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Part of the scientific temperament is this tolerance for holding multiple hypotheses in the mind at the same time – David Eagleman

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We want to thank Drs. Moser, van Meurs, and Zijlstra for their valuable comments regarding our recent review article entitled, “*Sepsis Pathophysiology, Chronic Critical Illness, and Persistent Inflammation-Immunosuppression and Catabolism Syndrome*,” published in the *Critical Care Medicine* February 2017 issue. The authors clearly identify the dilemma: earlier detection and better implementation of best-care practices are transforming the natural history of sepsis and septic shock, increasing the number of patients who survive their early inflammatory challenge, but fail to fully recover, and experience chronic critical illness (1). The crux of their argument (2) is that the labeling of this newly described phenotype as a persistent inflammatory, immunosuppressive, protein catabolic syndrome (PICS) is unwelcome, because the “*dysregulated immune response*” contained in the new definition of sepsis (3) also includes smoldering organ injury, mitochondrial dysfunction, neuro-humeral dysfunction, endothelial responses and programmed death of the organism. In their opinion, the acronym, PICS, limits or de-emphasizes other important aspects of sepsis pathophysiology, and hinders a broader understanding of the syndrome. The authors go on to conclude that host immunity is not central to recovery from sepsis by using the oft referred statement, “*over 150 trials aimed at intervening with the immunological response associated with sepsis have failed to improve patient survival*”.

Such a statement fails to recognize that studying “*the immunological response associated with sepsis*” over the past three decades has led to a better understanding of early and late MOF pathogenesis, and has advanced care that has reduced in-hospital mortality. Further progress in sepsis is in desperate need of testable hypotheses, if interventions other than supportive therapy are ever to improve the outcomes of this cohort. As stated in our review (1), PICS is a hypothesis, and testing our PICS hypothesis will advance our understanding of sepsis regardless of whether the hypothesis is or is not correct. The authors' statement that “*We simply do not understand the pathophysiology of prolonged critical illness and a premature focus on the immune system is not helpful*” is contrary to the scientific method, and PICS provides the framework to explain the long-term disabilities associated with chronic critical illness. Host protective immunity represents one of the most fundamental

responses to infection and sepsis, even when focusing on individual organ injury, as proposed by the authors. There is ample experimental evidence on which to base our proposed paradigm, and emerging data suggest that we may be correct (4,5). PICS is intended to provide a hypothesis that can be experimentally tested, and if correct, can then be the basis for novel interventions and biomarkers.

We appreciate the authors' concern about the proliferation of acronyms in sepsis and chronic critical illness. But acronyms serve a valuable purpose. Rather than attempt to explain sepsis pathophysiology in its entirety, the acronym, PICS, apportions sepsis into a collection of testable hypotheses, and provides a framework for future investigation into the long-term consequences of sepsis-associated chronic critical illness. Testable hypotheses focusing on other features of sepsis pathophysiology are needed, and if another acronym assisted in the understanding of the underlying biology, it too would be welcome.

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