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Current Controversies in Sepsis Management

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Semin Respir Crit Care Med. 2019;40(5):594-603.

Abstract and Introduction

Abstract

The overarching goals of early sepsis management include early recognition, appropriate antibiotic therapy and source control, maintenance of hemodynamic stability, and supportive care of organ dysfunction. Despite increasing awareness of the global burden of sepsis, and general agreement on the goals of management, there is ongoing controversy regarding the implementation of specific treatment strategies to optimize patient outcomes. This article will address five current points of controversy in the management of sepsis and septic shock. These include optimal timing of antibiotics in patients with potential sepsis, the role of glucocorticoids in septic shock, vitamin C as a novel therapy for sepsis, the ideal intravenous fluid for resuscitation, and the optimal balance of fluid resuscitation and vasopressor administration in septic shock. For each of these topics, we review relevant literature, discuss areas of controversy, and present our current approach to management.

Introduction

Sepsis is a well-established cause of morbidity and mortality worldwide, resulting in an estimated 19 million hospitalizations and 5.8 million deaths annually.[1] Beyond the initial hospitalization, survivors of sepsis are at increased risk for new morbidity, re-hospitalization, and death in the months and years afterwards.[2–4]

Despite increasing awareness of the magnitude of the problem,[5] new targeted therapies for sepsis have been limited.[6] Therefore, management has focused on early recognition, expedient treatment of the underlying infection,[7] and optimization of resuscitation.[6] Despite broad acceptance of these general principles, however, there is controversy about how best to implement them. In the article we discuss current evidence and debate regarding antibiotic timing, adjunctive corticosteroids, vitamin C, type of crystalloid, and early resuscitation strategies.

Antibiotic Timing—Should all Patients With Suspected Sepsis Receive Antibiotics Within 1 Hour?

In 2016, the Surviving Sepsis Campaign (SSC) released updated guidelines, which recommend initiating antibiotics within 1 hour for any patient with suspected sepsis or septic shock.[8] In 2018, this recommendation was also incorporated into a new 1-hour sepsis care bundle.[9]

The recommendation is supported by several large observational studies demonstrating measurable increases in mortality with every hour delay in antibiotic administration.[7,10] Additionally, delays in antibiotic delivery have been associated with increased length of stay and severity of organ dysfunction.[11–13]

However, despite the evidence that delays in antibiotics are associated with worse clinical outcomes among septic patients, there is substantial concern that striving for 1-hour antibiotic delivery in all patients with suspected sepsis may cause harm. Over the past 2 years, several editorials, perspectives, and blogposts have criticized the 1-hour threshold.[14–17] Moreover, the Infectious Diseases Society of America did not endorse the 2016 SSC guidelines, in part due to concerns that the 1-hour antibiotic goal may lead to indiscriminate antibiotic use.[18] The most compelling arguments against a 1-hour antibiotic threshold are as follows.

Diagnostic uncertainty: Most studies supporting earlier antibiotics are retrospective studies focusing on patients deemed to have sepsis at the time of hospital discharge. However, early on in a patient's course when initial antibiotic decisions must be made, clinicians are often uncertain regarding sepsis diagnosis. Physicians frequently disagree about sepsis diagnosis in standardized vignettes, [19] and in one cohort study, 43% of patients admitted to the intensive care unit (ICU) with a presumptive diagnosis of sepsis were determined to have no (13%) or only possible (30%) sepsis at hospital discharge. [20] Enforcing early treatment decisions in the setting of diagnostic ambiguity is likely to increase unnecessary antibiotic use, contributing to antibiotic-

associated harms and resistance.

Unequal benefit across patients: The current guidelines recommend a 1-hour threshold for both sepsis and septic shock. However, studies consistently show that the benefit of earlier antibiotics is greater for sicker patients—in particular, patients with septic shock requiring vasopressors. [7,10]

Distrust of observational data: Studies supporting earlier antibiotics are observational studies which adjust for differences in illness severity using regression. The opportunity for residual confounding always exists, but quantitative bias analysis suggests that a strong and common unmeasured confounder would be needed to negate the results. [7] The 2,698-patient PHANTASi trial randomized patients to antibiotic delivery in the ambulance en route to the hospital versus routine care. Despite speeding up the delivery of antibiotics by a median of 96 minutes in the intervention arm, there was no improvement in 28-day mortality. [21] This study has been interpreted by some as refuting the findings of observational studies. However, even if the hourly relative risk reduction values of earlier antibiotics were identical to those of the observational studies, one would not expect to see a significant impact on mortality in a study population of 2,698 patients with a baseline 28-day mortality rate of 8%. Rather, the lack of effect in the PHANTASi trial is likely a reflection of the lower baseline illness severity in enrolled patients.

For now, clinicians should focus their efforts on administering antibiotics within 1 hour to those patients with the most severe presentations (e.g., those with shock, respiratory failure, altered mentation, or lactic acidosis), acknowledging that the risks of inappropriately withholding antibiotics are greater in sicker patients.[22] Additional studies are needed to empirically define the threshold of illness severity below which is it safe to delay antibiotics to complete additional diagnostic evaluation to confirm or refute the presence of infection to clarify the source of infection.

Steroids in Septic Shock—Sometimes, Always, or Never?

Owing to their myriad anti-inflammatory properties, glucocorticoids have been considered for treatment of septic shock for decades. Short courses of high-dose (6,000–42,000 mg hydrocortisone equivalent over 24 hours)[23] steroids became common practice in the mid-1970s after a study by Schumer demonstrated a marked mortality benefit.[24] However, subsequent studies not only failed to replicate the results,[25–27] but also found increased mortality due to secondary infection among steroid-treated patients.[26] Two subsequent meta-analyses found no mortality benefit,[23,28] and a third meta-analysis excluding the Schumer study found decreased survival among patients treated with high-dose steroids.[29]

However, the debate did not end there (). In the 1990s, the concept of "relative adrenal insufficiency" in sepsis gained traction.[30–32] Some patients with septic shock were found to have abnormal responses to adrenocorticotropic hormone stimulation testing, and these patients seemed to have worse outcomes than those with a normal adrenal response.[33,34] There was renewed interest in using lower "stress-dose steroids" (200–300 mg of hydrocortisone daily) for longer courses to manage relative adrenal insufficiency in vasopressor-dependent septic shock but avoid immunosuppression and secondary infections.[31,35] Several small randomized controlled trials (RCTs) found decreased time to shock reversal with stress-dose steroids,[36–39] and some demonstrated decreased mortality.[36,38] Meta-analyses pooling studies of low-dose and longer course (5–7 days) corticosteroid therapy showed improvement in survival and shock reversal.[29,40] Based on these results, the 2004 SSC guidelines recommended empiric stress-dose hydrocortisone (200–300 mg daily) in patients with septic shock who require vasopressors despite adequate fluid resuscitation.[41] The largest study included in these meta-analyses, Annane et al, demonstrated both a survival benefit and improved time to shock reversal in patients who were nonresponders to an adrenocorticotropin stimulation test.[38]

Table 1. Selected randomized controlled trials evaluating glucocorticoids in severe sepsis and septic shock

Study	Location	Sample size	Steroid type and dose	Primary outcome	Major findings
Schumer, 1976[24]	United States—single center	172	Dexamethasone 3 mg/kg or methylprednisolone 30 mg/kg as a single dose (repeat at 4 h)	-Sepsis-related mortality	10.4 vs. 38.4% ($p < 0.05$)
Sprung et al, 1984[25]	United States—two centers	59	Dexamethasone 6 mg/kg or methylprednisolone 30 mg/kg as a single dose	-Shock reversal -In-hospital mortality	Shock reversal: (at 24 h) 25.6 vs. 0% ($p < 0.05$)

			(repeat)		(total) 58.1 vs. 37.5% ($p < 0.05$) In-hospital mortality: 76.7 vs. 68.8% (NS)
Bone et al, 1987[26]	United States—19 centers	382	Methylprednisolone 30 mg/kg q6h ×4	-14-d mortality -14-d shock reversal	14-d mortality: 34.0 vs. 25.3% ($p = 0.06$) 14-d shock reversal: 65.4 vs. 72.8% (NS)
VASSCSG study, 1987[27]	United States—10 centers	223	Methylprednisolone 30 mg/kg bolus then 5 mg/kg/h for 9 h	-14-d mortality	14-d mortality: 20.5 vs. 21.6% ($p = 0.97$)
Bollaert et al, 1998[36]	France—single center	41	Hydrocortisone 100 mg TID ×5 d	-7-d shock reversal -28-d mortality	7-d shock reversal: 68.2 vs. 21.1% ($p = 0.007$) 28-d mortality: 31.8 vs. 63.2% ($p = 0.091$)
Briegel et al, 1999[37]	Germany—single center	40	Hydrocortisone 100 mg bolus then 0.18 mg/kg/h infusion until shock reversal then 0.08 mg/kg/h for 6 d	-Time to shock reversal -ICU mortality	Time to shock reversal: 2 vs. 7 d ($p = 0.005$) ICU mortality: 20 vs. 30% ($p = 0.72$)
Annane et al, 2002[38]	France—19 centers	299	Hydrocortisone 50 mg q6h and fludrocortisone 50 µg daily for 7 d	-28-d mortality in ACTH nonresponders -Overall 28-d mortality -Time to shock reversal -28-d shock reversal	28-d mortality: 52.6 vs. 63.5% ($p = 0.02$) Overall 28-d mortality: 54.7 vs. 61.1% ($p = 0.09$) Time to shock reversal: 7 vs. 9 d ($p = 0.01$) 28-d shock reversal: 55.7 vs. 42.7% (NS)
Oppert et al, 2005[39]	Germany—single center	41	Hydrocortisone 50 mg/kg then 0.18 mg/kg/h infusion until shock reversal then 0.06 mg/kg/h	-Time to shock reversal -7-d shock reversal -In-hospital mortality	Time to shock reversal: 53 vs. 120 h ($p = 0.02$) 7-d shock reversal: 73 vs. 79% ($p = 0.73$) In-hospital mortality: 39 vs. 48% ($p = 0.6$)

Sprung et al, 2008[42]	United States—52 centers	499	Hydrocortisone 50 mg q6h for 5 d	-28-d mortality in ACTH nonresponders -Overall 28-d mortality -Time to shock reversal -28-d shock reversal	28-d mortality in ACTH nonresponders: 39.2 vs. 36.1% (p = 0.69) Overall 28-d mortality: 34.3 vs. 31.5% (p = 0.51) Time to shock reversal: 3.3 vs. 5.8 d (p < 0.05) 28-d shock reversal: 79.7 vs. 74.2% (p = 0.18)
Venkatesh et al, 2018[47]	Australia, United Kingdom, New Zealand, Saudi Arabia, Denmark—69 centers	3,658	Hydrocortisone 200 mg/d continuous infusion ×7 d	-90-d mortality -Time to shock reversal	90-d mortality: 27.9 vs. 28.8% (p = 0.50) Time to shock reversal: 3 vs. 4 d, (p < 0.001)
Annane et al, 2018[48]	France—64 centers	1,241	Hydrocortisone 50 mg q6h and fludrocortisone 50 μg daily ×7 d	-90-d mortality -Time to shock reversal -28-d shock reversal	90-d mortality: 43.0 vs. 49.3% (p = 0.03) Vasopressor-free days: 23 vs. 19 d (p < 0.001) 28-d shock reversal: 85.1 vs. 80.7% (p = 0.04)

Abbreviations: ACTH, adrenocorticotropic hormone; ICU, intensive care unit; TID, three times a day.

Following the 2004 SSC guidelines, a larger trial evaluating steroid therapy in septic shock was published, the CORTICUS trial (n = 499).[42] CORTICUS found no difference in 28-day mortality (34.3 vs. 31.5%, p = 0.51), regardless of corticotropin response. Time to shock reversal was faster in the steroid-treated group, but the rate of superinfection was higher.

Updated meta-analyses, including data from CORTICUS, came to differing conclusions.[43–45] Based on the available evidence, the 2016 SSC guidelines recommend intravenous (IV) hydrocortisone when adequate fluid resuscitation and vasopressors do not achieve hemodynamic stability (weak recommendation, low quality of evidence).[8]

Given the differing results of trials evaluating glucocorticoids in septic shock, variation in practice is to be expected. The PROGRESS registry is an international database including 276 contributing ICUs in 37 countries documenting use of vasopressors and steroids in patients with severe sepsis (n = 8,968).[46] It confirmed regional variability in steroid usage, with the highest rates in Europe (51.1%) and the lowest rates in Asia (21.6%). It also found that 14% of all patients received steroids despite not being on vasopressors.[46] The PROGRESS registry demonstrates that despite conflicting evidence, steroid use is widespread, including in situations (lack of vasopressor requirement) where it is not recommended.

In 2018, two large, multicenter RCTs of adjunctive glucocorticoids were published—ADRENAL (n = 3,658 patients) and APROCCHSS (n = 1,241 patients).[47,48] Whereas prior studies examined 28-day mortality, the primary outcome in both these trials was 90-day mortality. ADRENAL randomized patients to a continuous infusion of hydrocortisone (200 mg/kg) for 7 days, or until discharge from the ICU. Meanwhile, APROCCHSS randomized patients to hydrocortisone 50 mg IV every 6 hours plus fludrocortisone 50 μg daily for 7 days. (In the earlier years of

the APROCCHSS trial, patients were also randomized in a factorial fashion to activated protein C, prior to its removal from the market in 2011.)

ADRENAL found no difference in 90-day mortality.[47] However, patients randomized to steroids fared better on several secondary endpoints, including faster time to shock reversal (3 vs. 4 days, $p < 0.001$), faster time to extubation (6 vs. 7 days, $p < 0.001$), shorter ICU length of stay (10 vs. 12 days, $p < 0.001$), and lower rate of blood transfusion (37.0 vs. 41.7%, $p = 0.004$). There was no difference in new bacteremia or fungemia at day 14.[47] By contrast, APROCCHSS had lower 90-day mortality in the steroid arm (43.0 vs. 49.1%, $p = 0.03$). Secondary endpoints were likewise better in the steroid arm: greater vasopressor-free days (17 vs. 15 days, $p < 0.001$) and organ-failure-free days (14 vs. 12 days, $p = 0.003$).[48]

The conflicting mortality findings from these two studies have generated much discussion. There are several differences that could potentially explain the discrepant results. Control group mortality was substantially higher in APROCCHSS (49 vs. 29%). However, even in the sicker subset of 903 ADRENAL patients who would have met enrollment criteria for APROCCHSS, the difference in mortality was still nonsignificant, and the relative risk reduction associated with steroids was less than in APROCCHSS. Thus, differences in illness severity alone do not fully explain the discrepant results. Other potential explanations include the use of fludrocortisone, the trial location (France for APROCCHSS vs. Australia, United Kingdom, New Zealand, Saudi Arabia, and Denmark for ADRENAL), or the trial enrollment dates (2008–2015 for APROCCHSS vs. 2013–2017 for ADRENAL). Regardless of the differences in mortality, however, both studies suggest overall benefit from steroids in secondary outcomes, with no signal for increased harm.[47,48]

Since the publication of the ADRENAL and APROCCHSS trials, two updated meta-analyses have been published. The first evaluated 42 RCTs enrolling 10,194 patients and found that steroid treatment had a relative risk (RR) of 0.93 (95% confidence interval [CI]: 0.84–1.03) for short-term (28-day) mortality and a RR of 0.94 (95% CI: 0.89–1.00) for long-term (60-day to 1 year) mortality.[49] They concluded that there may be a possible small versus no reduction in mortality with steroids.[49] The second meta-analysis evaluated 37 RCTs of 9,564 patients and found decreased 28-day mortality with steroids (RR: 0.90; 95% CI: 0.82–0.98) but no difference for 90-day mortality (RR: 0.94; 95% CI: 0.85–1.03).[50] Both meta-analyses found earlier shock reversal and lower sequential organ failure assessment (SOFA) scores at day 7 with steroid treatment and neither showed a difference in rates of superinfection.[49,50] These meta-analyses both conclude that although the absolute benefit is small, there is low risk of adverse events, and therefore there is likely net benefit to low-dose glucocorticoids, particularly in the sickest patients.[49,50]

In summary, there remains controversy regarding the role of glucocorticoids in septic shock. RCTs do not show a consistent mortality benefit. However, they do show a consistent decrease in time to shock reversal with steroid treatment. Our practice is to use glucocorticoids on a case-by-case basis for patients with high or persistent (i.e., cannot down-titrate within 8–12 hours) vasopressor requirements.

Vitamin C in Sepsis

In recent years, there has been interest in evaluating the ability of vitamin C to attenuate sepsis-related organ dysfunction and mortality.[51] During critical illness, such as trauma, ischemia/reperfusion, and sepsis, cytokine release and reactive oxygen species lead to oxidative stress and tissue injury.[52,53] This can be mitigated by antioxidants such as vitamin C, but vitamin C levels are low in most patients with septic shock.[54] In animal models, vitamin C supplementation attenuated sepsis-related organ dysfunction,[55–57] and so there has been increasing interest in testing vitamin C supplementation in clinical practice. Vitamin C has a good safety profile in numerous patient populations,[57–60] although increased oxalate levels (via endogenous conversion) have been reported in some patients with standard supplementation levels (2,000 mg/day), which can increase risk of renal stone formation, particularly among men.[61,62] Also, there have been case reports of renal failure in patients who receive very high doses (e.g., 45 g/day) of vitamin C.[63,64]

Several studies have evaluated vitamin C supplementation in trauma and burn populations. In one study of a critically ill surgical population, 595 patients (91% trauma patients) were randomized to vitamin C supplementation versus standard care, and the vitamin C arm had lower rates of multiorgan failure, shorter duration of mechanical ventilation, and shorter ICU length of stay.[65] A large retrospective observational study of 4,294 trauma patients found a 28% relative risk reduction in mortality, and decreased length of stay with an antioxidant protocol including vitamin C.[66] Two small studies, one randomized and one observational, of burn patients in Japan found that high-dose vitamin C infusion (66 mg/kg/h for 24 hours) was associated with decreased fluid requirements and increased urine output, without an increase in renal dysfunction.[60,67]

With respect to sepsis management, a small (*n* = 24) phase I randomized placebo-controlled clinical trial assessed safety and tolerability of vitamin C (at 50 and 200 mg/kg/day dosings) in a medical ICU population with severe sepsis.[68] There were no adverse events with vitamin C, and reductions in SOFA score, procalcitonin, and C-reactive protein compared with controls. In a more recent randomized study in a surgical population with septic shock, patients randomized to vitamin C required lower doses and shorter duration of vasopressor therapy.[69] The proposed mechanism for this effect is that vitamin C acts as a cofactor for endogenous norepinephrine and vasopressin synthesis.[70]

In a recent publication in Chest, Marik et al performed a retrospective pre/postclinical study comparing patients treated with IV vitamin C (1.5 g every 6 hours), hydrocortisone (50 mg every 6 hours), and thiamine (200 mg every 12 hours) to matched patients treated with standard practice.[71] This particular three-drug regimen was prescribed because prior literature suggests that glucocorticoids have a synergistic effect with vitamin C in regard to antioxidant and anti-inflammatory activity.[71] Thiamine was added because thiamine deficiency has been associated with increased mortality in sepsis.[72] Moreover, thiamine deficiency increases the conversion of glyoxylate to oxalate;[73] therefore it was hypothesized that thiamine supplementation would minimize any risk of oxalate deposition conferred by the vitamin C itself.[71]

The study included a total of 94 patients split evenly between control and experimental groups. Control patients received hydrocortisone based on provider discretion (60% were treated with hydrocortisone). Patients treated with the vitamin C protocol had dramatically lower mortality—an 87% relative reduction and 32% absolute reduction in in-hospital mortality relative to the matched controls. In addition, vitamin C-treated patients had a shorter duration of vasopressor-dependent shock, a faster clearance of procalcitonin, and a lower rate of renal replacement (despite concerns about oxalate deposition in acute kidney injury with vitamin C therapy).[71]

The results from Marik et al are on one hand exciting. Vitamin C, thiamine, and hydrocortisone are inexpensive, widely available, and could be readily implemented at scale, even in lower resource settings. However, it was a small, single-center, nonrandomized study with historical controls. These factors limit the generalizability of the findings. Moreover, the effect size is implausibly large. Two recent reviews of vitamin C therapy in sepsis conclude that there is insufficient evidence to recommend changes to clinical practice.[53,57] Rather, the results of Marik et al must be replicated in a prospective, multicenter RCT before vitamin C should be used in standard practice. Fortunately, several trials are underway. The VICTAS trial is multicenter, placebo-controlled and double-blinded, with a goal recruitment of 2,000 subjects from 40 medical centers in the United States (NCT #03509350).[74] Meanwhile the Australian and New Zealand Intensive Care Society is conducting a randomized, open-label trial called VITAMINS (NCT # 03333278).[75]

"Normal" Saline Versus Balanced Crystalloids for Resuscitation

IV crystalloid solutions are ubiquitous in the hospital setting, and play an integral role in resuscitation of the septic patient. 0.9% sodium chloride (so-called "normal" saline) has long been the most common crystalloid solution used for fluid resuscitation, although practice varies by region and treating specialty.[76] However, balanced crystalloid solutions (including Ringer's lactate and PlasmaLyte) more closely approximate the composition of extracellular fluid (). In particular, the concentration of chloride in normal saline far exceeds the concentration in extracellular fluid. The popularity of normal saline was examined in a historical review by Awad et al, in which the composition of numerous early crystalloid solutions was examined.[77] 0.9% sodium chloride was first described by a Dutch chemist, Hartog Hamburger, in the late 19th century based on in vitro experiments. They postulate that its subsequent popularity despite no in vivo evidence may have stemmed from its low cost and ready availability.[77]

Table 2. Composition of commonly used crystalloid solutions

Fluid name	Normal saline (0.9% sodium chloride)	Ringer's or Hartmann's lactate	PlasmaLyte	Human plasma
Osmolarity (mOsm/L)	308	280.6	294	291
Sodium (mmol/L)	154	131	140	135–145
Chloride (mmol/L)	154	111	98	94–111
Potassium (mmol/L)		5.4	5.0	4.5–5.0

Calcium (mmol/L)		2.0		2.2–2.6
Magnesium (mmol/L)			3.0	0.8–1.0
Lactate (mmol/L)		29		1.0–2.0
Acetate (mmol/L)			27	
Gluconate (mmol/L)			23	
Bicarbonate (mmol/L)				23–27

Source: Myburgh JA, Mythen MG. Resuscitation fluids. N Engl J Med 2013;369(13):1243–1251.[76]

Despite (or perhaps because of) its widespread use, there has been increasing concern about adverse effects from normal saline, including hyperchloremic metabolic acidosis[78] and acute kidney injury.[79] A systematic review of 14 studies of 18,916 patients found a possible survival advantage with balanced crystalloids versus normal saline (90-day mortality, odds ratio [OR]: 0.78; 95% CI: 0.58–1.05) although the results were not statistically significant.[80] However, a subsequent RCT of 974 patients randomized to balanced crystalloids versus normal saline did not demonstrate any differences in mortality or adverse kidney events.[81]

In 2018, the SMART trial—the largest study of normal saline versus balanced crystalloid solutions for resuscitation of critically ill patients (n = 15,802)—was published.[82] This was a pragmatic, single-center, multiple-crossover, unblinded trial in which ICUs at a single institution were randomized to either normal saline or a balanced crystalloid on a monthly basis. The primary endpoint was a composite outcome of mortality, new renal replacement, or persistent renal dysfunction at 30 days. Patients in the balanced crystalloid group had a lower rate of the composite outcome (14.3 vs. 15.4%, p = 0.04). Likewise, 30-day in-hospital mortality was 10.3 versus 11.1%, p = 0.06.[82]

The trial included all ICU patients, but also examined prespecified subgroups by diagnosis. The effect size was greatest in patients with sepsis (OR: 0.80; 95% CI: 0.67–0.94; p = 0.01, for the development of the primary composite outcome in patients who received a balanced crystalloid).[82] Likewise, 30-day in-hospital mortality was also lower in the balanced crystalloid group (25.2 vs. 29.4%, p = 0.02).[82] Although the SMART trial had a large study population size, it was a single-center study, so needs to be validated in a multicenter trial.

Several large-scale multicenter clinical trials are currently randomizing patients to balanced crystalloids versus 0.9% sodium chloride. The BASICS trial led by the Brazilian Research in Intensive Care Network has recruited more than 7,000 of a planned 10,000 patients from 100 sites (NCT # 02875873) as of April 1, 2019.[83] The PLUS trial led by the Australian and New Zealand Intensive Care Society is also underway and has recruited 880 of a planned 8,800 patients from 50 sites (NCT #02721654).[84] Both BASICS and PLUS will have the advantage of being blinded with respect to fluid type. While we await these study results, we favor balanced solutions for the resuscitation of septic shock patients.

Fluid Heavy Versus Early Vasopressor Resuscitation Strategy

Historically, fluid resuscitation has been a cornerstone of management in septic shock, predating the advent of antibiotics.[85] In the United States in particular, a liberal fluid strategy prevails. The SSC guidelines and CMS SEP-1 measure both promote an initial 30 mL/kg fluid bolus in septic patients with shock or elevated lactate.[8,86] However, this standard practice has been driven largely by expert opinion, as many studies evaluating fluid resuscitation in sepsis are observational, and results are mixed.[87]

The physiological argument for fluid resuscitation in septic shock is to correct intravascular volume depletion which occurs as a result of capillary endothelial dysfunction and decreased systemic vascular resistance.[88] Increasing intravascular volume can increase cardiac preload and stroke volume, which in turn increases tissue perfusion.[89] The physiological argument for restricting fluids in sepsis shock is that fluids only transiently increase intravascular volume, because they do not correct endothelial dysfunction, and ultimately lead to pathologic edema which can result in organ dysfunction and worse functional outcomes.[90,91] Meanwhile, vasopressors increase systemic vascular resistance, which increases cardiac preload without edema;[92] however, vasopressors increase the risk for several complications, including tachyarrhythmias, myocardial ischemia, mesenteric hypoperfusion, and skin

necrosis.[93–96]

In animal models of sepsis, crystalloid bolus improves perfusion and survival,[97,98] but also results in a paradoxical increase in vasopressor requirements.[99] Extrapolating these findings to humans is difficult. Whereas humans tend to develop hyperdynamic shock with increased cardiac output and decreased systemic vascular resistance, many animal models develop hypodynamic shock.[85]

In a seminal RCT, Rivers et al evaluated "early goal-directed therapy" (EGDT)—a septic shock resuscitation strategy which included a 500-mL crystalloid bolus every 30 minutes to achieve central venous pressure of 8 to 12 mm Hg.[100] Patients randomized to EGDT developed less severe organ dysfunction and had improved survival. Thus, this strategy was recommended by the 2004 SSC guidelines and widely adopted into practice.[41] However, as EGDT is a multicomponent protocol, it is impossible to tease out the independent impact of early fluid bolus.[85]

Three multicenter RCTs (ProMISe, ARISE, and ProCESS)[101–103] subsequently evaluated EGDT versus usual care (and also "protocol-based usual care" in the ProCESS study). In all three RCTs, mortality was indistinguishable between patients randomized to EGDT versus usual care.[101–103] A patient-level meta-analysis likewise found no difference in mortality, but did show an increase in ICU resource utilization.[104] Importantly, however, the median fluid bolus prior to randomization was 2 L (just over 27 mL/kg), and total resuscitation in the first 6 hours was 4 to 5 L for patients in both treatment arms.

The 2016 SSC guidelines recommend that at least 30 mL/kg of crystalloid fluids be given within the first 3 hours of presentation for patients with sepsis-induced hypotension (strong recommendation, low-quality evidence).[8] While RCT data to support an early 30 mL/kg bolus are lacking, the amount was viewed as standard practice based on the prerandomization fluid resuscitation in ProMISe, ARISE, and ProCESS.[101–103]

However, as the pendulum has swung toward fluid-heavy resuscitation, there have been growing concerns among the critical care community about the potential harms of fluid boluses.[105] In RCTs of postresuscitation fluid management, fluid-heavy strategies are associated with increased ventilator days, increased ICU length of stay, and increased severity of organ dysfunction.[106,107] Multiple observational studies suggest that a positive fluid balance is associated with increased mortality, even after adjustment for potential confounders.[108–112] Finally, RCTs in lower resource settings—where there is less ability to manage potential negative sequelae of fluid resuscitation—have shown increased mortality with fluid resuscitation. The FEAST study of pediatric patients in Africa was stopped early due to increased mortality in the treatment arm.[113] Similarly, a RCT of an early resuscitation protocol in Zambia revealed increased mortality in the treatment arm, with a number needed to harm of just seven patients.[114] Taken together, these studies have led many clinicians to question the necessity of early fluid bolus in patients with sepsis-induced hypotension.[85]

From a practical standpoint, clinician reliance on fluid resuscitation has also been influenced by a reluctance to administer vasopressors prior to obtaining central IV access, which takes time to establish. Central administration is preferred due to risk of tissue injury from extravasation, although the frequency of this complication has been poorly quantified.[115] Moreover, newer studies suggest vasopressors can be given peripherally,[115–117] with lower rates of complication than previously described for central venous catheters.[118]

One of the main goals of fluid resuscitation or vasopressor support is to maintain adequate blood pressure. The SSC guidelines recommend targeting a mean arterial pressure (MAP) of 65 mm Hg for initial resuscitation (strong recommendation, moderate quality of evidence).[8] RCTs that have randomized patients to a target MAP of 65 mm Hg versus 85 mm Hg have found similar lactate levels, renal function and urine output, and oxygen delivery.[119,120] However, in some RCTs, higher MAP targets have been associated with higher rates of new-onset atrial fibrillation,[121] and increased mortality among patients 75+ years of age.[122]

Given concerns about excessive fluid resuscitation in early septic shock management, several ongoing RCTs are assessing early resuscitation practices.

The REFRESH pilot RCT was a multicenter, unblinded trial which enrolled 99 patients with suspected infection and systolic blood pressures of <100 mm Hg after administration of 1000 mL of balanced crystalloid fluid from Australian emergency departments.[123] Patients were randomized to protocolized standard care versus restricted volume management. Standard care included a second 1,000 mL bolus, followed by additional 500 mL boluses if deemed necessary based on perfusion parameters until euvolemia was judged to have been achieved, followed by initiation of norepinephrine if MAP was <65 despite indicators of euvolemia. Patients in the experimental arm received norepinephrine immediately if MAP was <65. Fluid boluses of 250 mL each hour up to 1,000 mL total and IV fluids at maintenance rate (maximum 150 mL/h) could be given at physician discretion. In both groups, norepinephrine was administered peripherally until central access could be obtained. The primary outcome was total fluid

administered at 6 hours.[123] Patients in the restricted volume arm received less IV fluid compared with standard care (2,387 vs. 3,000 mL at 6 hours, $p < 0.001$; 3,543 vs. 4,250 mL at 24 hours, $p = 0.005$) and had earlier initiation of vasopressors, but no difference in the total time spent on vasopressors.[124] A larger study with goal enrollment of 3,000 patients is being planned.[125]

Meanwhile, in the United States, the CLOVERS trial sponsored by the PETAL Network is underway.[89] CLOVERS is a multicenter, randomized, unblinded trial of liberal fluid management (additional 2 L of fluid prior to consideration of vasopressors) versus restrictive fluid management (immediate initiation of vasopressors) in patients with persistent sepsis-induced hypotension after 1 to 3 L of IV fluids.[89] The primary outcome is 90-day mortality.

Finally, in the United Kingdom, the 65 trial, assessing the clinical effectiveness of permissive hypotension (MAP target 60–65 mm Hg during vasopressor therapy) versus usual care in critically ill patients aged 65+ years, recently finished recruiting patients in March 2019.[126] The primary outcome is all-cause 90-day mortality.

While we await results from the above studies, we favor an initial 30 mL/kg fluid bolus in patients with sepsis-induced hypotension or lactic acidosis, followed by prompt initiation of vasopressors for patients who are still hypotensive (via peripheral access until central access can be established). We generally target a MAP goal of 65, except for patients who are known to have a lower baseline MAP.

Conclusion

In summary, sepsis is a heterogeneous response to infection that requires a multifaceted approach to management. There remains uncertainty in how to optimize multiple aspects of sepsis management to improve patient outcomes. Antibiotics should be given promptly when there is clinical suspicion of sepsis, and as soon as possible in the cohort of patients with the greatest illness severity. Glucocorticoids are effective in reducing time to shock reversal, but their role in reducing mortality is less certain. We favor their use in patients with high or persistent vasopressor requirements. There are ongoing RCTs to better evaluate the potential role for vitamin C in sepsis. We are awaiting the results of these trials before incorporating vitamin C supplementation into our practice. Content and quantity of fluid resuscitation are undergoing rigorous evaluation after longstanding historical rather than evidence-based practice. While additional data accrue, we favor balanced fluids, an initial 30 mL/kg bolus for sepsis-induced hypotension or lactic acidosis, and prompt initiation of vasopressors for patients who remain hypotensive. We look forward to learning the results of multiple ongoing and planned RCTs to help refine our early sepsis management.

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Funding
This work was supported by K08 GM115859 (H.C.P.) from the National Institute of Health. The views expressed in the article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the U.S. government.

Semin Respir Crit Care Med. 2019;40(5):594-603.