Acute kidney injury (AKI), particularly when accompanied by critical illness, remains a devastating condition, and recent evidence consolidates the view that in the critically ill, AKI is associated with sepsis in more than 50% of cases (1). To date, therapy remains supportive, with little evidence that any specific therapy may influence outcome. Indeed, this is apparent when one consults the clinical guidelines for management of AKI, although within this is the recommendation that protocolized hemodynamic management for patients with septic shock be adopted (2). It is therefore timely that in this issue of the Journal, Kellum and colleagues (pp. 281–287) report the results of the preplanned ancillary analysis of the ProCESS (Protocolized Care for Early Septic Shock) trial (3). The authors examine the employment of protocol-based fluid resuscitation (early goal-directed treatment [EGDT]) on the development of new-onset AKI of any stage during the first 28 days of enrollment, as well as secondary outcomes, including duration of AKI, recovery of renal function, volume overload, and the need for renal support. The results of the three main studies investigating EGDT in septic shock are well documented, with no significant advantage regarding mortality or morbidity being observed (4–6). However, they did show that timely volume resuscitation and delivery of antibiotics to this patient group appear to have improved dramatically since 2001, given that the crude mortality in the usual care group was just over 18% compared with the crude mortality of 46.5% observed by Rivers and colleagues (7). So what of the effect of alternative resuscitation strategies on AKI in septic shock? Given the absence of difference in outcome in the main analysis, it is perhaps unsurprising that no difference is noted with regard to the primary endpoint of development of new AKI when protocolized care is used compared with usual care.

However, despite any obvious benefit from EGDT, several lessons can be learned from this excellently performed study that may well inform future treatment goals in this patient group. Clearly, the observed incidence of AKI is in keeping with other studies in the critically ill, with more than 50% of patients having AKI at presentation, increasing to almost 70% throughout admission (1, 8, 9). Therefore, this cohort accurately reflects the case mix commonly seen in intensive care practice. The patients with, or who develop, AKI have the usual risk factors, including older age, diabetes, and heart failure, and in particular, those who present with AKI have a degree of chronic kidney disease and are more likely to develop positive blood cultures. The severity of illness of those presenting with AKI on admission appears to be worse. Do these results then support a nihilistic view with regard to volume resuscitation in these patients? Clearly not, as the authors themselves concede. However, the results do suggest that overall care may have improved with time, and that by the time of presentation, one is faced with damage limitation with regard to further organ failure, including AKI, rather than a reversal of the fundamental pathological processes. Indeed, of those who develop AKI, most do within a few days of admission, which probably reflects events occurring prehospital; hence, intervention may not be as fruitful.

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### Treating Acute Kidney Injury

**One Less Weapon in the Armamentarium?**

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However, despite any obvious benefit from EGDT, several lessons can be learned from this excellently performed study that may well inform future treatment goals in this patient group. Clearly, the observed incidence of AKI is in keeping with other studies in the critically ill, with more than 50% of patients having AKI at presentation, increasing to almost 70% throughout admission (1, 8, 9). Therefore, this cohort accurately reflects the case mix commonly seen in intensive care practice. The patients with, or who develop, AKI have the usual risk factors, including older age, diabetes, and heart failure, and in particular, those who present with AKI have a degree of chronic kidney disease and are more likely to develop positive blood cultures. The severity of illness of those presenting with AKI on admission appears to be worse. Do these results then support a nihilistic view with regard to volume resuscitation in these patients? Clearly not, as the authors themselves concede. However, the results do suggest that overall care may have improved with time, and that by the time of presentation, one is faced with damage limitation with regard to further organ failure, including AKI, rather than a reversal of the fundamental pathological processes. Indeed, of those who develop AKI, most do within a few days of admission, which probably reflects events occurring prehospital; hence, intervention may not be as fruitful.

A major criticism of many interventional studies on AKI is the fact that both creatinine and urine output criteria are rarely
employed, given the perceived difficulties in achieving accurate urine output. This is not the case in this study, where data are robust and almost complete, with only seven patients excluded from enrollment. Interestingly, patients who developed AKI after admission were classified predominantly on the basis of urine output criteria, rather than change in serum creatinine. This is of note, as it may reflect an inadequacy to excrete the solute load in individuals who one assumes are catabolic, and despite the fact that there is no observed creatinine rise, this still translates into a worse outcome. Herein lies one of the confounders of AKI diagnosis, in that creatinine, a robust marker of chronic kidney disease in relatively stable patients, performs poorly in the acute arena. Thus, a "rise" in creatinine may be masked by a reduction in creatinine production that can fall by up to 50% in sepsis (10). This study highlights the observation that functional change in urine output may herald significant risk, which may have been overlooked previously and may not be identified in terms of renal recovery. Indeed, this study provides further insights into recovery from sepsis-associated AKI, in that individuals who survive to resolution of AKI (as defined by a serum creatinine of &lt;1.5 baseline) appear to approach the same long-term outcomes as those who did not suffer AKI. It would be interesting to see whether individuals classified as having AKI by urine output criteria alone have a similar or different longer-term risk profile.

So where does that leave the treatment of AKI complicating septic shock? Clearly initial resuscitation and prompt use of antibiotic therapy remain the mainstay in treating sepsis, and it is doubtful that EGDT, even if the protocols are changed slightly, will result in significant improvements. We should consider fluid therapy as a drug therapy, with more attention given to the different phases of fluid therapy during the patient’s course of illness. This includes lifesaving fluid resuscitation in the rescue phase, titration of fluids to tissue perfusion in the optimization and stabilization phases, and mobilization of accumulated fluid in the deescalation phase (11, 12). In addition, the choice of fluids deserves further study, as cohort studies suggest worse outcomes for patients resuscitated with unbalanced crystalloid solutions (13–15). In addition, therapies aimed at restoring function to near baseline may be the future. This may, of course, be as simple as avoiding episodes of hypotension, restricting volume, and avoiding nephrotoxins. Such attention to detail should be mandatory to avoid the scenario in which renal function is killed, as perhaps the most sobering statistic from this study is the appalling outlook for those who do not recover, given a mortality rate approaching 80% at 28 days. So fluids remain in the armamentarium of those charged with treating AKI, but protocolized goal-directed therapy does not seem to be a magic bullet.

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**Eric A. J. Hoste, M.D., Ph.D.**
Ghent University Hospital
Ghent University
Ghent, Belgium
and
Research Foundation-Flanders
Brussels, Belgium

Lui G. Forni, M.D., Ph.D.
Faculty of Health and Medical Science
University of Surrey
Guildford, United Kingdom

**ORCID ID:** 0000-0001-9301-8055 (E.A.J.H.)

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