SEPSIS

# Protocolized care for critically ill patients with AKI

*Bantayehu Sileshi and Andrew Shaw*

**Findings from the ARISE and TRISS trials indicate that protocolized therapy might be no better than contemporary management for patients in intensive care, and that in the absence of coronary disease a haemoglobin level of 70 g/l should be the new trigger for transfusion in patients with sepsis.**

Sileshi, B. & Shaw, A. *Nat. Rev. Nephrol*. advance online publication 4 November 2014; doi:10.1038/nrneph.2014.204

Photodisc/Getty

The results of the Australasian Resuscitation in Sepsis Evaluation (ARISE)[1] and Transfusion Requirements in Septic Shock (TRISS) trials,[2] published in the *New England Journal of Medicine*, suggest that early, protocolized aggressive administration of fluid and blood products to patients with septic shock might not be as beneficial as once thought. In the ARISE trial, 90 day mortality was similar among patients randomly assigned to receive early goal-directed therapy (EGDT) and those assigned to receive usual care, despite patients in the EGDT group receiving significantly more intravenous fluid, vasopressor infusions and red-cell transfusions in their first 6 h of resuscitation. This finding is contrary to the findings of Rivers *et al.*[3] from which the Surviving Sepsis Campaign recommendations originated. In the TRISS trial, investigators assessed blood transfusion thresholds by randomly assigning patients with septic shock to receive a transfusion of packed red blood cells either when they reached a haemoglobin threshold of ≤90 g/l or a lower threshold of ≤70 g/l. Their results showed that 90 day mortality, rates of ischaemic events and use of life support were similar between the groups.

As clinicians involved in the care of critically ill patients consider these findings, it is important to ask how externally valid these data are; that is, can these results be extrapolated beyond the trial inclusion criteria, more specifically to patients with impaired kidney function? In the TRISS trial 219 (44%) of the patients in the lower threshold haemoglobin group (restrictive cohort) had kidney failure compared to 232 (47%) in the higher threshold group (liberal cohort).[2] 68 (13.5%) patients in the restrictive cohort were on renal replacement therapy before randomization versus 53 (10.7%) in the liberal cohort ($P = 0.17$ by our estimation). At 28 days, 24 of 330 patients were receiving renal replacement therapy in the restrictive cohort compared to 28 of 322 in the liberal cohort. At 90 days, 85 patients in the restrictive cohort (versus 83 in the liberal cohort) were alive without renal replacement therapy. Although no subgroup analyses were performed, it is instructive to see that the two groups started with similar incidences of impaired renal function, and remained similar in terms of their sustained reductions in renal function after 90 days. A higher haemoglobin threshold does not, therefore, seem to reduce the need for renal replacement therapy.

> “These findings oppose the widely held belief that fluid accumulation somehow protects the kidneys”

In the ARISE trial, in which patients with septic shock received either EGDT or usual care, 34 (4.3%) patients in the EGDT group had chronic renal insufficiency compared to 30 (3.8%) in the usual care group.[1] Mortality outcome stratified by baseline renal disease burden is not provided. Given the low percentage of patients that had renal insufficiency at baseline (as compared to the TRISS trial), it is difficult to make any conclusion with regard to the effect of the two resuscitative strategies on patients with baseline renal insufficiency. What is informative is the effect of the two resuscitative strategies on the development of new onset renal failure. Baseline serum creatinine levels were similar between the two groups (133 μmol/l [1.50 mg/dl] in the usual care group versus 127 μmol/l [1.44 mg/dl] in the EGDT group). Although post-randomization serum creatinine levels were significantly different in the usual care group compared to the EGDT group at 24 h (102 μmol/l [1.15 ml/dl] versus 92 μmol/l [1.04 mg/dl]; $P = 0.01$) and 72 h (83 μmol/l [0.94 mg/dl] versus 81 μmol/l [0.92 mg/dl]; $P = 0.05$), the need for renal replacement therapy (13.5% versus 13.4%; $P = 0.94$) and duration of renal replacement therapy (median of 85.9 h versus 57.8 h; $P = 0.40$) was similar between the two groups. In addition 24 h and 72 h serum creatinine levels were lower than baseline levels, suggesting an element of ‘pre-renal’ insufficiency that was corrected by the interventions. The multivariable regression model for mortality showed no difference in outcome based on renal replacement therapy, despite the EGDT group receiving significantly more intravenous fluid in the first 6 h (mean: 1,964 ± 1,415 ml versus 1,713 ± 1,401 ml), more vasopressor infusions (66.6% versus 57.8%), and red-cell transfusions (13.6% versus 7.0%). These

findings challenge the notion that fluid and inotrope therapy to the point of maximal cardiac performance results in improved long-term renal protection.

Consistent with ARISE and TRISS, the outcomes of another large multicentre trial, the Protocolized Care for Early Septic Shock (ProCESS) trial[4] showed comparable 60 day mortality outcomes in patients with septic shock that were randomly assigned to one of three groups: EGDT, protocol-based standard therapy or usual care. The incidence of severe acute kidney injury (AKI), as indicated by a need to initiate renal replacement therapy was higher in the protocol-based standard-therapy group (which received the greatest fluid volume initially and overall), than in the other two groups ($P = 0.04$). In addition, other studies have shown an association between a positive fluid balance and an increased risk of AKI in patients with septic shock.[5,6] These findings oppose the widely held belief that fluid accumulation somehow protects the kidneys.

Why does aggressive fluid and blood product resuscitation, which should theoretically increase renal blood flow (RBF), seem not to be renal protective? Several possible explanations for this apparent contradiction exist. First, development of AKI is multifactorial, especially in the context of sepsis. Loss of kidney function can be secondary to local and systemic inflammatory responses, microcirculatory dysfunction and glomerular haemodynamics, despite maintenance of, or even increased, RBF.[7] Although fluid and inotrope therapy to achieve maximal cardiac performance augments both cardiac output and RBF, increased RBF might not translate to an overall increase in renal oxygen delivery, and might in fact increase delivery of septic nephrotoxins to at-risk renal tubular tissue. Second, increased renal oxygen extraction itself could help meet the oxygen demand without an increase in RBF. In addition, critically ill patients might meet oxygen demand while still operating on the initial steep portion of Starling's curve where volume responsiveness still exists. Hence further volume loading might not provide any additional benefit. Third, aggressive volume resuscitation comes at the cost of worsening lung function and poor overall oxygen delivery. A link between lung function and kidney injury has been demonstrated in conservative versus liberal fluid management in patients with established acute lung injury. Improved lung function and oxygenation is beneficial to the kidneys and other extrapulmonary organs.[8,9] Lastly, given that the kidney is an encapsulated organ, fluid congestion secondary to aggressive volume resuscitation can raise venous and intra-capsular pressures, resulting in a significant decrease in RBF and glomerular filtration rate.[10]

On the basis of the ARISE, TRISS and ProCESS trials, we believe that management of critically ill patients will and should transition to a more conservative (that is, optimized) volume resuscitation strategy and a transfusion threshold of 70 g/l in critically ill patients, including those with severe sepsis and septic shock. Probable exception should be given to patients with acute coronary syndrome, as evidence supporting a conservative approach is still weak in this population.

*Vanderbilt University Medical Centre, Division of Cardiothoracic Anaesthesiology 1215 21st Avenue South, Suite 5160 MCE NT, Campus Box 8274, Nashville, TN 37232 (**B.S.**, **A.S.**). Correspondence to: A.S.*
andrew.shaw@vanderbilt.edu

**Competing interests**
The authors declare no competing interests.

1. The ARISE Investigators and the ANZICS Clinical Trials Group. Goal-directed resuscitation for patients with early septic shock. *N. Engl. J. Med.* **371**, 1496–1506 (2014).
2. Holst, L. B. *et al.* Lower versus higher hemoglobin threshold for transfusion in septic shock. *N. Engl. J. Med.* **371**, 1381–1391 (2014).
3. Rivers, E. *et al.* Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N. Engl. J. Med.* **345**, 1368–1377 (2001).
4. Yealy, D. M. *et al.* A randomized trial of protocol-based care for early septic shock. *N. Engl. J. Med.* **370**, 1683–1693 (2014).
5. Payen, D. *et al.* A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Crit. Care* **12**, R74 (2008).
6. Bouchard, J. *et al.* Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int.* **76**, 422–427 (2009).
7. Ergin, B., Kapucu, A., Demirci-Tansel, C. & Ince, C. The renal microcirculation in sepsis. *Nephrol. Dial. Transplant*. http://dx.doi.org/10.1093/ndt/gfu105.
8. Wiedemann, H. P. *et al.* Comparison of two fluid-management strategies in acute lung injury. *N. Engl. J. Med.***354**, 2564–2575 (2006).
9. Liu, K. D. *et al.* Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes. *Crit. Care Med.* **39**, 2665–2671 (2011).
10. Herrler, T. *et al.* The intrinsic renal compartment syndrome: new perspectives in kidney transplantation. *Transplantation* **89**, 40–46 (2010).