Intensive Care Med (2016) 42:1048–1050
DOI 10.1007/s00134-016-4295-6

EDITORIAL

Early goal-directed therapy: do we have a definitive answer?

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Early goal-directed therapy (EGDT) for the treatment of septic shock was first proposed in 2001 by Rivers et al. [1]. These authors reported that patients with hypotension refractory to a fluid challenge of 20–30 ml/kg of crystalloids over 30 min or with plasma lactate levels of at least 4 mEq/l and who were treated to restore and maintain a central venous oxygen saturation ($ScvO_2$) of greater than 70 % had lower 28-day mortality rates than control patients (33 vs 49 %). That publication generated considerable enthusiasm but also much debate. The resuscitation protocol was incorporated into the Surviving Sepsis Campaign (SSC) guidelines [2] and several uncontrolled studies reported similar improvements in outcome [3–5]. However, concerns were raised about the single-center nature of the trial, the limited sample size (263 patients), the multiple interventions proposed in the EGDT package making it difficult to differentiate which was most effective, and the potential influence of confounding factors including the increased presence of doctors at the bedside of patients randomized to the intervention.

Three large-scale multicenter studies published in 2014 and 2015 [6–8] were unable to replicate the results of the Rivers study, but is there a plausible explanation for this? Among the important differences between the trials, the mortality rate in the control groups in the recent trials was markedly lower than that in the Rivers study (Table 1). In addition, $ScvO_2$ values in the study groups were markedly reduced (to an average of 49 %) in the Rivers trial but were already within the greater than 70 % target zone in the three other trials. One explanation may be that Rivers et al. treated a special patient population with severe comorbidities and/or who presented quite late to the emergency department. Another possible explanation is that there has been a marked improvement in prehospital and initial care of patients with septic shock, maybe as a direct result of the Rivers trial and the SSC guidelines. However, adequacy of antibiotic treatment and amounts of fluid administered prior to randomization do not seem to account for these differences (Table 1).

A third explanation may be that the patients included in the more recent trials were quite selected and may not have been as sick as many other patients who presented at the same time to these emergency departments. Several indices suggest that these populations were indeed quite specific. The inclusion rate was 7.4 patients per month in the Rivers trial [1], but only 0.5–0.9 patients per center per month in ProCESS [6], ARISE [7], and ProMISe [8]. Do these findings suggest that admissions with septic shock requiring resuscitation are no longer an issue? Of course not! Indeed, these numbers contrast with the increased incidence of sepsis admissions in observational studies [9]. Moreover, most of the screened patients were included in the Rivers trial but only 20–30 % in the subsequent studies (Table 1).

The patients enrolled in the recent multicenter trials were less severely ill than those in the Rivers study, being less often treated with mechanical ventilation and having a lower mortality rate. Other studies [4, 10] have also reported higher mortality rates than those in these multicenter studies. For example in the SSC database, 2633 of the 6268 septic patients with a lactate of greater than 4 mEq/l died, resulting in a hospital mortality rate of 42 % [11], which is markedly higher than the mortality rates observed in the three recent trials [6–8]. Even patients with lactate levels between 3 and 4 mEq/l had higher mortality rates (30 %). The mortality reported in these three studies may, therefore, reflect patient selection at least as much as true improvements in care.

There may be a bias towards including less severe patients in clinical trials. Physicians declining to enroll particular patients may be an important factor here,

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Table 1 Comparison of some features of the Rivers, ProCESS, ARISE, and ProMISe studies

	Rivers et al. [1]	ProCESS [6]	ARISE [7]	ProMISe [8]
Publication year	2001	2014	2014	2015
Inclusion years	1997–2000	2008–2013	2008–2014	2011–2014
Number of patients in control/EGDT groups	133/130	902/439	796/792	620/623
Number of patients screened/center/month	8	3.9	1.6	2.6
Number of patient included/center/month	7.4	0.9	0.5	0.5
$ScvO_2$, % (EGDT group)	49	71	73	70
Lactate at inclusion (mEq/l)	7	5	4	5
Time from arrival at ED to randomization (min)	Median 55/mean 80	Mean 190	Median 168	Median 162
Fluids administered before randomization	20–30 ml/kg in 30 min (received NA)	≥20 ml/kg in 30 min later >1000 ml (received 2200)	>1000 ml (received 2500)	>1000 ml (received 1600)
Antibiotics within 6 h (%)	89	97	100	100
Adequate antibiotics (%)	95	NA	90	NA
Achievement of resuscitation goals in EGDT (%)	99.2	88.1	80 ($ScvO_2$ at 6 h)	85
Mortality control/EGDT (%)	50/33	19/21	19/19	29/29

although it is often neglected [12]. As an example, in the ProMISe trial, 449 patients were excluded by the clinician. This bias is particularly likely when the tested intervention is available, because physicians may prefer to apply the therapy they think appropriate rather than including the patient in the trial. The result is often that less severely ill patients are enrolled, in whom the intervention is less likely to be effective [13]. The lower severity of illness in the three recent trials is suggested by a longer time interval between arrival in the ED and randomization, the smaller amount of fluids administered prior to randomization, and the higher $ScvO_2$ and lower blood lactate at inclusion than in the Rivers study (Table 1).

The rate of admission of patients to the intensive care unit (ICU) was also remarkably low in the three large-scale randomized trials: Close to one patient in five (422/2324 = 18 %) in the control groups of these three trials was not even admitted to the ICU [14]. This questions the definition of septic shock as hypotension refractory to fluid administration and/or lactate levels of at least 4 mEq/l. As it is likely that patients receiving vasopressors would have been admitted to the ICU, one can speculate that about half of the patients with blood lactate levels greater than 4 mEq/l (which represented 45 % of the total number of patients) did not require vasopressors and were not admitted to the ICU. It is likely that these patients had only transient hyperlactatemia, maybe facilitated by shivering, hyperventilation, or agitation. Intriguingly, the authors of the ARISE trial [7] stated that "Of the 793 patients randomized to receive EGDT, [...] 111 patients (15.9 %) were admitted only for implementation of the EGDT resuscitation algorithm", implying that these patients appeared so well that attending physicians did not want to admit them to the ICU. Hence, a significant proportion of these patients did not meet true shock criteria [15].

A final point suggesting a marked degree of patient selection in these trials is their inclusion primarily during office hours in the ProMISe study [8]. In that trial, 90 % of patients were included between 8 am and 8 pm on weekdays (Figs. S3A and B in the electronic supplement of that article) and less than 10 % during the night and at the weekend [8]. This may have been due to the restricted working hours of research assistants, but protocolized care may, in fact, be more useful when less experienced physicians are in charge, which is often during the night and at the weekend. To what extent this also occurred in the other trials is unknown, but it should be noted that 1191 patients, a number almost equivalent to the 1351 included patients, were not included because of study logistics issues in ProCESS [6] and 282 did not have access to a study team member in ARISE [7].

This patient selection issue does not challenge the internal validity of these recent trials, but clearly raises questions about their external validity. These trials have indicated that patients with low severity septic shock who rapidly respond to therapy do not benefit from routine

EGDT. However, the results of the Rivers trial have not been invalidated as patients with high disease severity and low $ScvO_2$ were not included in these recent trials. EGDT may still be beneficial in the most severely ill patients, especially when less experienced staff who may appreciate using simple protocols are in charge.

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Compliance with ethical standards

Conflicts of interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

Received: 20 February 2016 Accepted: 24 February 2016
Published online: 7 March 2016

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