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# Bad Brains, Bad Outcomes: Acute neurologic dysfunction and late death after sepsis

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Each year, 1.6 million Americans are hospitalized with sepsis[1]. And, while most patients now survive to hospital discharge, they face an increased risk for death in the months-to-years after discharge[2]. Among older patients surviving sepsis hospitalization, 1 in 5 has a late death due to the lasting effects of sepsis[2].

Because of this late mortality, and also the well-described morbidity (e.g. new cognitive impairment, functional disability) associated with surviving sepsis hospitalization[3], the 2017 World Health Assembly resolution on sepsis specifically calls for "reducing the incidence of, mortality from, and long-term complications of sepsis"[4]. In this issue of *Critical Care Medicine*, Schuler *et al.* get us closer to understanding the drivers of late sepsis-related deaths[5].

Schuler *et al*. report on 30,000 patients admitted with sepsis, and carefully examine the effect of each individual organ dysfunction on late mortality among patients surviving a sepsis hospitalization[5]. Severity of organ dysfunction was calculated every 6 hours during the hospitalization using modified SOFA scores. Notably, neurologic dysfunction was measured not only by Glasgow Coma Scale, but also by extracting clinical documentation of agitation or delirium—a clear strength of the study.

The effect of organ dysfunction on late mortality was then measured using several time-to-event models, one for each organ dysfunction. In addition, to isolate the effect of acute organ dysfunction on late mortality (independent of a patient's risk for developing organ dysfunction), the authors performed a thoughtful sensitivity analysis. They adjusted for pre-

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existing risk of organ dysfunction using a machine-learning-derived propensity score developed from *all* diagnoses (ICD-9 codes) in the year prior to sepsis.

Consistent with prior studies, the cohort had a high rate of late mortality. In-hospital mortality occurred in just 9.4%, and was strongly associated with the severity of acute organ dysfunction (particularly, neurologic, respiratory, and cardiac). However, by 3 years, 60% of the cohort had died.

Of the six organ systems examined, neurologic dysfunction was most strongly associated with late mortality. There was a 6% absolute increase in 1-year mortality among survivors who experienced acute neurologic dysfunction. Interestingly, neither respiratory, cardiac, nor renal dysfunction were associated with increased late mortality among patients surviving sepsis hospitalization. These main findings were also replicated in the propensity-matched sensitivity analysis.

A prior study of long-term mortality after critical illness found that cardiovascular, respiratory, and liver dysfunction were strongly associated with long-term survival to 5 years[6]. It is important to note that Schuler *et al* have focused on a slightly different question —the effect of acute organ dysfunction on late mortality, among patients who survive sepsis hospitalization.

Prior studies specifically examining this question of late mortality after sepsis have found that use and duration of mechanical ventilation, vasopressors, and renal replacement therapy are each associated with measureable increases in late mortality[7,8] – although the impact of these acute organ dysfunctions wanes with time[8,9]. It is possible that these differing findings may be due to measuring organ dysfunction vs. proxies of organ failure (mechanical ventilation, vasopressors, and renal replacement). Alternatively, it may be because Schuler *et al* have studied a more recent cohort (2010–2013 hospitalizations), during which time the use of sedation or injurious ventilator practices is perhaps less common.

This present study–one of the first to measure neurological dysfunction—found that, of six measured organ systems, acute neurological dysfunction is most strongly associated with late mortality in patients who have survived sepsis. While the study cannot prove a causal relationship, it provides compelling evidence. The association between neurological dysfunction and late mortality persists even after adjusting for baseline diagnoses, suggesting that acute neurologic dysfunction is not merely a marker of poor outcomes, but may also be a mediator of poor outcomes.

The importance of acute neurological dysfunction is supported by several prior studies. Delirium is common, present in at least 30% of critical care patients[10,11], and is an independent predictor of 6-month mortality[12]. There is widespread agreement that preventing delirium is important, and should focus on re-orientation, promotion of normal sleep-wake cycles, and avoidance of deliriogenic triggers[13]. Liberalizing ICU visitation hours is also helpful[14].

However, there is poor consensus on the treatment of delirium in already-delirious patients. Antipsychotics are used commonly, but have little supporting evidence, and have been

associated with increased mortality and worse symptom control among inpatient palliative care patients[15]. Dexmedetomidine, in contrast, was recently shown to decrease the incidence of post-operative delirium[16], and also shorten time to extubation among ventilated patients with agitated delirium[17]—suggesting that it may be an effective pharmacologic option.

Beyond the challenge of treating patients with recognized delirium, it is often difficult to detect and quantify the severity of acute brain injury—due the confounding effects of sedation and pre-existing cognitive impairment. In preliminary studies, neuron-specific enolase appears to be a potentially useful test for identifying and quantifying neurologic dysfunction in septic patients[18], as well as for assessing response to treatment[19]. However, whether this test, or pharmacological treatment of delirium, can improve acute or late mortality remains unproven.

As the number of patients surviving sepsis continues to grow, post-sepsis morbidity and late morbidity are increasing public health concerns. We must consider the effect of our ICU care on long-term survivorship. Schuler *et al.* nicely demonstrate that neurological dysfunction is strongly associated with both acute and late mortality post-sepsis, and should be a key focus of our treatment plan each day in the ICU.

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## References

1. Rhee C, Dantes R, Epstein L, et al. Incidence and Trends of Sepsis in US Hospitals Using Clinical vs Claims Data, 2009–2014. JAMA. 2017; 318(13):1241–9. [PubMed: 28903154]
2. Prescott HC, Osterholzer JJ, Langa KM, Angus DC, Iwashyna TJ. Late mortality after sepsis: propensity matched cohort study. BMJ. 2016; 353:i2375–i2375. [PubMed: 27189000]
3. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA. 2010; 304(16):1787–94. [PubMed: 20978258]
4. Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, Finfer S. Recognizing Sepsis as a Global Health Priority - A WHO Resolution. N Engl J Med. 2017
5. Schuller A. The impact of acute organ dysfunction on long-term survival in sepsis. Crit Care Med. 2018 in press.
6. Lone NI, Walsh TS. Impact of Intensive Care Unit Organ Failures on Mortality during the Five Years after a Critical Illness. Am J Respir Crit Care Med. 2012; 186(7):640–7. [PubMed: 22837381]
7. Lemay AC, Anzueto A, Restrepo MI, Mortensen EM. Predictors of long-term mortality after severe sepsis in the elderly. Am J Med Sci. 2014; 347(4):282–8. [PubMed: 23689053]
8. Linder A, Lee T, Fisher J, et al. Short-Term Organ Dysfunction Is Associated With Long-Term (10-Yr) Mortality of Septic Shock. Crit Care Med. 2016; 44(8):e728–736. [PubMed: 27428136]
9. Garland A, Olafson K, Ramsey CD, Yogendran M, Fransoo R. Distinct determinants of long-term and short-term survival in critical illness. Intensive Care Med. 2014; 40(8):1097–105. [PubMed: 25011575]
10. Salluh JI, Soares M, Teles JM, et al. Delirium epidemiology in critical care (DECCA): an international study. Crit Care Lond Engl. 2010; 14(6):R210.

11. Burry LD, Williamson DR, Mehta S, et al. Delirium and exposure to psychoactive medications in critically ill adults: A multi-centre observational study. J Crit Care. 2017; 42:268–74. [PubMed: 28806561]
12. Ely EW, Shintani A, Truman B, et al. Delirium as a Predictor of Mortality in Mechanically Ventilated Patients in the Intensive Care Unit. JAMA. 2004; 291(14):1753–1753. [PubMed: 15082703]
13. Oh ES, Fong TG, Hshieh TT, Inouye SK. Delirium in Older Persons: Advances in Diagnosis and Treatment. JAMA. 2017; 318(12):1161–74. [PubMed: 28973626]
14. Rosa RG, Tonietto TF, da Silva DB, et al. Effectiveness and Safety of an Extended ICU Visitation Model for Delirium Prevention: A Before and After Study. Crit Care Med. 2017; 45(10):1660–7. [PubMed: 28671901]
15. Agar MR, Lawlor PG, Quinn S, et al. Efficacy of Oral Risperidone, Haloperidol, or Placebo for Symptoms of Delirium Among Patients in Palliative Care: A Randomized Clinical Trial. JAMA Intern Med. 2017; 177(1):34–42. [PubMed: 27918778]
16. Su X, Meng Z-T, Wu X-H, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet Lond Engl. 2016; 388(10054):1893–902.
17. Reade MC, Eastwood GM, Bellomo R, et al. Effect of Dexmedetomidine Added to Standard Care on Ventilator-Free Time in Patients With Agitated Delirium: A Randomized Clinical Trial. JAMA. 2016; 315(14):1460–8. [PubMed: 26975647]
18. Anderson BJ, Reilly JP, Shashaty MGS, et al. Admission plasma levels of the neuronal injury marker neuron-specific enolase are associated with mortality and delirium in sepsis. J Crit Care. 2016; 36:18–23. [PubMed: 27546742]
19. Li Y, Yu Z-X, Ji M-S, et al. A Pilot Study of the Use of Dexmedetomidine for the Control of Delirium by Reducing the Serum Concentrations of Brain-Derived Neurotrophic Factor, Neuron-Specific Enolase, and S100B in Polytrauma Patients. J Intensive Care Med. 2017 885066617710643.