these outcomes do not appear to have been well-defined *a priori*. |
| **What are the results?** |
| **How likely are the outcomes over time?***For the defined follow-up period, how likely were subjects to have the outcome of interest?*  | * Patients with a hypoperfusion context had similar baseline lactate values compared with those without hypoperfusion context (4.8 ± 2.8 vs. 4.7 ± 3.7 mmol/L).
	+ Patients with a hypoperfusion context required more norepinephrine (0.19 ± 0.24 vs. 0.09 ± 0.11 mcg/kg/min), had higher baseline SOFA scores (9.5 ± 3.8 vs. 8.4 ± 2.6), were more likely to receive dobutamine (31% vs. 5%), and received more IV fluids (6732 ± 2524 vs. 5940 ± 2756 mL).
* Death occurred in 11 patients with a hypoperfusion context (16%) and only 1 without a context (5%): RR 2.86, 95% CI 0.39-21.
* Patients with a hypoperfusion context required higher doses of norepinephrine at 0 and 6 hours, but not at 24 hours, and exhibited a trend toward a higher number of days requiring mechanical ventilation, higher need for HVHF, and longer ICU length of stay (though these outcomes did not achieve statistical significance).
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| **How precise are the estimates of likelihood?***In other words, what are the confidence intervals for the given outcome likelihoods?* | See above. |
| **How can I apply the results to patient care?** |
| Were the study patients and their management similar to those in my practice?  | Possibly. This study was conducted in Chile, where comorbidities and risk factors may exist in difference proportions than in patients in the US. The authors do not provide any information regarding past medical history to allow us to make this comparison. Additionally, over half of included patients had an intra-abdominal source of infection. This is likely more typical of patients in our surgical ICU, but likely quite different than those in the typical medical ICU, or in the general ICUs of smaller community hospitals. |
| Was the follow-up sufficiently long? | Yes. All outcomes were measured in-hospital which should be sufficient given that the aim of this study was to compare hospital course between those with and without a hypoperfusion context. The study did not look at long-term functional outcomes. |
| Can I use the results in the management of patients in my practice?  | Uncertain. While the authors were hoping to identify a group of patients at higher risk of morbidity and mortality by looking at those with a “hypoperfusion context”, their cohort was too small to achieve statistical significance for most of their outcomes, despite potentially clinically meaningful differences observed. Additionally, if we assume a difference in outcomes does exist, this observational study does not suggest how care should differ between groups or whether changes in management would affect these outcomes. |

**Limitations:**

1. **Several reporting issues were noted inconsistent with** [**STROBE guidelines for reporting in observational studies**](https://www.equator-network.org/reporting-guidelines/strobe/)**:**
	1. **No past medical history was provided for patients included in the cohort.**
	2. **No** [**primary outcome**](http://pmid.us/26528658) **was identified.**
	3. **No information provided as to how the sample size was chosen.**
2. **A large number of patients was excluded due to lack of complete data. Outcomes for these patients was not provided**
3. **The sample size was inadequate to identify statistical significance differences for most outcomes, despite observing potentially clinically meaningful differences,** [**a practice some view as unethical**](http://pmid.us/12117401)**.**
4. **Over half of included patients had an intra-abdominal source of infection. This is likely more typical of patients in our surgical ICU, but likely quite different than those in the typical medical ICU, or in the general ICUs of smaller community hospitals (**[**external validity**](http://www.epmonthly.com/archives/features/understanding-external-validity/)**).**

**Bottom Line:**

**This small, observational study suggests that patients with septic shock who have a “hypoperfusion context” (ScvO2 < 70%, P(cv-a)CO2 ≥ 6 mmHg, or CRT ≥ 4 seconds) have higher vasopressor needs at 6 and 24 hours, longer need for mechanical ventilation, increased need for HVHF, and higher mortality than those without a hypoperfusion context. Unfortunately, this study was underpowered to detect clinically meaningful differences in outcomes and does not suggest how management should be altered by the results.**