Editorial

Early goal directed therapy: where do we stand after the individual patient's meta-analysis?

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In the recent years, the issue of early goal directed therapy (EGDT) has led to many debate. EGDT became popular after the Rivers' trial (1). In that single center trial including 263 patients with septic shock, EGDT application in the emergency department (ED) resulted in an important decrease in 28-day mortality from 46.5% to 30.5% (P<0.01). Even though the main difference in hemodynamic goal was the target of central venous oxygen saturation (ScvO2) that has to be maintained above 70%, the entire package, including maintenance of mean arterial pressure (MAP) ≥65 mmHg, central venous pressure (CVP) between 8-12 mmHg and urine output ≥0.5 mL/kg.h, was adopted in resuscitation guidelines (2). The trial was heavily criticized. Many of the criticisms were directed to the targets, and especially CVP as CVP is not an excellent indicator of fluid responsiveness, as well as to some of the interventions used to increase ScvO2 and in particular to the frequent use of red blood cell transfusions. Also the incidence of low ScvO2 at baseline was higher than in subsequent observational trials. All these factors raised the issue of the external validity of the trial.

Interestingly, several before and after trials evaluating the implementation of EGDT in clinical practice repeatedly reported an improvement in outcome (3,4). Without surprise, meta-analyses tacking into account these before and after trials demonstrated a survival benefit of EGDT (5). It was however difficult to ascertain that the improvement in outcome has to be attributed to EGDT as many other factors may also have contributed. Interestingly, adherence to all the components of EGDT was often low, also mitigating the potential role of EGDT in the reported improve in mortality.

Three large scale multicentric studies, (ProCESS (6), ARISE (7), and ProMISE (8), addressed the issue whether protocolized care guided on ScvO2 may improve mortality. The three trials failed to show any significant effect on mortality. In a meta-analysis combining these to the Rivers' trial, no beneficial effect but also no harm was reported (9). A striking difference between the Rivers' trial and the three recent trials was that the ScvO2 was already in target at inclusion, leaving minor room for improvement and hence for efficacy of the interventional protocol. Also mortality in the control group was much lower in the recent trials 18.9%, 15.7%, 24.6% respectively compared to 46.5%. These two factors were considered as indicators of improved care of patients with septic shock over time, including better resuscitation prior to inclusion so that ScvO2 was already at target at inclusion, and contributing to the decreased mortality so that EGDT could be considered as no more effective.

While one may have suggested that the issue was closed, the debate wasn't over as these recent trials were also heavily scrutinized (10,11). In particular, their low inclusion rate (0.5–0.7 patient/center/month) was considered to potentially lead to selection bias (10,11). Indeed, it is quite surprising to consider that these centers were able to

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include only 6–12 patients per year. In these conditions, sepsis would not be considered as an important health issue. For the comparison, a mandatory report in the New York State of patients admitted to the ED with sepsis and submitted to bundled care inspired from SSC guidelines, included 49,331 patients (of whom 45.3% in septic shock—meeting the same definitions as in the three interventional trials) in 149 hospitals in 27 months, which corresponds to 5.5 patients per center per month (or 65 patients per center per year). While inclusion may have been limited by logistical reasons (required presence of research assistant) this extremely low ratio of included patient (1 patient included for 8–11 potential patients) suggest that other factors played a role in patients selection and patient selection may impact the result of the trial (12). Several indices pointed out that less severe patients were included, as illustrated by a predominant inclusion during office hours (while protocolized care may be more beneficial during out-of-office hours when more junior doctors are taking care of the patients) and, even more importantly, by the observation that 20% of the patients were not admitted to the ICU but rather to the wards (9). Accordingly, De Backer and Vincent questioned whether the three negative trial provided a definitive answer (10).

Recently a patient-level meta-analysis was conducted by the authors of the three recent trials (13) and may perhaps help to provide this definitive answer. It has the advantage to achieve enough power (the three recent trials were underpowered, as the mortality was lower than that expected at time of planning the study). Given the similar design of the three recent trials and the fact that this meta-analysis was planned in advance by the authors before completion of the trials so that common information would be collected in their respective trials, this meta-analysis can almost be considered as a trial in itself. Conducting it at the individual level allows to explore heterogeneity of the effects of EGDT, looking at several subgroups and at the influence of various factors. The meta-analysis comprised 3,723 patients at 138 hospitals in seven countries. Mortality at 90 days was similar for EGDT [462 of 1,852 patients (24.9%)] and usual care [475 of 1,871 patients (25.4%)]. The adjusted odds ratio was 0.97 (95% CI, 0.82–1.14; P=0.68). Subgroup analyses showed no benefit from EGDT. The authors specifically evaluated whether the more severe patients might benefit from EGDT. There was no difference in the risk of death between patients treated with EGDT and control in the subgroups of patients with higher serum lactate level, nor inpatients with combined hypotension and hyperlactatemia. Similarly, the risk of death was similar with both approaches in patients with higher predicted risk of death. There was no impact of EGDT according to of the time from shock to randomization, delay in antibiotic administration, or inclusion during office hours or not. Similarly, there was no benefit of EGDT in hospitals with a lower propensity to use vasopressors or fluids during usual resuscitation. These results altogether confirm that there was no signal that EGDT provided any benefit in the entire population as well as in any predefined subgroup in these three recent trials.

This meta-analysis also confirmed the excellent care provided to these patients: 97% received fluids in a median amount of 28 mL/kg before randomization and 93% received antibiotics before randomization with a median time from ED presentation to antibiotic administration of 75 min. The median time from ED presentation to randomization was 160 min.

What these result do not overcome is the selection bias: 385/1,973 (20.5%) of the patients in the control group were not admitted to the ICU, 87% of the patients were included in office hours. In addition, some subgroup analyses were still limited by the number of patients in that specific subgroup. While the authors did not find any difference between patients included during in-office hours and during out-of-office hours, this last subgroup was restricted to only 485 patients (13% of the trial population). Similar comments apply when considering the most severe groups (combination of refractory hypotension and hyperlactatemia at inclusion represented only 17% of the population). Unfortunately, it was not feasible to conduct a subgroup analysis in the patients admitted to the ICU, as this may have been affected by therapy and was not predefined at baseline. Finally, the fact that ScvO2 was already at target when patients were enrolled can also not be overcome as ScvO2 was measured only in the interventional groups in the three multicentric trials. Hence, even though strengthening the information already provided by each of the three trials, this meta-analysis provides only minimal new information and, beyond the sample size, cannot abolish the limitations of the original trials.

Thus, where do we stand in 2017? Each of the four trials (the Rivers' trial and the three multicentric trials) provide its own information and none can be neglected. Clearly the multicentric trials demonstrate that there is no room for EGDT in the less severe patients. But the doubt remains in the most severe patients. In the Rivers' trial, these patients were shown to benefit from EGDT. The individual meta-

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analysis does not contradict nor confirm the Rivers' trial. Accordingly, we are left with the same uncertainties. The Surviving Sepsis Campaign guidelines does not recommend anymore the use of EGDT but also recognizes that it does not cause harm (14). Accordingly, EGDT may be considered in the most severe patients, even though some aspects of the "package" may be adapted (i.e., fluid assessment and need for red blood cell transfusions).

ScvO2 has been repeatedly shown to be associated with a poor outcome. The Rivers' trial included mostly patients with altered ScvO2 and demonstrated an improve outcome. The recent multicentric trials included patients with a ScvO2 already on target in the vast majority of the patients, and these patients did not benefit from ScvO2. Identification of the patients who may benefit from ScvO2 before measuring it is clearly a challenge, as most of the measurements tended to be similar, except perhaps for the greater lactate values in the Rivers' trial. Our suggestion would be that patient who fail to improve their lactate, blood pressure and clinical signs of tissue hypoperfusion in response to initial therapy might be the patients who are more likely to benefit from EGDT.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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