The recent publication of the ProCESS,[1] ARISE[2] and ProMISE[3] trials have been interpreted by some to sound the end for Early Goal-Directed Therapy (EGDT) and the value of protocol-driven resuscitation in critically ill patients with septic shock. All three trials failed to demonstrate any benefit of EGDT or protocolized resuscitation when compared to “usual care.” In discussions at international conferences, both formal and casual, one hears of a wide range of opinions about the implication and interpretation of these important and well-done RCTs. The value of EGDT has long been controversial and, based on one’s prior attitude towards the EGDT data, the interpretation of these three trials will vary widely. How do we interpret these results and their impact on our bedside practice for patients with severe sepsis and septic shock? The short piece in this issue of Lung India by Dhooria and Agarwal[4] does an excellent job of objectively describing the results and implications of these three RCTs, and mention several points worth emphasizing and repeating:

First, the patients in ProCESS, ARISE and ProMISE were less sick than the patients enrolled in the original Rivers[5] trial, making direct comparison of these three trials to the Rivers data more challenging.

Second, in all three studies, patients received aggressive fluid resuscitation prior to randomization. Patients received at least 20 cc/kg before randomization, and in the ARISE trial, patients received 35 cc/kg prior to randomization. Even in the control arms of each trial, patients received 3-4 liters of fluid in the first 6 hours. This represents a significant evolution of fluid resuscitation from the past. Clinicians have clearly embraced the importance of early, aggressive fluid resuscitation.

Third, although there was a difference in fluids between the interventions and control group, this difference was 300-500 cc. The clinical significance of this difference remains unclear.

Therefore, it is safe to say that “early aggressive” fluid resuscitation, the hallmark of EGDT, was also administered as a routine part of “usual care.” In addition, at least in the ProCESS trial, as stated by the authors, “all other care was consistent with the Surviving Sepsis Guidelines.”[6] Taken together, all of these factors contribute to the accuracy of the point, made by Dhooria and Agarwal, that the “usual care” group in all three recent RCTs was delivered by “a very experienced physician population” which may not be the case in the “real world” in which sicker patients are cared for by less experienced physicians who are not operating under the rigor of a randomized, controlled trial. Thus, population severity, administration of fluids prior to randomization, the overall mortality rate, and the physicians providing care provoke concerns about comparing these three trials to the original Rivers study.[5]

The challenge for practicing clinicians is how to understand “usual care” in the settings of these large RCTs. In both ProCESS and ARISE, the usual care mortality was 18%, while in the ProMISE trial, the mortality rate was 29%. These are low mortality rates for a population with septic shock. Most clinicians would ask whether this population reflects their clinical practice, and whether these results can be generalized to a sicker population seen outside the confines of an RCT in which many “real world” patients may be excluded for a variety of reasons. In the US, mandated public reporting of sepsis is now a reality.[6,7] Will regulatory agencies hold clinicians to this mortality rate?

As a result of these trials, many clinicians already look forward to managing these patients without protocols or targets. The recent data do support the management of patients with septic shock without mandated central lines, CVP and ScvO2 monitoring. However, almost 2/3 of the patients in the two large RCTs were on pressors; therefore, the majority of patients in these three trials were managed with the use of central lines. Furthermore, as mentioned by Agarwal, therapeutic targets, such as initial volume resuscitation and antibiotic administration were utilized in the “usual care” groups in all studies. Therefore, protocols, albeit for the purposes of research, were very much part of usual care in all studies.

Fortunately for patients and clinicians, the opportunity to address the question of what comprises “usual care” will emerge over the next several years as mandated national reporting reporting takes hold in different countries. Metrics will be collected from large populations of septic patients. Over time, analyses of these large databases should create clarity about the use of hemodynamic monitoring and protocolized care as “routine care” in guiding clinicians to improve outcomes of patients with this common illness.
CONCLUSIONS

In conclusion, the results of the recent trials reinforce the importance of early, aggressive resuscitation of patients with septic shock with fluids and antibiotics.

The message from these robust, well-done clinical trials seems, in part, to be that if our clinical practice is to be consistent with “usual care,” then we must routinely identify patients, administer appropriate antibiotics rapidly, give about 4 liters of fluids to all of our patients with severe sepsis and septic shock in the first 6 hours and insert central lines only in patients that require vasopressors. If that is our routine clinical practice, then “usual” can be viewed as the high quality care our patients with septic shock deserve.

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How to cite this article: Levy MM. Early goal-directed therapy: Sorting through confusion. Lung India 2015;32:435-6.