# Protocolized Sepsis Care Is Not Helpful for Patients

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A protocol is an accepted or established code of procedure for a given situation or, more specifically in a medical context, the established procedure for carrying out a course of medical treatment. The publication of the highly influential study of the early goal-directed therapy resuscitation protocol for patients with severe sepsis and septic shock (1) and the subsequent dissemination of the Surviving Sepsis Guidelines (2) advocating a specific resuscitation protocol have been important milestones on the current pathway to reduced mortality for patients with sepsis. As the mortality rate for patients with sepsis has fallen significantly over recent years (3), it is tempting to assume that the implementation of this specific protocol of care for patients with sepsis has been instrumental in causing the fall in mortality. There are however many reasons to conclude that this is not the case. These include the significant heterogeneity within the population of patients with sepsis, which essentially precludes the delivery of a strict protocol of therapy. As well, the lack of evidence that either the components of the resuscitation protocol or the protocol as a whole are associated with improved patient-centered outcomes, and the fact that the improvements in mortality rates for patients with sepsis began prior to the introduction of the concept of protocolized care. These reasons all lead to the conclusion that the protocolized care currently being advocated for patients with sepsis is not helpful.

Protocolized care is most applicable to patients whose clinical course is anticipated to follow a predetermined pattern and who have a limited number of comorbidities (4). This is clearly not the case in sepsis. The updated definition of sepsis; life threatening organ dysfunction caused by a dysregulated host response to infection, which is operationalized as an increase in the Sequential Organ Failure Assessment score of 2 points or more (5), recognizes that the clinical manifestations of sepsis will vary from patient to patient. This may involve a worsening of cardiovascular, respiratory, neurologic, hematologic, or renal function. It is difficult for a single protocol to accommodate treatment recommendations to guide clinicians under the myriad of circumstances that fall under the clinical definition of sepsis. There is substantial heterogeneity associated with the causal infectious agent, the primary source of infection, the chronic comorbidities of the patients as well as diversity in the genetically determined host response to infection (6). It is not possible for a strict protocol to allow for the differing treatment needs of an otherwise healthy young female with urinary sepsis and a patient with relapsed hematologic malignancy, and neutropaenic sepsis those with chronic renal disease or heart failure, who present with severe community-acquired pneumonia.

In spite of these theoretic obstacles, a single resuscitation protocol for patients has been advocated and is based on the early goal-directed therapy approach to resuscitation for patients with sepsis (1). A number of the integral components of the resuscitation protocol have been assessed and found not to be associated with improved outcomes. The liberal use of blood transfusion, as used in the early goal-directed therapy protocol, was associated with no improvement in mortality in a study of 1,005 patients with severe sepsis (7). The adoption of a mean arterial blood pressure target of 65–70 mm Hg was associated with an increased requirement for renal replacement therapy in patients with preexisting chronic hypertension in a randomized clinical trial of 776 patients with septic shock (8), providing evidence that the single blood pressure target advocated in the early goal-directed therapy resuscitation protocol is not necessarily appropriate for all patients with sepsis. Perhaps most notably, the use of large volumes of fluid for resuscitation of patients with sepsis has been recently called into question (9). A systematic review of the use of central venous pressure (CVP) to guide fluid management neither found evidence that CVP was a reliable method to assess volume status nor fluid responsiveness (10). Importantly, the results of the Fluid Expansion as Supportive Therapy study, where the use of bolus fluid administration was associated with increased mortality in children with sepsis in Africa, also raises doubts

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regarding the use of large volumes of fluid in the early resuscitation of patients with sepsis (11).

One may argue that the improvements in care associated with the use of a complex intervention, such as the early goal-directed therapy protocol, come not from the individual components but from the implementation of the protocol as a whole (12). Again, in the specific case of the early goal-directed therapy protocol, there is no evidence to support this contention. In three large methodologically sound randomised clinical trials, the total bundle of therapies that constitute the early goal-directed therapy protocol was compared with standard care, where treatment was provided by individual clinicians based on their clinical judgments and therapy adjusted according to the prevailing pathophysiologic status of the individual patient (13–15). There is no suggestion from any of these trials or from the pooled data from all trials comparing early goal-directed therapy to standard care (16) that the specific early goal-directed therapy protocol is associated with improvements in any patient-centered outcome. It is important to draw attention to the fact that protocolized care was compared with standard care as delivered in the setting of these clinical trials. For example, in the Australasian Resuscitation In Sepsis Evaluation study (14) to be eligible for inclusion in the study, patients were required to have received at least 1,000 mL of fluid resuscitation and a dose of IV antibiotics. The median time to achieve this in the trial was less than 90 minutes. Thus "standard care" as delivered in the setting of these trials may not represent standard care as delivered in all clinical settings. It may also be argued that it is not the specifics of the early goal-directed therapy protocol, but the mandated attention of additional medical staff with specific guidance to achieve physiologic goals early on in the course of the illness that leads to improvements in outcomes. The Protocolized Care for Early Septic Shock study specifically sought to address the question of whether protocolized care per se, not specifically the early goal-directed therapy protocol, is associated with improved outcomes for patients with sepsis, and found no evidence that protocolized care was better than standard care (15). Given that neither the components nor the total bundle that constitutes the resuscitation protocol is associated with benefits for patients, one must conclude that protocolized care, as is currently advocated, is not helpful for patients with sepsis.

Advocates might argue that the recent falling mortality rate for patients with sepsis constitutes evidence of the efficacy of protocolized care. This claim fails to recognize the trend of falling mortality in sepsis that been documented from the early 1980s (17). The continuation of this falling mortality (3) in more recent times cannot be attributed to the introduction of protocolized care as it clearly began well before the concept was introduced into clinical practice. A number of uncontrolled before and after studies have assessed the impact of the introduction of protocolized care as championed by the Surviving Sepsis Campaign. They have claimed to show a reduction in mortality associated with the introduction of sepsis bundles (18, 19). These studies did not take into account the established secular trend of falling mortality rates for patients with sepsis. It is also notable that the vast majority of patients included in these studies did not receive the protocolized intervention, with only 10–20% of patients at the end of the period of observation having received all components of the resuscitation protocol (18, 19). This further discredits the notion that the introduction of a strict resuscitation protocol is associated with benefits for patients with sepsis.

Patients with sepsis do not present with a common set of symptoms and signs. They frequently have significant preexisting comorbidity that affects their pathophysiologic response to infection. The host response varies greatly determined largely by individual's genetic phenotype (20). The sites of infection vary, as do the causative organisms. Given this diversity, a single one-size-fits-all approach to therapy for sepsis would seem to be inappropriate. Recent clinical trials, in more than 4,000 patients with sepsis (13–15), have confirmed that protocolized care is not superior to therapy adjusted by clinicians based on the patients' clinical status and response to therapy. This is not to suggest that clinicians should ignore the general principles for treating patients with sepsis; individualized resuscitation, early targeted antibiotics, and control of the source of infection. Achieving these goals as expediently as possible should remain a focus of clinical care for each individual patient with sepsis, as it was in the standard care arms of the Australasian Resuscitation In Sepsis Evaluation, Protocolized Care for Early Septic Shock, and Protocolised Management In Sepsis trials (13–15). Although protocolization of sepsis therapy does not lead to improvements in outcomes, there is still hope that with a greater understanding of the pathophysiology of sepsis, the morbidity and mortality of this common disease can still be reduced. The future of therapy in sepsis is very likely to be a more personalized approach (20), with treatments based on the individuals unique phenotype (21) combined with an assessment of their response to therapy (9) and taking into account their premorbid condition and patient preferences. Protocolized sepsis care, taking a single rigid approach to all patients with sepsis, not only lacks a rational pathophysiologic basis given the heterogeneity of the clinical condition but also lacks any support in the medical literature. Given the current state of knowledge, one can safely conclude at this time that protocolized sepsis care is not helpful for patients.

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# Protocolized Early Sepsis Care Is Not Only Helpful for Patients: It Prevents Medical Errors

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## UNPROTOCOLIZED EARLY SEPSIS CARE: AN UP CLOSE AND PERSONAL MEDICAL ERROR

The following excerpt from the article "As She Lay Dying: How I Fought To Stop Medical Errors From Killing My Mom" is a real-life experience of an emergency physician whose mother was treated for sepsis in his hometown community hospital (1):

> "When I was entangled in my first medical error, I played an unexpected role: I was a thirty-three-year-old son trying to save my mom's life….On the line was an emergency physician in the Wisconsin town where I'd grown up, telling me my mom was sick with sepsis at 9 am. He sounded harried, and I heard papers rustling in the background….The condition is well known, is easily diagnosed, and has a clear and standard treatment protocol…. The first twenty-four hours of my mom's hospitalization would be critical to saving her life. Studies of sepsis have shown that early and aggressive treatments during that time can make the difference between life and death…. The hospital now was twelve hours into its critical opportunity to halt her systemic infection…. My mom was moved to the ICU around midnight, fifteen hours after she'd arrived at the hospital. I figured I'd get a bit of rest once her central-line IV and other treatments were started….. By 1 am. I was panicking. The next time I saw my mom's nurse, I asked about the treatment plan. Her response was a not-so-veiled criticism of my mom's doctor. "We do have a sepsis treatment protocol," she said, "but your mother's doctor hasn't ordered it."….But, by the time the sepsis protocol was finally put in place, it was 8 am the next day. A total of twenty-three hours without appropriate treatment had passed since my mom had entered the hospital. She still had a chance to survive, but because of the squandered opportunity, it was a small one….Toward the end, in a final moment of brief lucidity, she opened her eyes and whispered, "I never got to say good-bye." She was dead by the end of the week…. Today—and tomorrow—in hospitals across the nation, there are patients whose survival and well-being will depend on it. Their lives, like my mom's, hang in the balance. With lives on the clock, and as hours and days tick away, we need to listen to every voice and do everything possible to avoid repeating terrible mistakes (1)."

## UNPROTOCOLIZED EARLY SEPSIS CARE IS DEADLY AND COSTLY

Sepsis is the most deadly and costly diagnosis to hospitals in the United States. It is also the most frequent ICU admission for the elderly (2). Of over 1 million patients are diagnosed with sepsis, approximately 25% die of sepsis per year in the United States. Sepsis is the diagnosis for 11% of hospital admissions but is responsible for over 40% of hospital deaths. Sepsis (including pneumonia) accounts for $33.1 billion or 8.7% of the aggregate costs of inpatient care in the United States (3). This U.S. system which includes "unprotocolized" sepsis care is the most costly and inefficient among industrialized countries in the world (4).

The inpatient costs of sepsis care in the U.S. exceed the valuation of automobile companies such as Ford, General Motors, and Chrysler. Although these companies have protocols for quality and safety for automobiles, our distinguished colleague, Delaney (5) believes that early goal-directed therapy (EGDT) or protocolized early sepsis care (PESC) is not needed. This position is influenced by recent sepsis trials, the Protocolized Care for Early Septic Shock (ProCESS), Australasian Resuscitation In Sepsis Evaluation (ARISE), and Protocolized Management In Sepsis (ProMISe) trials, that characterized EGDT as a hemodynamic strategy (5). In contrast, we consider these trials as a confirmation of an all-time low in sepsis mortality (**Figs. 1** and **2**). We interpret that the equal outcomes in all of the treatment groups of these

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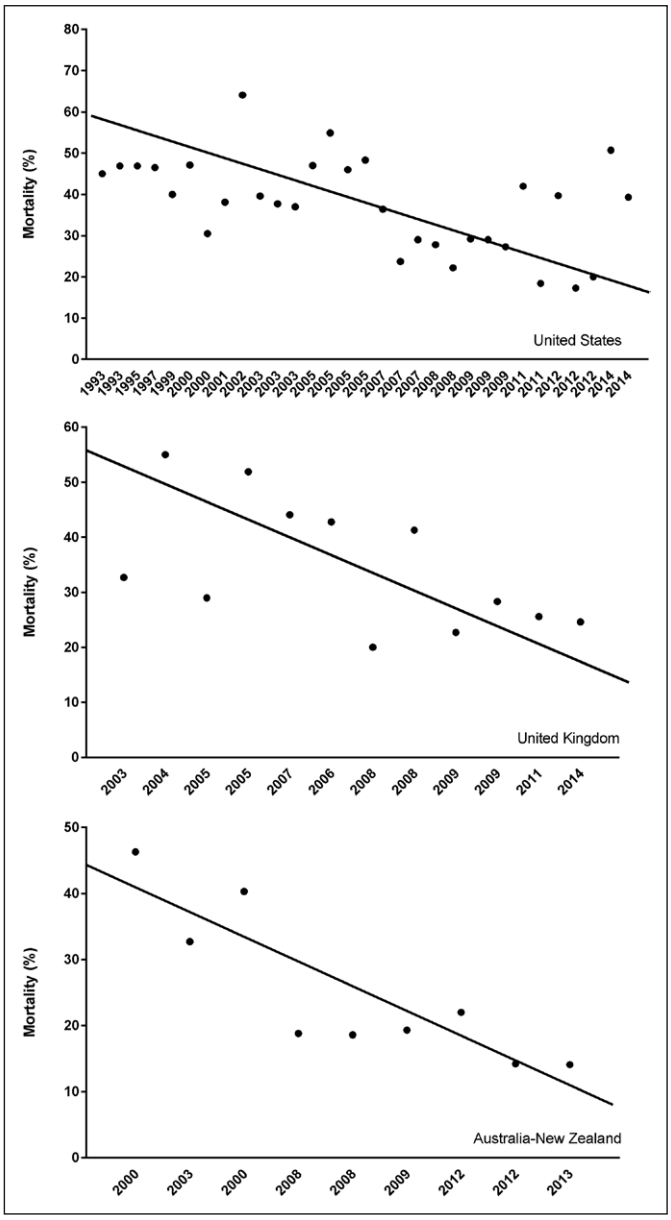


**Figure 1.** Trending mortality rates of observational studies of severe and septic shock in the United States, United Kingdom, and Australia and New Zealand. References for this figure are provided in the **supplement** (Supplemental Digital Content 1, http://links.lww.com/CCM/C301).

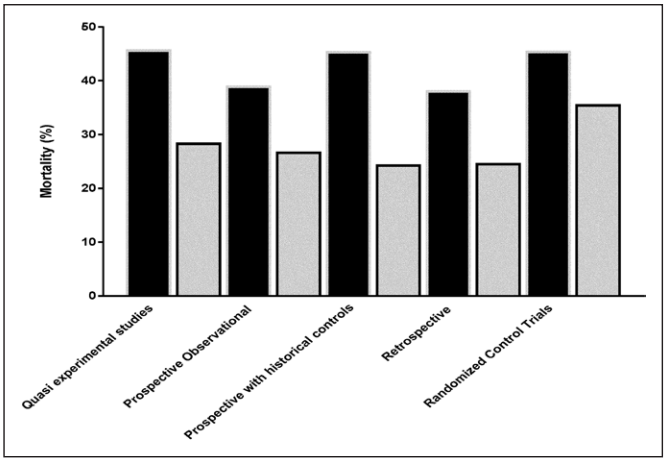


**Figure 2.** Outcome studies of protocolized sepsis interventions. Accompanying the decrease in sepsis mortality is a consistent reduction in mortality irrespective of study design. The *black columns* are the intervention group and the *gray columns* are the control or nonintervention groups. *n* represents the number of studies followed by the total number of patients. The mortality reflects the average of all studies. References for this figure are provided in the supplement (Supplemental Digital Content 1, http://links.lww.com/CCM/C301).

trials to multiple methodologic issues of trial conduction and the assimilation of EGDT into usual care.

## PESC IS A SYSTEMS-BASED APPROACH TO ELIMINATE MEDICAL ERRORS

The Institute of Medicine notes that medical error is the third leading cause of death in the United States. Medical error is the failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim (6). Lapse is a type of medical error which is the inability to recall something such as the order in which medications are to be given. This leads to active (immediate) or latent (delayed) harm. Latent harm results from errors in design, organization, training, or maintenance of skill. As with sepsis care, these errors are many times hidden, dormant in the system for lengthy periods before a systems-based approach such as EGDT exposes them (**Table 1**). Overcrowding of the emergency department (ED) and early processing sepsis of patients are examples of latent failure. This is largely attributed to poor communication between personnel and specialties; inadequate staffing and lack of supervision.

The Institute of Healthcare Improvement describes a bundle or protocolized care as "a group of interventions related to a disease process that, when executed together, result in better outcomes than when implemented individually" (7). The aim is to convert complex guidelines into meaningful changes in behavior and clinical outcomes. This increases the reliability of patient care, eliminate turnover errors, and decrease the variation of clinical practice (Table 1) (8). In keeping with this concept, EGDT challenged the paradigm of sepsis as an "ICU disease" in the 1990s by applying similar protocolized urgent diagnostic and therapeutic principles used for acute myocardial infarction, stroke, and trauma at the earliest point of presentation. EGDT was derived from decades of a longitudinal examination of the realities of sepsis care, followed by implementation of evidence-based and best practice interventions (Table 1) (9, 10).

## PESC SIMPLIFIES A COMPLEX DISEASE AND IMPROVES PRECISION CARE

PESC frequently begins when sepsis is undifferentiated. This occurs when a healthcare worker (i.e., paramedic, ED triage nurse, or technician) encounters a patient with sepsis. Thus, PESC is not physician centric; it is a transparent standard operating procedure that involves many specialties and healthcare personnel of varying levels of experience. PESC not only provides structure and accountability; it is amendable to continuous quality improvement (11).

**TABLE 1. History of the Systems-Based Approach to the Development of Early Goal-Directed Therapy**

| Quantifying the Size of the ED Sepsis Problem | Identifying the Poor Quality of Care in the ED | Addressing Early Identification and Treatment | Risk Stratification: Hypotension, Lactate and Fluid Challenge | Cultures, Antibiotics, and Source Control | Origin of Protocolized Hemodynamic Optimization | Protocolized Early Hemodynamic Optimization for Sepsis | Continuous Quality Improvement |
|---|---|---|---|---|---|---|---|
| Of the 120 million ED visits per year in the United States, 2.9% or 1,600,000 are sepsis related. The ED comprises over 50% of all hospital sepsis cases. The average ED waiting times was 5–6 hr and frequently approaches 24 hr nationally and internationally. The most common ICU admission in the elderly. | Prolonged ED LOSs negatively impact outcome. Early physiologic scoring systems revealed early interventions impact morbidity and mortality before ICU admission. Many ED patients are admitted to a non-ICU setting and later succumb to an acute cardiopulmonary deterioration. | The first study using SIRS in the ED revealed that the more SIRS criteria, longer the ED LOS, and greater degree of resource utilization. The evidence for early cultures, antibiotics, and source control translates into better outcomes. | From SIRS to severe disease, cardiovascular insufficiency is most significant. The first investigation of SIRS and lactate revealed a high degree of sensitivity for illness severity. A fluid challenge and shock index were also risk stratification methods insufficiency. The association of SIRS, inflammation, organ failure, and shock was examined in cardiac arrest patients. | In the experimental model, survival rates are superior combined therapy (antibiotics and hemodynamic optimization). By expert opinion and observation, antibiotic administration is most beneficial within 6 hr. This includes early surgical source control when indicated. | Protocolized care improves outcomes based on work by Hopkins et al (16). The hemodynamic optimizations reflect half a century of investigations in (postresuscitation phase of cardiac arrest, undifferentiated shock, trauma, and cardiac failure) prior to its application to sepsis. | The adult model of EGDT was derived from the American College of Critical Care Medicine and expert opinion. This protocolized care has long been part of the treatment for pediatric septic shock. | EGDT is a transparent standard operating procedure which increases awareness and decreases medical errors. It provides a systematic approach which can be quantitated and is amenable to a continuous quality improvement program. |

ED = emergency department, EGDT = early goal-directed therapy, LOS = length of stay, SIRS = systemic inflammatory response syndrome.
References for this table are provided in the supplement (Supplemental Digital Content 1, http://links.lww.com/CCM/C301).

The early hemodynamic perturbations of sepsis are consistent, predictable, and more importantly reversible when detected. They consist of hypovolemia (decreased central venous pressure [CVP]), vasodilatation (decreased mean arterial pressure), myocardial dysfunction (decreased cardiac output and central venous oxygen saturation), and increased metabolic demands which result in cardiovascular insufficiency (12). These hemodynamic perturbations which lead to cardiovascular insufficiency are complicated by comorbidities and chronic therapies (i.e., diuretics and antihypertensive medications) that may cloud the clinical presentation.

Early risk stratification for undetected and untreated cardiovascular insufficiency (cryptic shock) is an important aspect of PESC. Cardiovascular insufficiency leads to significant morbidity such as prolonged mechanical ventilation and sudden cardiovascular complications, the most preventable causes of death in the first 24 hours of sepsis care (13–16). PESC detects and mitigate these early pathogenic mechanisms; especially when the patient is in the hands of an inexperienced healthcare provider (17). This important step of risk stratification and hemodynamic phenotyping was included as standard of care in all groups of the ProCESS, ProMISe, and ARISE trials, which diminishes the treatment effect.

The debate continues regarding the components of PESC such as systemic inflammatory response syndrome, lactate, fluid therapy (amount and type), volume assessment, blood pressure target (vasopressors), transfusion, $Scvo_2$, inotropic therapy, and mechanical ventilation which were derived from the American College of Critical Care Medicine (9). In spite of these debates, these components have been shown to be beneficial when used in the context of PESC (18). Furthermore, increased compliance to all of its elements is significantly associated with improved mortality (19, 20). Even when compliance is suboptimal, improved mortality is seen because of improved performance to individual targets and not the bundle as a whole. PESC is a form of individualized precision medicine by providing hemodynamic phenotyping which enhances diagnostic, therapeutic, and outcome decision making (21). A patient with a $Scvo_2$ of 78% and a normal lactate after 6 hours of resuscitation is prognostically

much different than a patient with a $Scvo_2$ of 78% and a lactate of 5.6 mM/L (21). The latter may reflect a microcirculatory defect (i.e., vasopressor toxicity), cytopathic tissue hypoxia, or inadequate source control (i.e., bowel ischemia). The mortality difference between these hemodynamic phenotypes is over 10% (20). From an outcome trials perspective, enrolling patients of similar hemodynamic phenotypes can assure a greater degree of homogeneity. Without accounting for this, the heterogeneity of these hemodynamic phenotypes will diminish the treatment effect of an intervention. As a result, promising sepsis outcome studies (i.e., immunotherapy) may continue to fail (21, 22).

## PESC: A PHYSIOLOGIC RESUSCITATION STRATEGY

Although the EGDT study is considered synonymous with a liberal fluid strategy, patients in ProCESS, ARISE, and ProMISe trials all received similar volumes during the resuscitation phase. Because of the greater lead time prior to enrollment in the ProCESS, ARISE, and ProMISe trials, between 2 and 2.6 L of fluid was given prior to randomization (**Table 2**). From hospital arrival to the end of the 6-hour study period, the total fluid volume ranged from 3.5 to 5.5 L for all four sepsis studies (Table 2). Interestingly, the mechanical ventilation rate in ProCESS, ARISE, and ProMISe trials was half that of the EGDT trial even though similar amounts of fluid were given.

A prompt fluid challenge (30 mL/kg or approximately 2.5 L) is associated with increased mean arterial pressure, normalization of $Scvo_2$, and decreased vasopressor use at 6 hours. This is also associated with a 1.4–6.2% absolute mortality reduction or a 15–31% relative reduction in hospital/30-day mortality and hospital length of stay (LOS) (23–25). These findings were seen even in patients with a history of renal and heart failure (24). As a result, Lee et al (23) concluded: "earlier fluid resuscitation may account for the lack of outcome differences in the ProCESS, ARISE, and ProMISe trials and may have contributed to the overall low 60-day in-hospital mortality rate of 19%." Thus, it appears that 5 L of fluid over the initials 6–8 hours is uniformly associated with improved mortality.

In the EGDT study, the greater volume therapy or treatment effect during the resuscitation phase within the first

**TABLE 2. Comparison of Treatments Across the Early Goal-Directed Therapy, Protocolized Care for Early Septic Shock, Australasian Resuscitation In Sepsis Evaluation, and Protocolized Management In Sepsis Trials**

| | EGDT | | ProCESS | | | ARISE | | ProMISe | |
|---|---|---|---|---|---|---|---|---|---|
| Intervention | EGDT | Control | EGDT | PBST | UC | EGDT | UC | EGDT | UC |
| Fluid from emergency department arrival to 6 hr, mL[a] | 4,981 | 3,499 | 5,059 | 5,511 | 4,362 | 4,479 | 4,304 | 4,216 | 3,987 |
| Difference between groups[b], mL | 1,482 | | −452 and 667 | | | 175 | | 229 | |
| Fluids 6–72 hr, mL | 8,625 | 10,602 | 4,458 | 4,918 | 4,354 | 4,274 | 4,382 | 4,215 | 4,366 |
| Total fluids 0–72 hr, mL | 13,443 | 13,358 | 7,253 | 8,193 | 6,663 | 6,906 | 6,672 | 5,946 | 5,844 |
| Vasopressor 0–6 hr, % | 27.4 | 30.3 | 54.9 | 52.2 | 44.1 | 66.6 | 57.8 | 53.3 | 46.6 |
| Vasopressor 6–72 hr, % | 29.1 | 42.9 | 47.6 | 46.6 | 43.2 | 58.8 | 51.5 | 57.9 | 52.6 |
| Vasopressor 0–72 hr, % | 36.8 | 51.3 | 60.4 | 61.2 | 53.7 | | | 60.5 | 55.0 |
| Inotrope 0–6 hr, % | 13.7 | 0.8 | 8.0 | 1.1 | 0.9 | 15.4 | 2.6 | 18.1 | 3.8 |
| Inotrope 6–72 hr, % | 14.5 | 8.4 | 4.3 | 2.0 | 2.2 | 9.5 | 5.0 | 17.7 | 6.5 |
| Mechanical ventilation 0–6 hr, % | 53.0 | 53.8 | 26.4 | 24.7 | 21.7 | 34.8[c] | 32.9[c] | 20.2 | 19.0 |
| Mechanical ventilation 6–72 hr, % | 2.6 | 16.8 | 33.7 | 31.4 | 27.9 | 38.6[c] | 40.6[c] | 24.4 | 25.4 |
| Any mechanical ventilation, % | 55.6 | 70.6 | 36.2 | 34.1 | 29.6 | 30.0 | 31.5 | 27.4 | 28.5 |

ARISE = Australasian Resuscitation In Sepsis Evaluation, EGDT = early goal-directed therapy, PBST = protocol-based standard therapy, ProCESS = Protocolized Care for Early Septic Shock, ProMISe = Protocolized Management In Sepsis, UC = usual care.

[a]The prerandomization period refers to a time-frame prior to the time informed consent for study enrollment. Interventions were initiated as indicated, including fluid therapy or steroid administration.

[b]Difference between groups are early goal-directed therapy minus the treatment group in each trial.

[b]Prerandomization and 6 hr of study.

[c]Combined invasive and noninvasive mechanical ventilation.

6 hours was associated with a greater reduction (13.8%) in vasopressor therapy, lower mechanical ventilation rates (14.2%), and less administered volume (2 L or 23%) between the EGDT and control group over the subsequent 6–72-hour time period (Table 2). These findings were evident in the absence of aggressive glucose control, steroid use, protective lung strategies, and conservative fluid management strategies.

## PESC IS ENHANCED WITH A GOAL-DIRECTED DE-RESUSCITATION

Fluid therapy including the use of CVP is one of the most discussed aspects of PESC. Early, aggressive fluid therapy targeted to endpoints must be distinguished from late, aggressive fluid therapy (9, 13, 23). Weil et al (26) stated "central venous pressure does not accurately reflect blood volume but indicates the competence of the heart to accept and expel the blood returned to it. As such it is an excellent guide to "safe" volume repletion." When used in this context, CVP has been associated with improved outcomes (27). Brotfain et al (28) found an association between positive fluid balance and mortality in the first 72 hours. However, they also concluded the following: "on the other hand, we found a positive fluid balance in the early resuscitation period to have a beneficial effect on survival and to decrease the risk of readmission to ICU after discharge" (28). De-resuscitation is as important as the acute resuscitation and is associated with decreased mechanical ventilation, cardiopulmonary complications, and healthcare resource consumption (29). De-resuscitation consists of meticulous prevention of excess fluids (maintenance), quantification, organ assessment (renal and cardiac function), and timely removal with diuretic therapy or renal replacement therapy (30, 31). When renal replacement therapy is required in the treatment of septic shock, mortality approaches 50%. The optimal timing of renal replacement therapy is not clearly established (32).

## PEDIATRIC PESC

Aggressive fluid therapy has been a predominant part of pediatric sepsis management before the publication of EGDT (33). Furthermore, the essential elements of EGDT (including $ScvO_2$) have been part of pediatric septic shock for decades and have been shown to improve organ function and outcomes (33–37). Dr. Delaney and others understandably refer to a pediatric study to express concerns regarding the negative consequences of fluid therapy. However, the Fluid Expansion as Supportive Therapy study, where the use of bolus fluid administration was associated with increased mortality occurred in children where malaria was the cause in 57% (38). A recent study using blood (age or new) in children with malaria has shown improved hemodynamic endpoints (brain tissue oxygen saturation) and outcomes (39, 40). Therapies confirmed in adults are not necessarily translated to pediatric patients whose mortality is 5–10 times less than adults (41).

## PESC REPRESENTS AN ERA OF DIMINISHING MORTALITY

A significant reduction in sepsis mortality began after the millennium and coincided with seminal studies and the introduction of the Surviving Sepsis Campaign guidelines (Figs. 1 and 2) (18). A recent international examination of over 52 studies (166,479 patients between January 1, 1992, and December 25, 2015) revealed this period began with a mortality of 46.5% (42). This mortality is identical to the control group of the EGDT trial which supports its external validity even though a single-center trial. The findings of the EGDT have been robustly reproduced in multiple trial designs (Fig. 2). While randomized controlled trials (RCTs) are considered the standard, large prospective observational studies provide an equally reliable scientific alternative to RCTs (43).

To declare that we have entered a new era of sepsis care and have no need for protocolized care is a mistake. There is already evidence that taking this approach may be deleterious (44). In the case of trauma, stroke, and acute myocardial infarction, mortality has improved but protocols have not been eliminated. On the contrary, they are continuously updated and refined. The majority of patients with acute myocardial infarction or stroke have comorbidities similar to those of patients with sepsis (cancer, renal failure, heart failure, etc). This does not impede the use of protocolized care. In fact, these dynamic and fragile patients, in the absence of structured recognition and treatment, may succumb to the previously described medical errors. For example, PESC has taught us that giving fluids to renal and heart failure patients (a well-recognized fear) actually improves mortality (24).

## COMPARING PROCESS, PROMISE, ARISE, AND EGDT

One must proceed with caution when interpreting and generalizing the results of the ProCESS, ProMISe, and ARISE trials. There are multiple methodologic issues that warrant consideration (**Table 3**). The majority of the 5,000 hospitals in the United States (over 90%) are not tertiary academic or large medical centers which largely comprised the hospitals in the ProCESS, ARISE, and ProMISe trials. Whether in the United States or other countries, lower volume and critical access hospitals (community and rural) have mortalities 9–38% higher, as well as increased costs of care (45–48). This mortality is largely related to inappropriate triaging and delays in early resuscitation (49). These hospitals in resource limited U.S. settings and their issues were unrepresented in the ProCESS, ARISE, and ProMISe trials which limits their external validity. Williams et al (45) conducted a paralleling prospective examination of patients presenting with septic shock at an enrolling site of the ARISE trial. Compared with patients enrolled in ARISE, patients prospectively observed during the same study period were sicker (higher Acute Physiology and Chronic Health Evaluation II scores, 19 vs 15.8), had longer LOSs in the ED (9.2 vs ≤ 2 hr), higher mortality (19.5% vs 14.5–15.7%), lower ICU admission rates

**TABLE 3. Summary of Methodologic Comparisons**

| Methodological Consideration | The Trio of EGDT Trials | EGDT Study |
|---|---|---|
| Requisite for enrollment and usual care | Considered as standard care:<br>Screening using systemic inflammatory response syndrome<br>Fluid challenge<br>Lactate screening for cryptic shock<br>Early antibiotic administration | No preexisting standards<br>Usual care was developed as a requisite for the EGDT study |
| Enrollment | Enrollment (8/site/yr)<br>2–12 hr window of enrollment in the ED<br>Weekdays and no weekends (Protocolized Management In Sepsis)<br>Exclusion rate of 2–1 | Single center<br>1–2 hr to enrollment<br>9% exclusion |
| Fluid challenge | Fluid challenge—1 L or surrogate<br>2–3 L administered before enrollment<br>Similar fluid in all treatment groups from ED arrival to 6 hr | 30 mL/kg<br>42% more volume in EGDT group for treatment effect |
| Trial duration and timing | Conduction began 7–8 yr after EGDT (2008–2015)<br>Duration ranging between 4 and 8 yr<br>Surviving Sepsis Campaign guidelines were published in 2004, 2008, and 2012 | No existing sepsis protocols<br>3 yr duration |
| Blinding | Open labeled study in the ICU | ICU was blinded to care provided in the ED and study variables.<br>ICU was blinded to lactate and $Scvo_2$ for 72 hr due to use of paper laboratory results and paper charting |
| Trial conduction | Duration of the ED stay < 3 hr and transferred to ICU<br>Average ED LOS is > 5 hr in reality<br>Delayed resuscitation bundle completion possible after 6 hr<br>High volume and tertiary care centers<br>CVP placement over 50% of control groups in trio of EGDT trials<br>The impact of delayed EGDT and it affect on the treatment effect is unknown.<br>A reduction in sample size after interim analysis low mortality | Performed in ED only<br>6–8 hr in the ED<br>Delayed care improves outcomes |
| Comorbidities | Fewer patients with heart failure and liver disease<br>Younger patients | Increased:<br>Cardiovascular, liver, neurologic, renal disease |
| Mechanical ventilation | Rate of 26%<br>No delayed increase after enrollment<br>Protective lung strategies<br>Conservative fluid management strategies | Rate of 54%<br>No protective lung or fluid management strategies<br>Increase use of delayed mechanical ventilation in the control group over 72 hr |
| Illness severity | Acute pulmonary edema excluded<br>Acute lung injury excluded | Lower temperature, lower $Paco_2$, higher respiratory rate |
| Hemodynamic phenotypes | $Scvo_2$ and CVP goals were met at baseline<br>50% more vasopressors (vasodilatory)<br>Steroid use 8–37% | Lower $Scvo_2$<br>Higher lactate<br>Lower CVP<br>No steroid use |

(*Continued*)

**TABLE 3. (*Continued*). Summary of Methodologic Comparisons**

| Methodological Consideration | The Trio of EGDT Trials | EGDT Study |
|---|---|---|
| Sudden cardiopulmonary events | Not a predominant feature because of early ICU admission and treatment team | Significant reduction from 20% to 10% |
| ICU phase of care (up to 72 hr) | Similar fluid, vasopressor therapy, and mechanical ventilation<br>Unblinded care<br>Delayed EGDT possible<br>Lactate and $Scvo_2$ use unblinded | More fluid in control group<br>Less vasopressor use, less fluid therapy, and mechanical ventilation in the EGDT groups<br>Blinded care<br>No use of lactate or $Scvo_2$ in the care of patients. |
| Sources of improved care | Preexisting sepsis protocols, prehospital care, sepsis alerts and screens, rapid response systems, telemedicine, glucose control, steroid use, protective lung strategies, conservative hemoglobin strategies, palliative care, national limits on ED LOS (Australia and United Kingdom), ultrasound, and other monitoring. | Preceded these advancements described for "Trio of EGDT Trials" |
| Generalizability and external validity | Performed in academic centers in industrialized countries<br>Specialized care delivery via sepsis team/ICU hybrid<br>Transferred patients excluded | EGDT replicated in community and academic centers worldwide<br>Effective in delayed care |

CVP = central venous pressure, ED = emergency department, EGDT = early goal-directed therapy, LOS = length of stay.
References for this table are provided in the supplement (Supplemental Digital Content 1, http://links.lww.com/CCM/C301).

(37.3% vs 76.9%), and appeared at a rate of 10.2 cases per month compared with 0.5 cases per month in ARISE (45). They stated that:

> "Study populations are often convenience cohorts and not representative of all patients presenting with septic shock. These were patients who were not indulged with the resources and attention associated with controlled trials (45)."

## IS USUAL CARE THE SAME AS PESC?

The ProCESS, ProMISe, and ARISE trials reveal that protocolized care yields an all-time low in sepsis mortality. The alleged controversy surrounds what constitutes what is usual care versus EGDT. When one considers the components of EGDT (early detection, risk stratification using lactate, antibiotics, fluids, vasoactive therapy, and early ICU admission) were provided in all groups, the conclusions are not surprising as quoted by ProCESS trial investigators:

> "The ephemeral nature of usual care puts clinical trialists in a quandary. If the goal of a control group is to emulate usual care, protocolizing usual care based on pre-study information is no guarantee that this group will reflect usual care during the conduct of the trial as usual care may change. Randomizing to unrestricted usual care runs the risk that usual care may merge with the intervention arm during the trial, narrowing differences between groups, and resulting in loss of power to detect a meaningful difference" (50).

In the final analysis, some of the investigators of ARISE and ProMISe conclude the following:

> "In instances where the patient fails to rapidly improve or shows signs of organ dysfunction, referral should be made to the intensive care unit. The role of rapid response teams and sepsis teams in the recognition and management of sepsis needs to be evaluated further. Although many of the elements of EGDT may not improve outcomes of severe sepsis, it is possible that protocolized care of early sepsis may improve outcomes by (1) providing an educational framework for bedside clinicians (2); creating an expected response to initial treatment and escalation of clinical deterioration (3); minimizing practice variation between clinicians; and (4) providing clinical indicators that can be measured and can be the focus of audit and quality improvement initiatives similar to the 'door to needle time' in patients presenting to hospital with an acute coronary syndrome. Finally, hospitals should have governance structures in place to review adverse events associated with sepsis. Audit of sepsis-related morbidity and mortality should focus on the degree to which clinical practice adhered to the general principles outlined here." (51)

## CONCLUSIONS

PESC reduces medical errors for the most deadly and costly cause of hospital admissions. While described as a hemodynamic optimization strategy, it is a transparent standardized operating procedure for all healthcare personnel involved in the landscape of diagnostic and therapeutic management of sepsis. PESC provides a template of accountability, decreases practice variation and is amenable to continuous quality improvement processes. PESC provides hemodynamic phenotyping which enhances diagnostic, therapeutic, and prognostic precision. The introduction of PESC has been associated with an unprecedented mortality reduction in the last 15 years and should

be a national standard of care similar to acute myocardial infarction, stroke, and trauma.

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