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Protocol-Based Management of Severe Sepsis and Septic Shock

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Abstract Sepsis remains a significant public health problem, with increasing incidence but decreasing mortality worldwide. The landmark Rivers study published in 2001 revolutionized the management of sepsis and septic shock, and brought early recognition, early antibiotic therapy, and protocol-based care to the forefront of sepsis management. However, certain components of the Rivers protocol have remained controversial and have not been widely accepted into practice. In addition, data for elements not included in the Rivers protocol have emerged. A series of three trials (ProCESS, ARISE, and ProMISe) designed with harmonized methods have recently demonstrated a lack of survival benefit for patients with septic shock treated with early goal directed therapy compared with usual care. Based on the results of these studies, the surviving sepsis campaign and national quality forum are revising their recommendations related to sepsis management.

Keywords Severe sepsis · Septic shock · Protocol-based care · Early goal directed therapy · Bundled care · Usual care

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Introduction

Despite advancements in management of critical illness, sepsis remains a major source of morbidity and mortality worldwide [1–3]. Even among survivors of severe sepsis, significant decrement in cognition, functional status, and quality of life are reported [4]. Therefore, considerable resources have been dedicated to continuing improvement in diagnosis and management of sepsis. Over the past decades, a paradigm shift has occurred, marked by adoption of early, aggressive treatment of sepsis using goal directed, and more recently, protocol-driven strategies.

The inception of protocol-based care for sepsis occurred in the 1990s. A consensus definition describing the sepsis syndrome as a continuum involving sepsis (known source of infection with evidence of a systemic inflammatory response), severe sepsis (presence of organ failure), and septic shock (hypotension refractory to resuscitation), was developed in 1992 [5]. Increasing recognition of the role of the host inflammatory response in precipitating organ dysfunction and hemodynamic collapse followed [6, 7]. The critical importance of early identification of patients at risk for systemic complications [8, 9], and the need for interventions aimed at restoration of the balance between tissue oxygen supply and demand [6, 10] were subsequently brought to the forefront. Furthermore, acknowledgement of the flaws in traditional endpoints of resuscitation [11] prompted support for development of goal-directed resuscitation strategies [6, 10, 12].

Significant effort has recently gone into development of protocols to guide multiple arenas of patient care [13], given the contribution of human factors to medical errors [14]. Systems of care that remove complete reliance on human memory by utilizing computerized systems [14, 15], memory aids [14], protocols [13], decision support

systems [16], and checklists [17] have been shown to improve outcomes and to reduce errors. Additional proposed benefits of automation of care include improvement in patient safety, quality of care, adherence to guidelines, clinical decision-making, communication and ordering patterns, and time optimization [15, 16].

Rivers et al.s' study [18] was the first to show a significant mortality reduction in the treatment of sepsis by implementing a protocol-based algorithm. Yet in the intervening 15 years, management of patients with sepsis still remains widely variable [19]. This article will discuss the recent evidence surrounding protocol-based management for the care of patients with early severe sepsis and septic shock.

Early Goal directed Therapy: The Rivers Trial

Rationale

Goal directed therapy is defined as manipulation of the determinants of oxygen delivery, including preload, afterload, contractility, hemoglobin, and oxygen saturation, to optimize tissue oxygenation [18]. Each of these components is addressed in the Rivers therapeutic protocol, using endpoints considered at the time to be more useful than traditional hemodynamic assessment [10, 12, 20].

The Protocol

The Rivers trial was a prospective, randomized trial that enrolled 230 patients who presented to the emergency department (ED) of a single large academic medical center over a 3-year time period. Inclusion and exclusion criteria are listed in Table 1. Patients were treated in a 9-bed unit within the ED by one attending emergency physician, two residents, and two nurses while routine care of other ED patients was taking place. 133 patients were randomized to receive standard therapy guided by the clinical discretion of the treating physician, based on a protocol using hemodynamic parameters (Table 1). All patients in the standard therapy (ST) group received arterial and central venous catheters and blood cultures prior to antibiotic therapy. Patients were admitted to the appropriate inpatient setting as soon as possible.

130 patients were randomized to receive early goal directed therapy (EGDT). These patients received continuous monitoring of central venous oxygen saturation ($ScvO_2$) via central venous catheter (CVC) as well as arterial blood pressure monitoring via an arterial line. Patients were treated in the ED for at least 6 h based on a specific protocol (Fig. 1), after which ICU admission occurred. After ensuring appropriate oxygenation, patients were given a 500-mL bolus of crystalloid every 30 min to achieve central venous pressure (CVP) $\geq$ 8–12 mm of mercury (mmHg). At that point, vasopressors were initiated to achieve mean arterial pressure (MAP) 65–90 mmHg. If $ScvO_2$ remained <70 %, red blood cells were transfused to hematocrit $\geq$30 %. If $ScvO_2$ was still <70 % after transfusion, a dobutamine infusion was initiated at 2.5 μg/kg/min and titrated by 2.5 μg/kg/min every 30 min to a goal $ScvO_2$ >70 % or to a maximum dose of 20 μg/kg/min. Dobutamine dose was decreased or discontinued for MAP <65 mmHg or heart rate (HR) >120 beats per minute (bpm). If hemodynamic goals were not achieved after these measures were completed, the patient received mechanical ventilation and sedation. Physicians assuming care for both groups of patients after discharge from the ED were blinded to initial treatment group.

Results

This study demonstrated a significant reduction in 28-day (40 vs. 49.2 %), in-hospital (30.5 vs. 46.5 %), and 60-day (44.3 vs. 56.9 %) mortality for the EGDT group compared with ST. During the first 6 h after initiation of therapy, MAP was significantly lower in the ST group, but all patients in both groups achieved MAP $\geq$ 65 mmHg. 60.2 % of patients in the ST group versus 95 % of patients in the EGDT group achieved $ScvO_2 > 70$ %. The hemodynamic goals of the respective groups were achieved in 86.1 % of ST and 99.2 % of EGDT groups. In the first 6 h, patients in the ST group had significantly lower $ScvO_2$ and a greater base deficit, but there was no difference in lactate, pH, HR, or CVP between groups. Between 7 and 72 h of admission, patients in the EGDT group had higher mean $ScvO_2$, lower lactate, lower base deficit, higher pH, better coagulation system function, and lower illness severity scores. Patients in the EGDT group received more fluid, red blood cell transfusion, and inotropic support in the first 6 h, but after 6 h, patients in the ST group received more fluid, transfusions, vasopressors, mechanical ventilation, and pulmonary artery catheterization. The incidence of death due to sudden cardiovascular collapse was 21 % in the ST group versus 10.3 % in the EGDT group, and both groups had a similar incidence of multi-organ failure.

Why Was the Rivers Trial So Successful?

The significant mortality reduction in the Rivers study can largely be attributed to the provision of early aggressive care to septic patients [21], which represented an important change from usual care at the time. The years preceding the Rivers trial were marked by increasing appreciation of the natural history of the systemic inflammatory response syndrome (SIRS), and recognition that delays in treatment

Table 1 Comparison of Rivers, ProCESS, ARISE, and ProMISe study protocols

	Rivers	ProCESS	ARISE	ProMISe
Study design	Prospective, randomized, blinded after ED treatment	Prospective, randomized, concealed	Prospective, randomized, concealed	Prospective, randomized, concealed
Sample size	263	1341	1600	1243
Inclusion criteria	Adult ≥2 SIRS criteria BP ≤ 90 mmHg after 20–30 mL/kg IVF OR lactate ≥ 4 mmol/L	Adult Suspected infection ≥2 SIRS criteria BP < 90 mmHg after 1 L IVF fluid bolus or blood lactate ≥ 4 mmol/L Enrollment within 2 h of identification of shock or 12 h after arrival	Adult Suspected infection ≥2 SIRS criteria BP < 90 mmHg after or MAP < 65 mmHg after 1L IVF fluid bolus OR blood lactate ≥ 4 mmol/L First dose of antibiotic started Eligibility criteria met within 6 h of ED presentation	Adult Known or presumed infection ≥2 SIRS criteria BP < 90 mmHg after or MAP ≤ 65 mmHg 1L IVF fluid bolus OR blood lactate ≥ 4 mmol/L Enrollment within 2 h of meeting inclusion criteria
Exclusion criteria	Pregnancy Primary diagnosis of acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, cardiac dysrhythmia, seizure, injury from burn or trauma, drug overdose Contraindication to CVC Active gastrointestinal hemorrhage Requirement for immediate surgery Cancer during chemotherapy Immunosuppression Do not resuscitate status Advance directives precluding inclusion	Same as Rivers AND Treating physician deems aggressive care unsuitable Transferred from another in-hospital setting Contraindication to blood transfusion Participation in another study ANC < 500/μL Known CD4 < 50/μL	Hemodynamic instability due to bleeding Treating physician deems aggressive care unsuitable A "limitation of therapy" order restricting implementation of the study protocol Underlying disease with life expectancy <90 days Death deemed imminent and unpreventable Contraindication to blood transfusion Contraindication to SVC CVC Inability to commence delivery of EGDT within 1 h of randomization or complete within 6 h In-patient transfer from another acute health facility Pregnancy	Same as Rivers AND Known AIDS Treating physician deems aggressive care unsuitable Transferred from another in-hospital Inability to commence delivery of EGDT within 1 h of randomization or complete within 6 h
Groups	EGDT versus standard therapy	EGDT versus protocolized standard care versus usual therapy	EGDT versus usual care	EGDT versus usual care
Standard therapy or usual care group	Arterial line and CVC placed Care provided at the discretion of attending physician Goals: CVP ≥ 8–12 mmHg MAP ≥ 65 mmHg UOP ≥ 0.5 mL/kg/h Admitted to inpatient setting as soon as possible Critical care consultation available	Care provided at the discretion of existing care providers	Care provided at the discretion of existing care providers, $ScvO_2$ monitoring not permitted	Care provided at the discretion of existing care providers

Table 1 continued

	Rivers	ProCESS	ARISE	ProMISe
Protocolized standard care group (stepwise)	None	Supplemental O_2 or intubation 2 large bore peripheral IV's (or CVC if appropriate) Sedation, analgesia, ± *p*aralysis if intubated 500–1000 mL IVF (minimum total IVF 2L) to SBP ≥ 100 mmHg or shock index ≤ 0.8 When fluid replete, vasopressors for SBP ≥ 100 mmHg Reassess every 30 min, if hypoperfusion start at the beginning	None	None
EGDT group (stepwise)	Optimize oxygenation Place continuous $ScvO_2$ CVC and arterial line 500 mL IVF every 30 min to CVP 8–12 mmHg Vasopressors for MAP 65–90 mmHg Transfusion to Hct > 30 % for $ScvO_2$ < 70 % Dobutamine for $ScvO_2$ < 70 % Mechanical ventilation and sedation Protocol completed in ED	Same as Rivers, except protocol can be completed outside the ED and arterial line not required	Same as Rivers, except protocol can be completed outside the ED	Same as Rivers, except protocol can be completed outside the ED and arterial line recommended but not not required
Primary outcome measure	In-hospital mortality	In-hospital mortality at 60 days or discharge	90-day all-cause mortality	90-day all-cause mortality
Secondary outcomes	Resuscitation endpoints (HR, UOP, BP, CVP, $ScvO_2$), organ dysfunction scores, coagulation studies, administered treatments, consumption of healthcare resources	Mortality at 90 days and 1 year, duration of organ failure, need for organ support, duration of stay in ICU and hospital, discharge disposition, illness severity scores, inflammatory markers	28-day mortality; death at ICU or hospital discharge; duration of survival; duration of stay in ED, ICU, hospital; receipt and duration of artificial organ support; adverse events	28-day, 1 year, and in-hospital mortality; SOFA scores; receipt and duration of artificial organ support; duration of stay in ED, ICU, hospital; health-related quality of life at 90 days and 1 year; resource use and costs at 90 days and 1 year; lifetime cost-effectiveness; cost per QALY gained at 1 year; adverse events
Study duration	60 days or death	1 year or death	90 days or death	1 year or death
Primary outcome results	In-hospital mortality 30.5 % EGDT versus 46.5 % ST ($p = 0.009$)	60-day mortality 21 % EGDT versus 18.2 % PSC versus 18.9 % usual care ($p = > 0.05$)	90-day mortality 18.6 % EGDT versus 18.8 % usual care ($p = 0.9$)	90-day mortality 29.5 % EGDT versus 29.2 % usual care ($p = 0.9$)

Table 1 continued

	Rivers	ProCESS	ARISE	ProMISe
Conclusion	EGDT associated with significant mortality reduction	Protocol-based care does not improve outcomes	EGDT did not improve 90-day all-cause mortality	EGDT did not improve outcomes

SIRS systemic inflammatory response syndrome (two out of four of the following: $T > 38$ or < 36 °C, heart rate > 90 bpm, respiratory rate > 20/min or partial pressure of arterial carbon dioxide < 32 mmHg, and white blood cell count $> 12{,}000$ or $< 4{,}000$/mL or > 10 % immature bands); *BP* blood pressure; *mmHg* millimeters of mercury; *mL* milliliters; *kg* kilogram; *mmol* millimoles; *L* liter; *EGDT* early goal directed therapy; *CVC* central venous catheter; *CVP* central venous pressure; *MAP* mean arterial pressure; *UOP* urine output; $ScvO_2$ central venous oxygen saturation; *IVF* intravenous fluid; *min* minutes; *ED* emergency department; *HR* heart rate; *ANC* absolute neutrophil count; O_2 oxygen; *IV* intravenous line; *SBP* systolic blood pressure; shock index, HR/SBP; *ICU* intensive care unit; *SVC* superior vena cava; *AIDS* acquired immunodeficiency syndrome; *SOFA* sequential organ failure assessment; *QALY* quality adjusted life year; *ST* standard therapy

places the patient at risk for developing septic shock with resultant tissue hypoxia and multiorgan dysfunction [6, 7]. In addition, several sources of bias have been alleged as possible contributors to the mortality benefit. More patients in the EGDT group than the ST group achieved all goals outlined by the protocol, suggesting that the EGDT patients may have received more aggressive bedside care during this unblinded study [22]. The single center tertiary academic medical setting and the involvement of a single attending physician in the care of all study patients also brings into question the reproducibility and the external validity of the results.

Impact on Clinical Practice

The Rivers trial has had a monumental impact on treatment of sepsis worldwide. Since its publication, many hospitals have developed and implemented protocols or bundles for treatment of sepsis in a variety of practice settings [23]. Many specific components of the protocol became elements of sepsis bundles released by agencies influencing national healthcare quality improvement and hospital reimbursement [24••, 25, 26], including central venous catheter placement and measurement of $ScvO_2$.

Although Rivers showed significant mortality reduction with early aggressive care in sepsis, which of the components of the published protocol had the greatest impact on mortality remains unclear. Multiple elements have been purported as unnecessary, erroneous, or even dangerous. For example, the inherent inaccuracies of $ScvO_2$ [27, 28] and CVP [29] interpretation bring into question the usefulness of these parameters. Placement of a CVC in every patient is invasive, time-consuming, and places the patient at risk of complications [30]. The use of transfusions to increase oxygen carrying capacity is controversial, and potentially harmful [31]. These unresolved questions have led to the provision of heterogeneous and patchy EGDT, and have prompted the design of further studies to validate the protocol and the study's outcomes.

Data from the Interim: 2001–2015

Incidence and Mortality

In the past two decades, since the development of consensus definitions for sepsis and the increasing implementation of EGDT, sepsis-related mortality has declined significantly, despite an increasing incidence [2, 32–34]. A meta-analysis of 14,000 patients with severe sepsis included in the usual care arms of 36 multicenter randomized controlled trials reported a reduction in 28-day mortality from 46.9 % between 1991–1995 to 29.2 % during 2006–2009 [33]. Similar results were reported in two recent retrospective studies, the first including data from over 480,000 admissions in multiple ICUs in the United States between 1988 and 2012 [35], and the second, examining all patients with severe sepsis admitted to 171 ICUs in Australia and New Zealand between 2000 and 2012 [2]. In the latter study, crude and adjusted mortality for all ICU patients also decreased to the same extent as sepsis-related mortality over the same timeframe, suggesting a significant role of improvements in overall ICU care in mortality reduction [2]. Patients with severe sepsis still require significant resources, however. A prospective multicenter observational study of nearly 11,000 consecutive patients with septic shock admitted to 14 ICUs in France between 2009 and 2011 reported rates of mechanical ventilation of 83.9 %, inotropic support of 27.7 %, continuous renal replacement therapy of 32.5 %, and hemodialysis of 19.6 % [34].

Implementation of Early Goal Directed Therapy

The mortality benefit associated with use of a routine EGDT protocol in the ED has been externally validated in multiple studies [36, 37]. A prospective longitudinal before and after study conducted among patients presenting with severe sepsis at a single large urban ED showed an in-hospital mortality reduction from 27 to 18 % after implementation of a sepsis management protocol nearly identical to the Rivers

protocol [36]. Patients treated after implementation of the protocol received significantly more crystalloid, vasopressors, and endotracheal intubation, and also received antibiotics within a shorter amount of time [36]. Given the wealth of evidence supporting EGDT, many institutions have implemented some form of guideline or protocol to guide management of patients with early sepsis. However, protocol implementation and compliance remains variable for a variety of reasons [19, 38]. In a 2007 survey of nurse managers and physician directors in 53 of the busiest urban teaching and non-teaching EDs in the United States, 23 % of institutions were not using and were not planning to use a written protocol, 45 % were currently using a written protocol, and 32 % were in the process of planning a protocol [38]. Protocols in the operational or planning phases also varied and included: unmodified Rivers protocol (54 %), Surviving Sepsis Campaign guidelines (13 %), modified Rivers protocol (4 %), another protocol (14 %), or unsure (15 %) [38]. A more recent survey in 2010 asking ED physicians and Intensivists in the United States, Australia, New Zealand, and the United Kingdom about their practices related to protocol implementation revealed that only 0.1 % of 1692 respondents were compliant with the entire EGDT protocol or Surviving Sepsis Campaign 6-h management bundle [19]. Compliance with individual components of the protocols among respondents was also low. 46.5 % measured lactate, 27.4 % gave the recommended initial intravenous fluid boluses, 44.4 % used CVP as a target for fluid management, 61.1 % inserted arterial catheters, 71.5 % inserted central venous catheters, 51.5 % of those inserting a central line measured $ScvO_2$, 48.5 % transfused red blood cells for $ScvO_2 < 70$ %, and 39 % administered an inotrope for $ScvO_2 < 70$ % [19].

The challenges inherent in implementation of a sepsis management protocol provide one explanation for the ongoing variability in sepsis management. Common barriers impeding successful implementation of EGDT are often primarily related to systems or operational issues [23]. Examples include identification of sepsis, need for time- and resource-intensive therapies, lack of staffing resources, lack of availability of equipment and monitors, need for staff training, and increased length of stay in the ED [23, 38]. In addition, lack of evidence for specific components of EGDT, specifically CVP and $ScvO_2$ monitoring, are also commonly perceived as barriers [19, 23, 38]. Institutions that incorporated collaboration and training across disciplines and departments were more successful in protocol implementation [23].

Bundled Care

To overcome the barriers posed by any specific written protocol, which often arise from differences in institutional practices or resources, sepsis bundles have been developed. A "bundle" describes a combination of effective component therapies that provide additive benefits when used collectively [39]. Bundles have been used successfully to reduce adverse events such as catheter-related bloodstream infections [40] and ventilator-associated events [41]. Healthcare governing bodies such as the Institute for Healthcare Improvement and the Centers for Medicare and Medicaid Services have proposed using bundle compliance to determine hospital performance measures and reimbursement, often using an "all-or-none" principle whereby failure to perform any component of the bundle is considered bundle noncompliance [39].

Sepsis bundles have been shown to improve sepsis-related mortality in multiple primarily retrospective and unblinded studies [39]. Common components of sepsis resuscitation bundles include early identification and risk stratification, lactate measurement, early appropriate antibiotic therapy, blood cultures prior to antibiotics, source control, intravenous fluid therapy, maintenance of MAP, use of vasopressor therapy, CVP monitoring, $ScvO_2$ monitoring, blood transfusion, inotropic therapy to support $ScvO_2$, and/or measures to decrease systemic oxygen consumption [37]. Like protocolized care, many aspects of bundled care have been criticized, because some components have little evidence for efficacy [39].

New Targets and Therapies

In the years since publication of the Rivers trial, advancements in care of critically ill patients and better understanding of the benefits and limitations of components of EGDT have provided an impetus for revisiting current practices. For instance, lactate clearance was not addressed in the Rivers trial; yet lactate clearance, defined as the percentage reduction in serum lactate compared with lactate at presentation, has been proposed as a marker of resolving tissue hypoxia and mitochrondrial dysfunction [42–44]. Lactate clearance has been shown to correlate well with reduction in serum biomarkers of inflammation, severity of organ dysfunction, and mortality [42]. Furthermore, targeting lactate clearance during sepsis resuscitation reduces mortality when compared with knowing only the initial lactate [43], and is non-inferior to use of $ScvO_2$ for the same purpose [44]. Other studies have also brought to light important aspects of sepsis management not addressed by the Rivers protocol, including choice of vasopressors [45], blood pressure targets [46], and transfusion thresholds [47]. Finally, general ICU care has improved significantly, with practices such as low tidal volume ventilation for patients with acute respiratory distress syndrome [48], early mobilization [49], prevention and management of delirium [50], venous thromboembolism prophylaxis, and stress ulcer

prophylaxis [51, 52]. The looming question is whether the substantial mortality benefit seen with EGDT could still be present compare with mortality improvements gained from current standard ICU care.

Surviving Sepsis Campaign

The Surviving Sepsis Campaign guidelines, first published in 2004 and subsequently revised in 2008 and 2012, are a set of best practice guidelines developed by expert consensus to provide guidance to clinicians managing early severe sepsis and septic shock [24••]. Management recommendations are organized into initial resuscitation, including resuscitation endpoints, screening, diagnosis, antimicrobial therapy, source control, and prevention; hemodynamic support and adjunctive therapies, including fluid therapy, vasopressors, inotropic support, and corticosteroids; and additional supportive therapy, including blood product administration, mechanical ventilation, pain and sedation management, glucose control, prophylaxis, nutrition, and goals of care. Recommendations for initial resuscitation include 3- and 6-h management bundles (Table 2). The initial resuscitation section of the surviving sepsis campaign (SSC) guidelines is closely modeled after the Rivers EGDT protocol. A notable difference is the recommendation for red blood cell transfusion for hemoglobin <7 g/dL once hypoperfusion has resolved, unless an indication exists for a higher transfusion threshold [24••].

After publication of the 2008 guideline, a performance improvement initiative was conducted at over 200 sites internationally to improve SSC bundle compliance [32]. Over the course of 8 quarters studied, compliance with SSC 6- and 24-h bundles improved from 10.9 to 31.3 %, and 18.4 to 36.1 %, respectively [32]. Unadjusted mortality decreased over the same time period from 37 to 30.8 %, an average of 0.9 % per quarter [32]. Early antibiotic therapy and blood cultures before antibiotic administration were factors found to be independently associated with survival. Of note, achieving targets for CVP > 8 mmHg and ScvO2 > 70 % were not associated with mortality reduction [32].

The New Trials: Usual Care 3, EGDT 0

To address, and hopefully put to rest, myriad lingering concerns regarding EGDT, three independent multicenter, government-funded randomized controlled trials comparing EGDT with usual care and/or protocolized standard care have been recently conducted. These studies were carried out in three geographic regions: the United States (ProCESS, Protocolized Care for Early Septic Shock), Australia and New Zealand (ARISE, Australasian Resuscitation in Sepsis Evaluation), and the United Kingdom (ProMISe, Protocolized Management in Sepsis). Protocols were written collaboratively, with inclusion criteria similar to those used in the Rivers trial, power calculation based on 6–8 % mortality reduction, and similar provider team structures [53•] in order to allow meta-analysis at the conclusion of the three studies. Variations in protocol design were intentionally planned to address regional differences in standard practices [53•]. Two studies, ARISE and ProMISe, compared EGDT versus usual care, and the other, ProCESS, compared EGDT to protocolized standard care and usual care using a three-arm study design.

ProCESS

The ProCESS trial [54••] was conducted in 31 large academic emergency departments in the United States. Participating centers adhered to SSC guidelines for non-resuscitation aspects of sepsis care, and had no protocol in place for sepsis management prior to the study. Interim analysis after enrollment of 650 patients revealed much lower mortality than predicted in the initial power calculation, so sample sizes were re-calculated to preserve the same power for the predicted absolute risk reduction. 1341 patients with early septic shock were randomly assigned to one of three groups: protocol-based EGDT, protocol-based standard care (PSC), and usual care. PSC, which was designed based on literature review, surveys of ED physicians, and expert consensus input, was intended to represent a simplified version of EGDT without mandating the more controversial components of the protocol, including invasive line placement, $ScvO_2$ monitoring, blood transfusions, and inotropes [54••]. Three arms were included to allow comparison between protocolized care (EGDT and PSC) with non-protocolized care (usual care). The protocol is described in detail in Table 1.

ProCESS did not demonstrate a 60-, 90-day, or 1 year mortality difference between study arms. The study reported a 60-day mortality rate of 21 % in the EGDT group, 18.2 % in the PSC group, and 18.9 % in the usual care group. Relative risk of death at 60 days in the protocol-based therapy versus usual care groups was 1.04 [95 % confidence interval (CI) 0.82–1.31], and EGDT versus usual care groups was 1.15 (95 % CI 0.88–1.51). In the first 6 h, use of central venous catheters (94 vs. 56–58 %), $ScvO_2$ monitoring (93.2 vs. 3.5–4 %), vasopressors (54.9 vs. 44.1–52.2 %), dobutamine (8 vs. 1 %), and blood transfusion (14.4 vs. 7.5–8.3 %) was higher in the EGDT group than the other two groups. At the end of 6 h, target MAP >65 mmHg was achieved in more patients in the protocol-based versus usual care groups, but there was no difference in HR between groups. More patients in the

Table 2 Surviving sepsis campaign sepsis management bundles

3-h Bundle
Measure lactate
Obtain blood cultures prior to antibiotic administration
Initiate broad spectrum antibiotics
Administer crystalloid bolus 30 mL/kg for hypotension or lactate $\geq$ 4 mmol/L
6-h Bundle
Start vasopressors to maintain MAP $\geq$ 65 mmHg
Measure CVP (If hypotension or elevated lactate persist despite volume resuscitation), increase to goal $\geq$ 8 mmHg
Measure $ScvO_2$ (If hypotension or elevated lactate persist despite volume resuscitation), increase to goal $\geq$ 70 %
Recheck lactate if initial lactate was elevated

Adapted from Fig. 1 in Dellinger et al. [24••]

mL milliliters; *kg* kilogram; *mmol* millimoles; *L* liter; *MAP* mean arterial pressure; *mmHg* millimeters of mercury; $ScvO_2$ central venous oxygen saturation

EGDT group required ICU admission. Non-adherence to the complete protocol was reported in 11.9 % of the EGDT group and 4.4 % of the PSC group. Patients in all groups received low tidal volume ventilation and moderate glucose control.

ARISE

ARISE [55••] was conducted at 51 centers, varying from tertiary academic centers to non-tertiary rural health centers, primarily located in Australia and New Zealand. Participating centers did not have a protocol for sepsis management prior to the study. 1600 patients were randomly assigned to EGDT versus usual care groups. In contrast to ProCESS, the study had only two arms to avoid increasing sample size and study complexity. The study protocol is described in Table 1. There was no difference in 90-day mortality between EGDT and usual care groups (18.6 vs 18.8 %), and patients in the EGDT group received more central venous catheters (90 vs. 61.9 %), intravenous fluids, vasopressor infusions (66.6 vs. 57.8 %), red blood cell transfusions (13.6 vs. 7 %), and inotropic therapy (15.4 vs. 2.6 %). MAP was higher in the EGDT group at 6 h. The number of patients requiring vasopressors and inotropes during the time period from 6 to 72 h was higher in the EGDT group. There was no difference in duration of survival, in-hospital mortality, duration of organ support, or length of hospital stay.

ProMISe

ProMISe [56••] was conducted at 56 hospitals in England. Participating centers were a mixture of rural and urban, teaching and non-teaching hospitals, and did not routinely use continuous $ScvO_2$ monitoring as part of an EGDT protocol prior to the study. 1260 patients were randomized to receive resuscitation for early sepsis according to either an EGDT protocol or usual care. The study was designed with two rather than three arms, because protocolized standard care was felt to be too similar to usual care in the UK [53•]. The study protocol is described in Table 1. There was no difference in 90-day mortality between groups (29.5 % EGDT vs. 29.2 % usual care). Patients in the EGDT group received higher intensity of care in the first 6 h, reflected by more CVCs (92.1 vs. 50.9 %), intravenous fluids (2000 vs. 1784 cc), vasopressors (53.3 vs. 46.6 %), dobutamine (18.1 vs. 3.8 %), and red cell transfusions (8.8 vs. 3.8 %). Patients in the EGDT group also had higher Sequential Organ Failure Assessment (SOFA) scores at 6 h, required more advanced cardiovascular support, and had longer stays in the ICU. The authors concluded that EGDT is most likely not cost effective, given higher average cost in this group.

Responses to New Trials

Since publication of ProCESS, ARISE, and ProMISe, support for the re-evaluation and revision of guidelines and management bundles has burgeoned [57•, 58, 59]. The SSC has released a series of statements indicating their intention to make appropriate revisions to their guidelines and bundles based on the most recent evidence [60•, 61•]. Since the publication of ProMISe, the SSC website has been updated to read, "As the results of PROMISE are in line with the results of the ProCESS and ARISE studies, the hemodynamic bundle will be revised soon. This re-evaluation by the Surviving Sepsis Campaign is currently underway" [62]. The National Quality Forum (NQF) has voted to remove element "F," which mandates measurement of CVP and $ScvO_2$ in the patient with persistent arterial hypotension despite volume resuscitation or lactate >4 mmol/L, from its management bundle for severe sepsis and septic shock [63•]. The final revisions to the

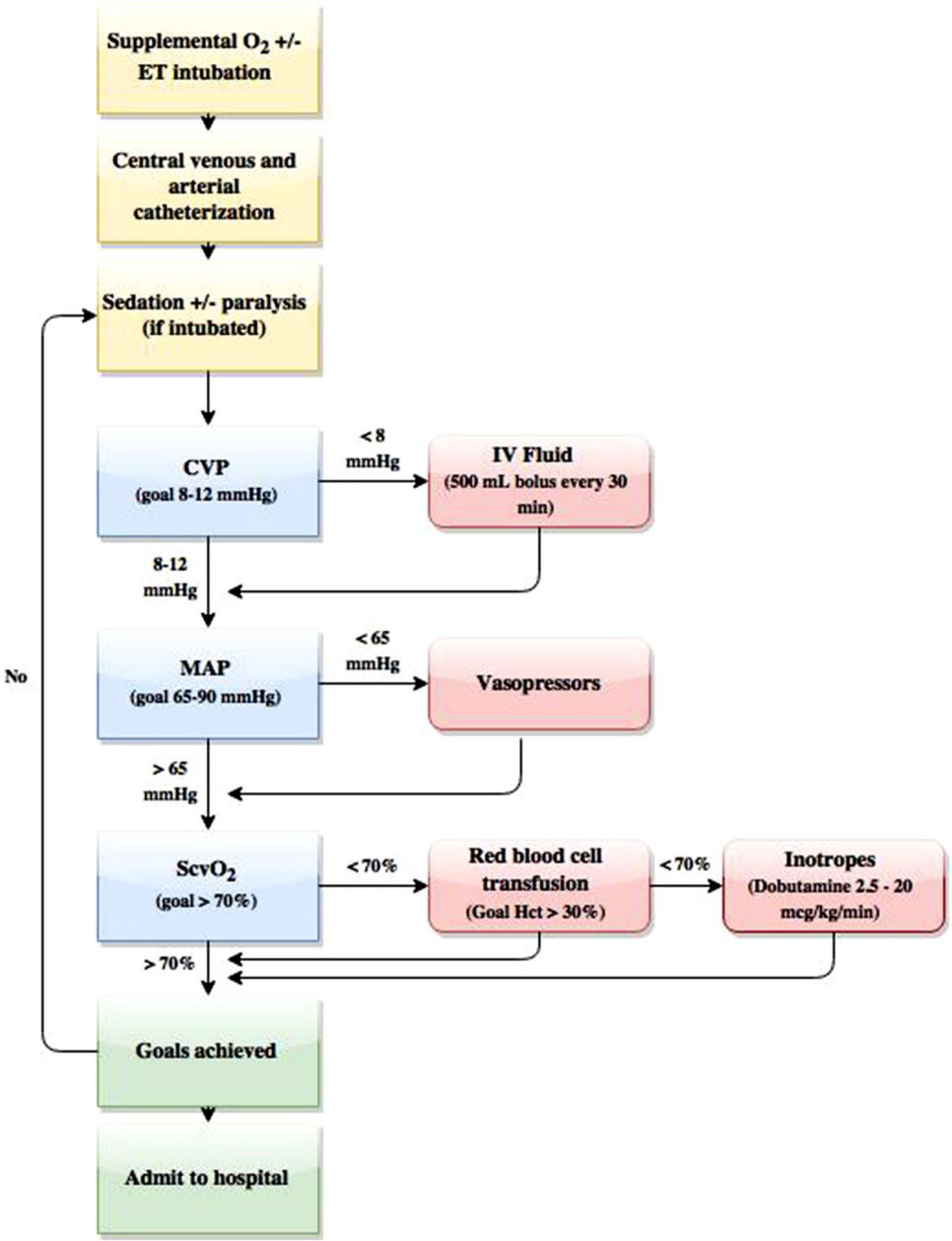

Fig. 1 Rivers EGDT protocol. Adapted from Rivers et al. [18], with permission from Massachusetts Medical Society. *ET* endotracheal; *CVP* central venous pressure; *mmHg* millimeters of mercury; *IV* intravenous; *mL* milliliters; *min* minutes; *MAP* mean arterial pressure; $ScvO_2$ central venous oxygen saturation; *Hct* hematocrit; *mcg* microgram; *kg* kilogram

bundle are still in the approval process at the time of publication of this article. Alternative questions, such as how to guide elements of usual care [59], and alternative targets for hemodynamic resuscitation such as ultrasound evaluation of inferior vena cava filling [64], have been raised and may represent the future of sepsis research.

Conclusion and Our Recommendations

Sepsis remains a significant public health problem, with increasing incidence but decreasing mortality over the most recent decades. The landmark Rivers study published in 2001 revolutionized the management of sepsis and septic shock, and brought early recognition, early antibiotic therapy, and protocolized management to the forefront. Drastic improvements in sepsis management have saved millions of lives since that time, and it is likely that usual care of sepsis has evolved to contain many of the elements of the EGDT protocol. However, certain components, such as CVP monitoring, $ScvO_2$ monitoring, and blood transfusion have remained controversial and have not been widely accepted into practice. In addition, data for elements not included in the Rivers protocol, such as lactate clearance, have emerged. A series of three trials designed with harmonized methods have recently demonstrated a

lack of survival benefit for patients with septic shock treated with EGDT compared with usual care. Based on the results of these studies, the SSC and NQF are revising their recommendations. We should look for the results of these revisions soon.

We recommend implementing a care paradigm for management of sepsis that incorporates best practices rather than a specific protocol. *Early recognition* and *triage* to an appropriate care setting are critical. At our institution, we have implemented a system on our electronic medical record that alerts practitioners when patients meet criteria for SIRS, severe sepsis, or septic shock, and directs them to a sepsis order set. We have also implemented an early response system for sepsis in the inpatient setting, whereby bedside nurses may send a lactate for any patient with clinical concern for sepsis, and if elevated, trigger a "code sepsis," which alerts the primary, ICU, and pharmacy teams. *Early, appropriate antibiotic therapy* (within 1 h of recognition) and *source control* are also uncontested and crucial aspects of sepsis management. Ideally, *cultures should be drawn before antibiotics* are given. We advocate for *early aggressive fluid resuscitation*, targeting clinical endpoints such as volume responsiveness, lactate clearance, and clinical evaluation of volume repletion, to determine adequacy of circulation and oxygen delivery, rather than use of surrogate endpoints. After the patient is volume replete, utilize *vasopressors* to support organ perfusion. Central venous catheters should be placed for patients requiring central venous access, but should not be placed in all patients as a compulsory measure. There may be a role for CVP, $ScvO_2$, inotropes, or red blood cell transfusion in specific circumstances, but the decision to use these endpoints and therapies should be made on a case-by-case basis only.

Compliance with Ethics Guidelines

Conflict of Interest Anne L. Donovan and David Shimabukuro declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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