Acute kidney injury (AKI) is a common form of organ failure in sepsis, with incidence rates of 40–60% (1, 2). Patients with sepsis-induced AKI have unacceptably high mortality rates (3). Despite the frequency of AKI complicating sepsis, treatments are limited (4). The Kidney Disease: Improving Global Outcomes consensus group defines AKI as an increase in serum creatinine or a decrease in urine output. However, the Kidney Disease: Improving Global Outcomes definition does not stratify patients on the basis of differences in AKI recovery patterns. Combining patients with different AKI recovery patterns may hide subgroups that are more tightly associated with clinical outcomes (5).

The trajectory of renal dysfunction is a clinically intuitive parameter by which to risk-stratify participants with AKI. Previous work has shown that the trajectory of serum creatinine after AKI informs short- and long-term prognoses (5, 6), but the value of longitudinal urinary biomarker concentrations within hours after an intervention has not been reported. In this issue of the Journal, Fiorentino and colleagues (pp. 1262–1270) report the findings from a secondary analysis of the ProCESS (Protocolized Care for Early Septic Shock) study (7), a multicenter randomized controlled trial (RCT) completed in the United States that recruited patients from the emergency department with septic shock and tested two alternative resuscitation strategies compared with usual care. The current study validates that prespecified cutoffs of the product of two urinary biomarkers, TIMP2 (tissue inhibitor of metalloproteinases 2) and IGFBP7 (insulin-like growth factor binding protein 7), are associated with the development of a composite outcome of stage 3 AKI, renal replacement therapy, or death within 7 days after study enrollment (8).

Among 1,341 participants recruited in ProCESS, 688 had urine available at Hour 0 (baseline) and Hour 6 (immediately after implementation of the 6-h resuscitation strategy), and 113 (16.4%) reached the primary outcome, which was mostly driven by rates of stage 3 AKI and death. Only two patients required renal replacement therapy. Participants were stratified into four biomarker subgroups (negative at both Hour 0 and Hour 6 [−/−], negative at Hour 0 and positive at Hour 6 [+/−], positive at Hour 0 and negative at Hour 6 [+/−], and positive at both Hour 0 and Hour 6 [+/+] on the basis of prespecified [TIMP-2] × [IGFBP7] ≥ 0.3 (ng/ml)^2/1,000 at (baseline) and 6 hours (after resuscitation). A majority of participants had a positive urinary [TIMP-2] × [IGFBP7] value at Hour 0 (n = 457), and 64% were in the +/− subgroup, whereas 32% were in the −/− subgroup. In contrast, 231 participants had a negative biomarker level at Hour 0 and 76% remained negative (−/−), whereas 24% became positive at Hour 6 (+/−). In the +/− subgroup, the odds for the primary outcome were twofold greater than those of participants in the −/− subgroup (composite 7-d outcome, 24% vs. 9%, respectively). This association was maintained after adjustment for demographics, serum creatinine, and nonrenal Sequential Organ Failure Assessment score.

The primary results of the parent ProCESS study were null despite significant differences in the volume of crystalloid resuscitation fluid given in each experimental group. On average, during the 6 hours of resuscitation, 2.3 L of fluid was given in the usual-care group, 2.8 L of fluid was given in the early goal-directed therapy group, and 3.3 L of fluid was given in the protocol-based standard therapy group. It is tempting then to speculate that urinary [TIMP-2] × [IGFBP7] status at Hour 0 would inform the response to fluid resuscitation and subsequent clinical outcomes. However, Fiorentino and colleagues were unable to demonstrate a treatment interaction between [TIMP-2] × [IGFBP7] concentrations at Hour 0 and resuscitation group for the composite 7-day outcome. Moreover, the concentration of [TIMP-2] × [IGFBP7] at Hour 6 was not influenced by the randomized treatment arms (early goal-directed therapy vs. protocol-based standard therapy vs. usual care). Heterogeneity in the AKI clinical syndrome may require the incorporation of multiple biomarkers to identify AKI subgroups that respond differently to therapies in septic shock (9).

This paper underscores the limitations of serum creatinine to diagnose AKI. Sepsis and hypoperfusion involve injury primarily to tubular epithelial cells and their microenvironment (10). Several mechanisms are postulated to explain the ensuing reduction in glomerular filtration rate, including 1) constriction of afferent arterioles in response to distal chloride delivery (tubuloglomerular feedback), 2) back leak of filtrate, and 3) tubular obstruction by intraluminal casts (11, 12). As the authors have indicated, both IGFBP-7 and TIMP-2 are secreted mostly by tubule epithelial cells; thus, both are more direct markers of kidney injury during sepsis than estimates of glomerular filtration (e.g., serum creatinine). The discordance in tubular injury and serum creatinine is underscored by the finding that among 457 patients with a positive [TIMP-2] × [IGFBP7] result at Hour 0, only 270 (60%) participants had AKI defined by changes in serum creatinine or urine output.

This study was strengthened by being a secondary analysis of a large RCT; however, some limitations exist. The choice of resuscitation fluid deserves further study, as cohort studies and RCTs have demonstrated worse outcomes for patients resuscitated with unbalanced crystalloid solutions (13, 14). Urinary biomarker measurements were specific to [TIMP-2] × [IGFBP7] and it is unknown whether longitudinal measurement of alternative biomarkers may better inform clinical outcomes. Although repeat urinary biomarker measurements at 6 hours improved the C statistic to predict the primary outcome, it is unclear if this is a clinically meaningful difference compared with simply measuring serum creatinine again at 6 hours after resuscitation.

So where does this leave us in risk-stratifying and treating patients with AKI complicating septic shock? Clearly persistent kidney injury is a worrisome sign and portends poor prognosis. In addition, an
individual patient’s response to a 6-hour resuscitation bundle in septic shock is quite variable. This begs the question of whether participants in the −/+ or +/+ subgroups may actually benefit from an alternative resuscitation strategy. Several RCTs are specifically seeking to clarify the optimal resuscitation strategy in participants with septic shock (15–17). The present study supports that the trajectory of biomarker measurements may inform prognostic enrichment strategies for clinical trial enrollment (18). The authors should be commended for their continuous advances in moving [TIMP-2] × [IGFBP7] from risk assessment toward clinical management. In sepsis, we are constantly searching for better tools to risk stratify patients. Perhaps the trajectory of kidney function is the canary in the coal mine that can inform clinical management and guide development of effective therapeutics for patients with septic shock.

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Pavan K. Bhatraju, M.D., M.Sc.
Mark M. Wurfel, M.D., Ph.D.
Jonathan Himmelfarb, M.D.
Department of Medicine
University of Washington
Seattle, Washington

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Rats Race to Keep Pace in the Growing Cystic Fibrosis Model Space

In cystic fibrosis (CF), which occurs in people with two mutant copies of the CFTR (cystic fibrosis transmembrane conductance regulator) gene, chronic airway infection and inflammation are the major causes of morbidity and mortality. Although the mechanisms underlying disease can be elegantly dissected using in vitro systems, a clear understanding of disease pathophysiology relies on effective animal models (1). A number of CF animal models have been developed through disruption of CFTR loci, with advantages and disadvantages to each (2). Mice and rats are less expensive to purchase and house, have faster reproductive cycles, and can be studied with commercially available reagents for immunologic evaluations. However, small mammals are more anatomically divergent from humans than larger mammals, and these models fail to develop all manifestations of CF pathophysiology (3). The ferret and pig CF models develop lung pathology more closely resembling human CF...