Selected Summaries

Goal-directed resuscitation in sepsis: The game continues but the goalposts have been removed

The ARISE Investigators and the ANZICS Clinical Trials Group. Writing Committee—Peake SL, Delaney A, Bailey M, Bellomo R, Cameron PA, Cooper DJ, Higgins AM, Holdgate A, Howe BD, Webb SA, Williams P. (The Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine; and the School of Public Health, Monash University, Melbourne, Victoria; University of Adelaide and Queen Elizabeth Hospital, Adelaide; Royal North Shore Hospital and University of Sydney, Sydney; Austin Hospital, Melbourne, Victoria; Alfred Hospital Melbourne, Victoria; Liverpool Hospital and University of New South Wales, Sydney, NSW; and Royal Perth Hospital and University of Western Australia, Perth, Australia; and Hamad Medical, Doha, Qatar.) Goal-directed resuscitation for patients with early septic shock. The ARISE Investigators and the ANZICS Clinical Trials Group. *N Engl J Med* 2014;**371:**1496–506.

SUMMARY

The Australasian Resuscitation in Sepsis Evaluation (ARISE) trial on which the present study is based, was a prospective, randomized, multicentre trial comparing an early goal-directed therapy (EGDT) protocol with usual care for adult patients presenting to emergency departments (ED) with severe sepsis or septic shock. Fifty-one tertiary care, metropolitan (non-tertiary care) and rural hospitals mostly from Australia and New Zealand participated in this trial.

Adult patients were eligible for enrolment if they had a suspected or confirmed infection, two or more criteria for a systemic inflammatory response and evidence of refractory hypotension or hypoperfusion within 6 hours of presentation to the ED. *Refractory hypotension* was defined as a systolic blood pressure (SBP) <90 mmHg or a mean arterial pressure (MAP) <65 mmHg after an intravenous fluid challenge of 1000 ml or more administered within a 60-minute period. *Hypoperfusion* was defined as a blood lactate level of $\geq$4.0 mmol/L. Patients were not eligible, if they were haemodynamically unstable due to active bleeding or were pregnant or had a life expectancy <90 days. Patients were also excluded if there was a contraindication to insertion of a central venous catheter (CVC) in the superior vena cava or to transfusion of blood products.

Eligible patients were randomly assigned to receive either EGDT or usual care for 6 hours. Patients and clinicians involved in their care were aware of study group assignment. Randomization was completed within 2 hours after fulfilment of the final inclusion criteria.

For patients in the usual-care group, decision about the location of care delivery, investigations, monitoring and therapeutic interventions were done by the treating clinical team. An arterial line and a CVC were inserted only if clinically appropriate. Measurement of central venous oxygen saturation ($ScvO_2$) was not permitted during the 6-hour intervention period.

In the EGDT group, an arterial line and a CVC capable of continuous $ScvO_2$ measurement were inserted within one hour after randomization. The resuscitation algorithm, which was followed for 6 hours, included central venous pressure (CVP)-guided boluses of crystalloids or colloids and infusion of a vasopressor to achieve a mean arterial pressure (MAP) >65 mmHg. If the $ScvO_2$ remained <70%, packed red cells were transfused to achieve a haematocrit of at least 30%. Once CVP, MAP and haematocrit were optimized, dobutamine was administered in the next step if $ScvO_2$ remained <70%. Patients in whom haemodynamic optimization could not be achieved by these measures were placed on mechanical ventilation and sedatives to decrease oxygen consumption.

The primary outcome of the study was death from any cause within 90 days after randomization. The study was powered (at a two-sided alpha level of 0.05) to detect an absolute risk reduction of 7.6% (or relative risk reduction of 20%) in the EGDT group assuming a baseline mortality rate of 28% in the usual-care group.

During the period of over five and a half years (5 October 2008 to 23 April 2014), 1600 patients were randomized; 1588 were included in the final intention-to-treat analysis. Demographic and clinical characteristics at baseline were similar in the two groups. The proportion of patients in the EGDT group, for whom the individual resuscitation goals were achieved at 6 hours or for whom the relevant therapy was delivered when a goal was not achieved, were 99.6% for saturation of peripheral oxygen, 88.9% for CVP, 94.1% for MAP and 95.3% for $ScvO_2$.

At 90 days after randomization, there was no difference in 90-day all-cause mortality either overall (18.6% in the EGDT group *v.* 18.8% in the usual-care group) or in any of the pre-specified subgroups. There were no significant between-group differences in secondary or tertiary outcomes other than more frequent use of vasopressors and earlier discharge from ED in the EGDT group. There was no significant between-group difference in the number of patients with one or more adverse event.

COMMENT

In 2001, a highly influential single-centre trial by Rivers *et al.*[1] showed that a protocol-based approach to early haemodynamic optimization substantially reduced mortality of patients with severe sepsis or septic shock. This strategy, which was termed early goal-directed therapy (EGDT), targeted pre-defined physiological goals of CVP, MAP and $ScvO_2$ with protocol-driven interventions that included intravenous fluids, infusion of vasopressors, dobutamine and red cell units. International guidelines[2] adopted EGDT as a standard of care long before results of multicentre studies were published.

The publication of this landmark study raised concerns about an unusually high control group mortality (46.5%)[3] and the use of surrogate end-points such as CVP and $ScvO_2$ to guide therapy.[4] Furthermore, there was a statistically significant difference in the rate of achievement of haemodynamic goals. The goals were achieved in 86.1% of patients assigned to standard therapy compared to 99.2% of those assigned to EGDT, thus raising concerns about differences in the intensity of treatment between the two groups during the conduct of a non-blinded trial. The early treatment group received 1500 ml more in total fluids in the first 6 hours than did the standard therapy group and had significantly higher MAP (95 [19] *v.* 81 [18] mmHg; p<0.001).[4] These objections notwithstanding, there was a broad conceptual support for early intervention, but not in the format enunciated by Rivers *et al.*[1]

The utility of banked 'old' blood in alleviating tissue dysoxia as part of the 'Rivers' protocol' has been the subject of some controversy. Contrary to popular belief, 'old' packed red cell units worsen tissue oxygenation among patients with sepsis. Transfusion of old packed red cells paradoxically results in higher mortality among critically ill patients with sepsis[5] and transfusion of blood

in general as part of a liberal transfusion strategy compared to a more restrictive strategy.[6] Thus, experimental research and clinical evidence from other trials directly contradict benefits shown in the original Rivers study.[1]

It has been argued that ARISE was a well-designed and executed trial, in contrast to the Rivers study.[1] However, ARISE randomized a sample of patients who were not very sick at the time of enrolment. Indeed, patients enrolled in ARISE had a lower mean APACHE-II score (15 [6.0] *v*. 21 [6.9]) and fewer comorbid conditions than those enrolled in the original study. An *a priori* subgroup analysis of ARISE patients with APACHE-II scores of >25 failed to show an outcome benefit in favour of EGDT. The Protocolized Care for Early Septic Shock (ProCESS) trial,[7] which enrolled patients with a higher mean APACHE-II score (21 [8.1]), did not show an outcome difference with EGDT in comparison with usual care either. The results of the Protocolised Management of Sepsis (ProMISe) trial, UK[8] anticipated this year and the planned individual patient data meta-analysis,[9] will hopefully settle this issue once and for all.

An average of 35 ml/kg intravenous fluids was given to all patients in ARISE (nearly as much in the ProCESS trial) prior to enrolment whereas this is not reported by Rivers *et al*.[1] In addition, the study protocol mandated that antimicrobial therapy be administered as soon as practicable which resulted in a relatively short median time to commencement of the first intravenous dose of any antimicrobial agent (70 minutes, interquartile range 38–114 minutes). In contrast, antibiotics in the Rivers' study were administered only after blood, urine and other cultures were obtained. At the time of enrolment to ARISE, the mean (SD) lactate level was 4.4 (3.3) mmol/L in the EGDT arm, while it was 7.7 (4.7) mmol/L in the Rivers study. ARISE did not report on outcomes for patients with elevated lactate but ProCESS[7] did and showed no benefit of EGDT in the analysis for this pre-specified subgroup. It is noteworthy that the mean (SD) $ScvO_2$ at baseline in the early therapy arm of ARISE was 73 (10)% and was 71 (13)% in ProCESS compared to 49 (11)% in the Rivers study.[1] Possibly as a consequence of this, red cells were transfused more frequently (4-times higher) in the early therapy arm of the original trial than in ARISE or ProCESS.

Clear separation of treatment arms in a randomized trial is important to detect a treatment effect. The choice of the ARISE investigators to compare EGDT to usual care carried the risk that active promotion of EGDT as part of the Surviving Sepsis campaign[2] and advocacy by professional bodies could result in similarities between the two arms of the study. Contamination of usual care with strategies that define EGDT in an open-label trial can result in loss of power to detect a meaningful difference and a type 2 error. The degree to which this occurred in ARISE can be estimated by comparison of therapeutic interventions in both arms. The difference in the total volume of intravenous fluids given over the first 6 hours following randomization was minor from a clinical point of view, although it was statistically significant (1964 [1415] *v*. 1713 [401] ml, p<0.001). This is especially so when considering the fact that patients were already administered >2.5 L before randomization and given approximately 4 L in the first 3 days following the intervention period. Whereas fluid resuscitation was guided exclusively by CVP in the EGDT group, this was not the case for at least one-third of patients in the usual-care group who did not have a CVC inserted. Vasopressors were used more often in the EGDT arm (67% *v*. 58%, p<0.001), transfusion of red cell units (14% *v*. 7%, p<0.001) and infusion of dobutamine (15% *v*. 3%, p<0.001) too, were more common. Only

a small fraction of patients, namely those who did not reach their $ScvO_2$ goal despite fluid resuscitation and infusion of vasopressors, were exposed to different treatment than usual care in the EGDT arm. ARISE was not designed to explore if these patients would benefit more from protocol-based management rather than individualized care guided by the clinician. Even if there was a benefit of the EGDT algorithm for these patients, there were too few of them enrolled to change the overall study results.

It is interesting to compare the 28-day mortality in the usual-care arm of ARISE with that of the original study by Rivers *et al*.[1] (15.9% *v*. 49.2%). The results of the ARISE trial emphatically underscore the importance of early recognition of sepsis, timely administration of antibiotics and early adequate volume resuscitation as mandated by the so-called '3-hour care bundle' of the Surviving Sepsis Campaign.[2] Even though ARISE did not rule out a potential benefit of $ScvO_2$-guided use of packed red cells and dobutamine, it certainly did not provide any evidence that patients with sepsis would in general benefit from continuous $ScvO_2$ monitoring or $ScvO_2$-based management.

Overall, it appears that septic patients who are diagnosed early and given appropriate antibiotics as well as the right amount of fluid resuscitation early while being monitored closely *do not* benefit from additional protocolized management if medical care is guided by a clinician-led assessment of the adequacy of circulation. These conclusions are consistent with previous studies showing that bias in small, single-centre trials may result in inflated effect size that cannot be replicated in larger multicentre studies.[10]

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