EDITORIAL

The ProCESS Trial — A New Era of Sepsis Management

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The importance of early detection and treatment for reducing the mortality associated with sepsis has been a tenet of medical training since the middle ages, when it was noted that ". . . the physicians say it happens in hectic fever, that in the beginning of the malady it is easy to cure but difficult to detect, but in the course of time, not having been either detected or treated in the beginning, it becomes easy to detect but difficult to cure."[1,2] The critical role of the clinician in the early recognition of sepsis continues to this day to be fundamental to our efforts to improve the rate of survival.[3] Identification of the combination of signs and symptoms that make up the systemic inflammatory response syndrome (SIRS)[4] in the context of an infection allows the astute clinician to recognize the malady.

Early recognition of sepsis was incorporated into the trial design, prompts, and protocols of the Protocolized Care for Early Septic Shock (ProCESS) trial, the results of which are now reported in the *Journal*.[5] For all the groups in the trial, the goal was early recognition of sepsis, as specified in the Surviving Sepsis Campaign guidelines,[3] and the design called for early treatment with antimicrobial agents[6] and conservative transfusion thresholds; in addition, the patients received low tidal-volume ventilation and had moderate glycemic control.

Indeed, septic shock was recognized early in a majority of the patients; 76% of the patients received antimicrobial agents by the time they underwent randomization, which occurred a mean of approximately 3 hours after patients' arrival in the emergency department. The rate of intravenous antimicrobial administration 6 hours after randomization was approximately 97%, a finding that suggests that notification that septic shock is present encourages the administration of antibiotics. A study that attributed increased mortality to delays in the administration of appropriate antibiotics[6] suggested that early administration of antibiotics increased survival in all groups of the trial. Indeed, in the ProCESS trial, the early or facilitated recognition of septic shock, administration of intravenous antibiotics, and other best practices were associated with rates of survival that were higher than projected and higher than predicted on the basis of scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II,[7] and a thoughtful design allowed the sample size of the trial to be recalculated to preserve the power of the study to test the primary outcome. One important contribution of the ProCESS trial is the evidence it provides regarding the ongoing role of early recognition of and antibiotic treatment for sepsis in improving survival.

The ProCESS trial also provides transformative insights about the treatments for septic shock that bring generalizable benefits when septic shock is recognized in the first hours after arrival in the emergency department. The use of central hemodynamic and oxygen-saturation monitoring in the protocol-based early goal-directed therapy (EGDT) group did not result in better outcomes than those that were achieved with clinical assessment of the adequacy of circulation. The finding that adjusting therapies to surrogate physiological targets measured with invasive catheters was not required to reduce mortality is consistent with the results of a study that showed that serial measurement of blood lactate levels was noninferior to catheter-derived measurements[8] and of analyses that have not found benefits of the use of pulmonary-artery catheters.[9] State legislation and clinical guidelines, including those endorsed by the National Quality Forum, should be updated to remove the requirement for central hemodynamic moni-

toring and to focus on less costly, lower-risk, and equally effective alternatives.

The association of the implementation of the multifaceted EGDT intervention with significantly lower mortality in an earlier study[10] launched the EGDT era of sepsis management. This milestone study encouraged coordinated efforts[3] to improve the outcomes in patients with this common[11] and life-threatening condition. These efforts translated into the earlier identification of septic shock and into an increased number of patients receiving earlier administration of a larger volume of resuscitation fluid. The ProCESS trial allows refinement of the EGDT approach to fluid administration by defining lower boundaries that are associated with equivalent outcomes and setting limits that are needed to avoid the twin problems of renal failure from too little fluid and pulmonary dysfunction from fluid overload. Another interesting and seemingly paradoxical finding is that patients in whom sepsis was managed without a protocol had an outcome as good as those in patients in whom the sepsis was managed with the use of a protocol. If one assumes that the treatments for septic shock, as well as the timing of the treatments, that would be administered in all emergency departments, regardless of size or available resources, would be equivalent to those used in the no-protocol (usual-care) group of the ProCESS trial (which included strategies for early recognition of sepsis), one could come to the dubious conclusion that protocols and decision prompts do not have a role in the treatment of septic shock. I prefer to think differently. I believe that the prompting, serum lactate screening and assessment of SIRS criteria, and reporting of activities that were parts of the study by Rivers et al. and the ProCESS trial can be applied in clinical practice to ensure early diagnosis and treatment for all patients with septic shock.

The ProCESS trial identifies early recognition of sepsis, early administration of antibiotics, early adequate volume resuscitation, and clinical assessment of the adequacy of circulation as the elements we should focus on to save lives. The publication of the ProCESS trial launches the era of early recognition and treatment in the management of sepsis.

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