Review

Septic Shock
Advances in Diagnosis and Treatment

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IMPORTANCE Septic shock is a clinical emergency that occurs in more than 230 000 US patients each year.

OBSERVATIONS AND ADVANCES In the setting of suspected or documented infection, septic shock is typically defined in a clinical setting by low systolic (≤90 mm Hg) or mean arterial blood pressure (≤65 mm Hg) accompanied by signs of hypoperfusion (eg, oliguria, hyperlactemia, poor peripheral perfusion, or altered mental status). Focused ultrasonography is recommended for the prompt recognition of complicating physiology (eg, hypovolemia or cardiogenic shock), while invasive hemodynamic monitoring is recommended only for select patients. In septic shock, 3 randomized clinical trials demonstrate that protocolized care offers little advantage compared with management without a protocol. Hydroxyethyl starch is no longer recommended, and debate continues about the role of various crystalloid solutions and albumin.

CONCLUSIONS AND RELEVANCE The prompt diagnosis of septic shock begins with obtainment of medical history and performance of a physical examination for signs and symptoms of infection and may require focused ultrasonography to recognize more complex physiologic manifestations of shock. Clinicians should understand the importance of prompt administration of intravenous fluids and vasoactive medications aimed at restoring adequate circulation, and the limitations of protocol-based therapy, as guided by recent evidence.

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Shock is life-threatening circulatory failure with inadequate tissue perfusion.[1] The typical presentation is hypotension (low systolic ≤90 mm Hg) or mean arterial blood pressure (≤65 mm Hg) accompanied by clinical signs of hypoperfusion. Historically, shock was attributed to a neurologic response to injury, vasomotor changes to the circulation, or a problem of missing blood.[2] By the mid- 20th century, Blalock and Weil organized shock into distinct constructs: cardiogenic, obstructive, hypovolemic, or vasogenic.[3,4] Although these categories are valuable teaching concepts, the diagnosis of shock is far more complex. We focus this review on septic shock, which is the most common cause of noncardiogenic shock and has several of the Blalock and Weil physiologic constructs at the same time.[5] Septic shock occurs in more than 230 000 US patients each year, with more than 40 000 US deaths annually. A recent Burden of Diseases article found that primary risk factors for septic shock (ie, infection) is the fifth leading cause of years of productive life lost due to premature mortality.[6] Given the public health burden, we review advances in diagnosis, treatment, and areas of uncertainty in septic shock from January 2010 to June 2015.

Methods

We performed a review of the MEDLINE and the Cochrane Database of Systematic Reviews from 2010 to 2015 using specific search strategies. Our primary search used the terms *shock, septic shock, diagnosis,* and *treatment,* among others. We provide search strings and Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram in eAppendix (in the Supplement). We restricted articles to adult (age ≥18 years) human data reported in the English language only. We screened articles published between January 1, 2010, and June 1, 2015, and excluded opinion articles, commentaries, case series, and cohort studies—focusing on randomized clinical trials (RCTs), meta-analyses, systematic reviews, and clinical practice guidelines. After screening 8329 titles and abstracts, more articles were identified for full-text review, after which manual review of bibliographies generated additional references. A total of 181 articles were manually reviewed, of which 35 were selected with relevant content (eFigure in the Supplement). We selected only articles deemed to provide major advances in the diagnosis or treatment of septic shock. We considered sources of bias in these articles

and defined areas of uncertainty as those in which the evidence conflicted. We used the American Heart Association classification of recommendations to grade the quality of evidence (grade A, data from many large RCTs; grade B, data from fewer, smaller RCTs, careful analyses of nonrandomized studies, or observational registries; and grade C, expert consensus).

Results

Major Diagnostic Advances

A conceptual framework for the diagnosis of shock has multiple domains including an initial evaluation of the etiology and clinical features, assessment of the primary hemodynamic manifestations, and consideration of alterations in cellular biology and the degree of local tissue injury. Major advances and areas of uncertainty within these domains (**Table 1**) will be discussed.

Initial Evaluation

At the bedside, a clinician begins by asking, "Is this patient in shock?" Consensus guidelines for septic shock agree on core diagnostic elements including suspected or documented infection accompanied by arterial hypotension and evidence of tissue hypoperfusion (eg, oliguria, altered mental status, poor peripheral perfusion, or hyperlactemia).[10,11] Yet the requirement for adequate fluid resuscitation, absence of vasopressors, or thresholds for blood pressure vary across shock definitions. In fact, a recent European Society of Intensive Care Medicine (ESICM) consensus statement suggests shock may present in the absence of hypotension.[12] There is no reference standard for the bedside diagnosis of shock. Rather, observational studies report how mortality varies across combinations of shock features from 29% to 46%.[13]

If shock is present, the clinician must determine the inciting cause by asking, "What just happened?" Such clinical risk factors will guide immediate intervention. And although severe infection may be evident, it is often more difficult to recognize. We found no changes to the typical clinical approach to the diagnosis of infection in septic shock during our review. However, many biomarkers and blood culture–independent, molecular diagnostics are undergoing study to help discriminate sterile inflammation from infection.[14]

The primary physiologic manifestations of shock should be assessed, although they are unlikely to fit simply into the Blalock and Weil framework. For example, patients with septic shock will develop myocardial depression in as many as 30% of cases.[5] A prompt assessment of the relevant mechanisms driving the shock state is imperative because patient delay prior to care and immediate therapy will complicate the evolving presentation.

Hemodynamic Monitoring for the Diagnosis of Septic Shock

Hemodynamic monitoring devices may clarify the primary physiologic manifestations in septic shock. The clinical usefulness of these monitoring devices can result from the device, the algorithm linked to the device, or the static/dynamic target of the algorithm (eTable 1 in the Supplement). As such, there is a lack of consensus and considerable debate about the role of these devices.

Table 1. Major Advances in the Diagnosis and Treatment of Traumatic and Septic Shock

Action	Caveat
Diagnostic	
Clinical diagnosis is the criterion standard: Typically, systolic blood pressure ≤90 mm Hg or mean arterial blood pressure ≤65 mm Hg or >40-mm Hg decrease from baseline; Poor peripheral perfusion, low urinary output, altered mentation, elevated lactate	Normotensive shock with isolated hyperlactemia needs clarity; Lactate and systolic blood pressure thresholds are uncertain; Biologic phenotyping may be promising but not yet feasible in real time or tested in randomized clinical trials
Pulmonary artery catheterization and continuous monitoring of central venous oxygen saturation not recommended for routine diagnosis	May have a role in right ventricular dysfunction, complex cases with diagnostic uncertainty
Focused ultrasonography is suggested if there is concern for overlapping hemodynamic manifestations of shock	Practical, easy to use, and recommended by expert consensus[7]
Arterial pulse contour analysis	Awaiting randomized clinical trials for patient outcomes; Requires controlled mechanical ventilation and sinus rhythm
Treatment	
Prompt fluid bolus is recommended (500-1000 mL) with appropriate safety limits	Fluid therapy with balanced crystalloids vs albumin is suggested based on meta-analyses,[8,9] while specific fluid comparisons undergo additional randomized clinical trials
Norepinephrine is recommended as a first-line vasopressor	Vasopressin may spare norepinephrine at higher doses
Hydroxylethyl starch may cause harm	Increases mortality and worsens renal outcomes among survivors
Protocolized early goal-directed therapy is not superior to usual care in early septic shock	Tested among patients with prompt shock recognition, intravenous fluid boluses, and early antibiotics
Low-dose corticosteroids to be considered for vasopressor-dependent shock	Dosing regimen and timing of discontinuation remains controversial

Invasive Hemodynamic Monitoring

Decades ago, the standard care of shock patients included invasive devices like the pulmonary artery catheter (PAC) or continuous central venous oxygen saturation ($ScvO_2$) catheterization. The PAC can estimate cardiac output and measure mixed venous oxygen saturation, among other parameters, to refine the etiology of shock and potentially affect patient outcomes. A 2013 Cochrane review of 2923 general intensive care unit (ICU) patients (proportion in shock not reported) found no difference in mortality comparing PAC vs no PAC management.[15] A secondary analysis of the Fluid and Catheter Treatment Trial of 774 patients with acute respiratory distress syndrome, among whom 40% were in shock, confirmed that PAC increases hospital costs with no change in mortality.[16] The continuous $ScvO_2$ catheter is an alternative to the PAC but had no advantage over lactate clearance when included in a recent RCT testing resuscitation of septic shock (**Table 2**).[17] Consensus recommends against the placement of PAC in routine management of shock and suggests its use only in the minority of cases with right ventricular dysfunction or severe acute respiratory distress syndrome.[12] Meanwhile, the United States has largely reduced PAC use over the past 15 years.[22]

Table 2. Major Diagnostic Advances in Septic Shock in Selected Trials

Source by Category	Diagnostic Management	Type of Evidence	No. of Studies	No. of Patients (% With Shock)	Setting	Conclusion	Grade Evidence[a]
Invasive Hemodynamic Device							
Rajaram et al,[15] 2013	PAC vs no PAC	Systematic review/ meta-analysis	5	2923 (NA)	ICU	No change in mortality for PAC	B
Clermont et al,[16] 2011	PAC vs central venous catheter	RCT	1	335 (39)	ICU	Greater hospital costs with no change in mortality for PAC	B
Jones et al,[17] 2010	$ScvO_2$ catheter vs lactate clearance	RCT	1	300 (100)	Emergency department/ICU	Equivalent hospital mortality rate for $ScvO_2$ vs lactate	B
Noninvasive Hemodynamic Device							
Labovitz et al,[7] 2010	Bedside ultrasonography	Guideline				Recommended in initial assessment for all undifferentiated shock	C
Zhang et al,[18] 2015	Noninvasive vs invasive device	RCT	1	350 (47)	ICU	No change in 28-d mortality with management by noninvasive device	B
Richard et al,[19] 2015	Noninvasive vs invasive device	RCT	1	60 (100)	ICU	No change in time to shock resolution from noninvasive device	B
Biomarkers of Local Tissue Injury							
Jansen et al,[20] 2010	Lactate-guided therapy every 2 hours for 8 hours vs lactate at admission only	RCT	1	348 (19)	ICU	No change in unadjusted hospital mortality but reduced ICU length of stay using lactate every 2 hours	B
Dellinger et al,[21] 2013	Lactate as target for resuscitation	Guideline				Weak recommendation based on low-quality evidence (grade 2C)	C

Abbreviations: ICU, intensive care unit; NA, not available; PAC, pulmonary artery catheter; RCT, randomized clinical trial; $ScvO_2$, continuous central venous oxygen saturation catheter.

[a] Grade of evidence was assessed using the American Heart Association classification of recommendations. Grade A indicates data from many large RCTs; grade B, data from fewer, smaller RCTs, careful analyses of nonrandomized studies, or observational registries; and grade C, expert consensus.

Noninvasive Hemodynamic Monitoring

The physiology underlying shock can be further clarified using minimally or noninvasive techniques such as arterial pulse contour analysis or focused echocardiography. Calibrated pulse contour analysis devices provide continuous estimations of cardiac output, beat-to-beat stroke volume, and pulse pressure variation, among other parameters. In one trial, 388 hemodynamically unstable patients in 3 ICUs were randomized to a minimally invasive hemodynamic monitoring device for 24 hours vs usual care.[23] With no protocol linked to the device, the intervention groups did not differ in resolution of hemodynamic instability at 6 hours or mortality. Two small, randomized trials also found no difference in 28-day mortality and time to shock resolution comparing pulse contour analysis–guided management vs other strategies.[18,19] Ongoing studies[24] are testing noninvasive estimates of stroke volume variation linked to fluid resuscitation protocols in septic shock. A recent systematic review did find benefit of hemodynamic optimization by pulse contour analysis in patients undergoing high-risk surgery.[25] The application of pulse contour analysis in shock patients outside the operating theater is practically limited by the requirement for controlled mechanical ventilation, adequate arterial pressure waveform, and the absence of arrhythmias.

Focused ultrasonograpy can help discern central hemodynamics and the etiology of shock in undifferentiated patients.[26] It can reveal right and left cardiac chamber size and contractility, pericardial fluid, and inferior vena cava size and collapsibility suggestive of hypovolemia, among other features. At the time of this publication, our search revealed no rigorous RCTs of focused cardiac ultrasonography affecting patient-centered outcomes in septic shock. Yet, recent guidelines and consensus statements recommend focused ultrasonography as best clinical practice in the initial assessment of hemodynamically unstable patients with septic shock (Table 2).[7,12]

Markers of Tissue Injury

Systemic markers of local tissue injury can suggest that organs are under stress in shock, including blood lactate level, base deficit, tissue oxygen saturation by near-infrared spectroscopy, or various microcirculatory changes. These tests may refine a clinical diagnosis but also serve as targets during optimization and stabilization of shock (Table 2).[26] Lactate levels are not currently included in the 2001 ESICM/SCCM (Society of Critical Care Medicine) consensus definition of septic shock, but suggested in the 2014 ESICM consensus panel on circulatory shock.[10,12] Serial lactate measurements are nonetheless widely used in practice,[27] but the specific threshold for diagnosing shock and its role in monitoring remains unknown. One open-label randomized clinical trial in 4 ICUs tested a protocol targeting a 20% reduction in lactate every 2 hours on top of recommended resuscitation guidelines. They found a significant reduction in only a secondary outcome (ICU length of stay), but included few patients in shock (19%).[20] The use of near-infrared spectroscopy or tissue oxygen saturation to either diagnosis or manage septic shock states has not been evaluated in clinical trials of patient centered outcomes during our review period.

Areas of Uncertainty

From a biologic perspective, no definition or cut point for shock is perfect, and guidelines, quality improvement, and trial enrollment deserve a uniform definition that balances sensitivity and specificity (**Box**). Not all patients with shock have a classic presentation, and cases on the margin may be as important as those that are clinically overt. For example, patients with normal arterial pressure and hyperlactemia may have similar outcomes to overt shock,[28] but hyperlactermia could be either hypoxia-induced microcirculatory hypoperfusion, high glycolytic flux from an inflammatory response, or impaired clearance.[28,29] The host response to shock is also complex, with both proinflammatory and antiinflammatory reactions at the local and systemic level.[30] Cases could be further identified using biologic phenotypes, although none are widely accepted. Some candidate approaches include immunophenotyping, genome-wide expression mosaics, or clinico-metabolomic profiles.[31-33] Third, a consensus definition for shock is needed across different phases of care (eg, from prehospital to emergency department to ICU). Major trials in each setting use different criteria for lactate and shock,[34,35] leading to uncertainty about optimal treatment.

Box. Areas of Uncertainty in the Diagnosis and Treatment of Septic Shock

Diagnostic

No consensus definition for shock across locations of care
- Thresholds for systolic blood pressure, lactate, and adequacy of fluid resuscitation lack consensus during prehospital care and in the emergency department and intensive care unit; this may hinder epidemiology, trial enrollment, and quality improvement efforts

Inconsistent definition for cryptic shock
- Isolated hyperlactemia with normal systolic blood pressure may reflect tissue hypoperfusion, and little is known about the epidemiology and outcomes of cryptic shock; may also be referred to as occult or normotensive shock

Biologic phenotypes of shock
- Novel biologic phenotypes are proposed using genetic, molecular, and metabolomic markers, but these lack validation and testing in clinical trials

Treatment

Choice and timing of fluid administration
- Both albumin and balanced crystalloid solutions may be superior in meta-analyses, but direct comparisons in randomized clinical trials of early shock are needed

Targets for hemodynamic optimization
- The ideal resuscitation target (static vs dynamic; microcirculation vs regional vs peripheral) is an urgent knowledge gap that may be different for different phases of resuscitation in shock

De-escalation and removal of fluid
- The optimal method and timing of fluid removal after shock resuscitation requires further study, with options including diuretics, ultrafiltration

Major Therapeutic Advances

Many factors contribute to a steadily improving case-fatality rate in shock,[36] including early recognition and prompt intervention. A sample treatment algorithm for septic shock typically proceeds through rescue, optimization, stabilization, and de-escalation of care (**Figure**).[26] Although rescue steps may differ depending specifically on the inciting cause, adult patients with septic shock typically receive immediate intravenous access, fluid administration, vasopressors, and care directed at restoring adequate circulation. We briefly review major advances in these topics (Table 1).

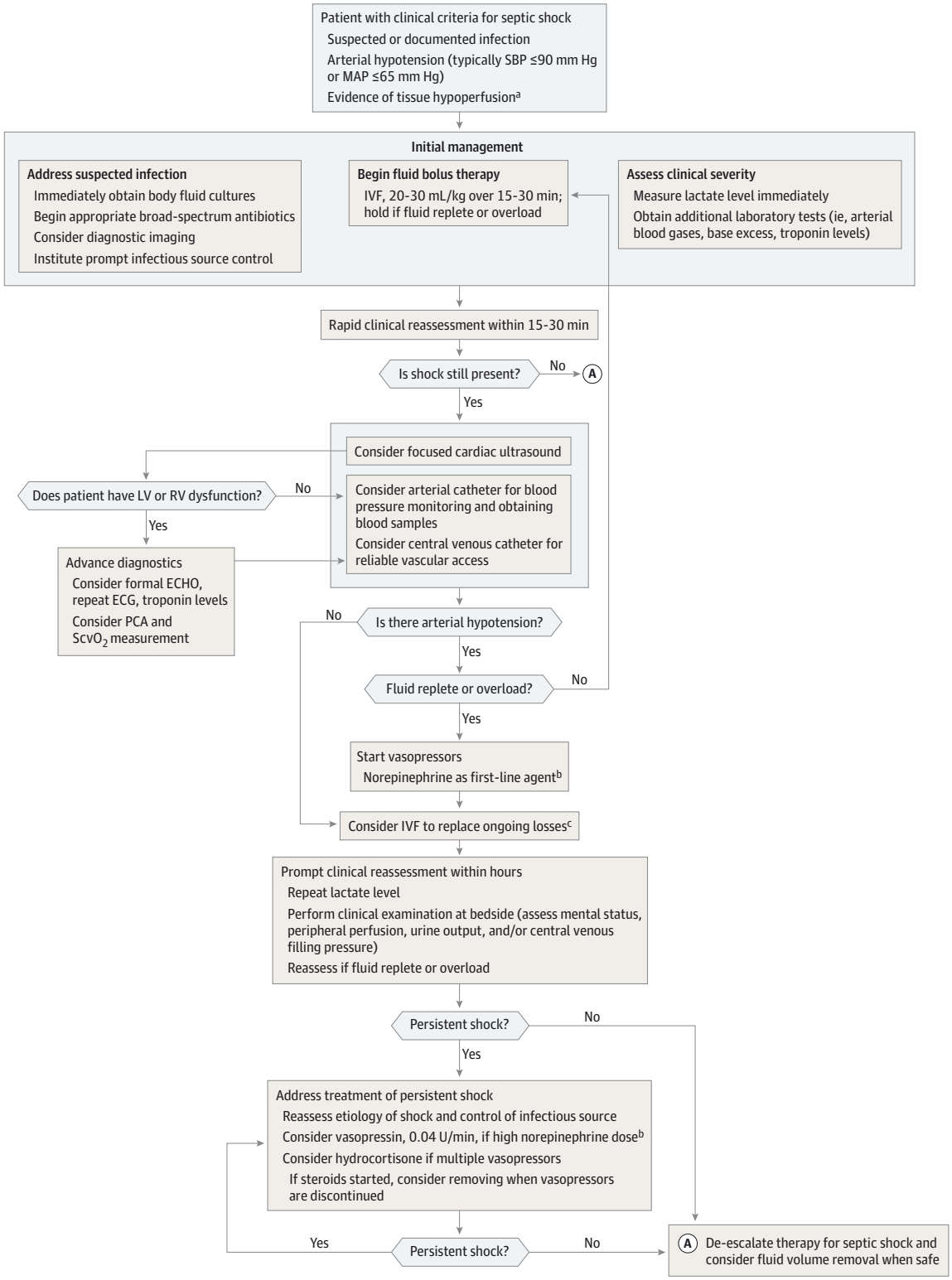
Crystalloids

There are many choices for crystalloids in septic shock.[37] Although there is variability across crystalloid solutions in tonicity and inorganic/organic anions, such that few entirely resemble plasma,[38] normal saline is widely used in the United States.[37] A sequential-period observational trial tested chloride-liberal vs chloride-restrictive fluids for all fluid therapy in a single ICU over 18 months, in which 10% of patients were in shock. They found an increase in injury and failure class (RIFLE-defined [Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease]) acute kidney injury during the chloride-rich period.[39] Others leveraged the indirect comparisons between 6 different fluids in 14 distinct RCTs in a network meta-analysis of 18 916 patients with sepsis. They report that balanced crystalloids were somewhat superior to normal saline (odds ratio [OR] = 0.78 [95% CI, 0.58-1.05]), although with low-moderate confidence and without reporting among the subset with septic shock.[8] The same authors report no difference in rate of renal replacement therapy for this comparison in a separate study.[9] Given the persistent equipoise, the SPLIT (Saline vs Plasma-Lyte 148 for Intensive Care Fluid Therapy) study is testing balanced crystalloids vs 0.9% normal saline.[40,41]

Colloids

Colloid solutions, such as albumin, dextran, gelatins, or hydroxyethyl starch, are the most widely used fluids in critically ill patients, although with variability across ICUs and countries.[42] Clinicians' choice among colloids is influenced by availability, cost, and desire to minimize interstitial edema. Many believe a greater intravascular volume is achieved from colloids in shock,[38] but the effects are modified by their molecular weight and concentration, and endothelial changes during inflammation.[43] The ALBIOS (Albumin Italian Outcomes Study) trial randomized nearly 1800 patients in 100 ICUs with severe sepsis to albumin with crystalloids vs crystalloids alone and found no difference in 28-day mortality.[44] A post hoc analysis restricted to patients with septic shock suggested a 28-day mortality benefit from albumin (relative risk [RR], 0.87 [95% CI, 0.77-0.99]), without affecting safety. The CRISTAL (Colloids vs Crystalloids for the Resuscitation of the Critically Ill) trial compared crystalloids with colloids in 2857 adults in shock in 57 ICUs, finding no difference in 28-day mortality or renal outcomes.[45] These studies build on data from the 6S (Scandinavian Starch for Severe Sepsis/Septic Shock) and CHEST (Crystalloid vs Hydroxyethyl Starch) trials in severe sepsis,[46,47] which together randomized more than 7000 patients to reduced concentration 6% hydroxyethyl starch 130/0.4 vs crystalloids, and found no mortality benefit at 90 days to 1 year,[48] but observed increases in the rate of renal replacement therapy. These studies outline no clear benefit (or harm) from albumin in septic shock, and continue to support harm from low concentration hydroxyethyl starch solutions (**Table 3**).

Figure. Proposed Algorithm for Treatment of Septic Shock



ECG indicates electrocardiogram; ECHO, echocardiogram; IVF, intravenous fluids; LV/RV, left ventricular/right ventricular; MAP, mean arterial pressure; PCA pulse contour analysis; SBP, systolic blood pressure; $ScvO_2$, continuous central venous oxygen saturation.

[a] Tissue hypoperfusion typically manifests as altered mentation, low urinary output, poor peripheral perfusion, and/or hyperlactemia (≥2.0 mmol/L).

[b] Norepinephrine may not always be the first choice in setting of tachycarrythmias or atrial fibrillation; consider adding vasopressin for norepinephrine rates that exceed 15 µg/kg/min.

[c] The choice for fluid repletion and type will be refined by ongoing safety checks for pulmonary edema/fluid overload, metabolic derangements from unbalanced crystalloids, and ongoing losses.

Table 3. Major Therapeutic Advances in Septic Shock in Selected Randomized Clinical Trials

Source by Category	Setting (Study Duration)	No. of Patients (% in Septic Shock)	Intervention	Control	Primary Outcome	Relative Risk (95% CI) for Primary Outcome	Conclusions	Grade of Evidence[a]
Fluids[b]								
Caironi et al,[44] 2014	100 Mixed ICUs (2008-2012)	1810 (63)	20% Albumin and crystalloids	Crystalloids alone	28-d Mortality	1.00 (0.87-1.14)	No difference in 28-d or 90-d mortality	B
Perner et al,[47] 2012	26 Mixed ICUs (2009-2011)	798 (84)	Hydroxylethyl starch 130/0.42	Ringer acetate	6-mo Mortality	1.12 (0.98-1.29)	No difference in 6-mo or 1-y mortality	A[c]
Annane et al,[45] 2013	57 Mixed ICUs (2003-2012)	2857 (54)	Gelatins, dextrans, hydroxylethyl starch, or 4% or 20% albumin	Isotonic, hypertonic saline, Ringer lactate	28-d Mortality	0.96 (0.88-1.04)	No difference in 28-d mortality	A[c]
Myburgh et al,[46] 2012	23 Mixed ICUs (2009-2012)	7000 (13)[d]	6% Hydroxylethyl starch 130/0.4 in 0.9% sodium chloride	0.9% Sodium chloride	90-d Mortality	1.06 (0.96-1.18)	No difference in 90-d mortality; increased risk of renal replacement therapy with hydroxylethyl starch	A[c]
Perner et al,[47] 2012	26 Mixed ICUs (2009-2011)	798 (84)	Hydroxylethyl starch 130/0.42	Ringer acetate	90-d Mortality	1.17 (1.01-1.36)	Greater 90-d mortality and renal replacement therapy with hydroxylethyl starch	A[c]
Vasopressors								
De Backer et al,[49] 2010	8 Mixed ICUs (2003-2007)	1679 (62)	Dopamine	Norepinephrine	28-d Mortality	1.17 (0.97-1.42)	No difference in mortality but more adverse events and arrhythmias with dopamine	B
Protocols								
Yealy et al,[35] 2014	31 Emergency departments (2003-2007)	1341 (100)	EGDT vs protocolized standard care	Usual care	60-d In-hospital mortality	1.04 (0.82-1.31)	No difference in 28-d, 90-d, or 1-y mortality for protocol-based vs usual care or in post hoc subgroups	A
Mouncey et al,[50] 2015	56 Centers (2011-2014)	1260 (100)	EGDT	Usual care	90-d Mortality	1.01 (0.85-1.20)	No difference in 90-d mortality, greater cost with EGDT	A
Peake et al,[51] 2014	51 Centers (2008-2014)	1600 (100)	EGDT	Usual care	90-d Mortality	0.98 (0.80-1.21)	No difference in 90-d mortality for EGDT vs usual care or any a priori subgroup	A
Jones et al,[17] 2010	3 Emergency departments (2007-2009)	300 (82)	Lactate-guided EGDT	$ScvO_2$ catheter-guided EGDT	In-hospital mortality		Noninferiority of using lactate-guided EGDT vs $ScvO_2$ catheter	B
Asfar et al,[52] 2014	29 Centers (2007-2009)	776 (100)	High mean arterial pressure target (80-85 mm Hg)	Low mean arterial pressure target (65-70 mm Hg)	28-d Mortality	1.07 (0.84-1.38)	No difference in 28-d mortality using a lower mean arterial pressure target	B
Andrews et al,[53] 2014	1 Center (2012)	112 (NR)	Modified EGDT	Usual care	In-hospital mortality	1.06 (0.79-1.41)	Trial stopped due to increased hypoxemia in intervention group	B
Holst et al,[54] 2014	32 ICUs (2011-2013)	1005 (100)	Hemoglobin threshold 7.0 g/dL	Hemoglobin threshold 9.0 g/dL	90-d Mortality	0.94 (0.78-1.09)	No difference in 90-d mortality or secondary outcomes with lower hemoglobin threshold	B

Abbreviations: EGDT, early, goal-directed therapy; ICU, intensive care unit; NR, not reported; RCT, randomized clinical trial; $ScvO_2$, central venous oxygen saturation.

[a] Grade of evidence assessed using the American Heart Association classification of recommendations. Grade A, data from many large RCTs; grade B, data from fewer, smaller RCTs, careful analyses of nonrandomized studies, or observational registries; and grade C, expert consensus.

[b] Excluded Siegemund et al[55] (BASES [Basel Starch Evaluation in Sepsis]) trial as results not yet publicly reported.

[c] Grade A evidence for null treatment effect (or harm) for HES vs other fluids for both mortality and renal replacement therapy outcomes.

[d] In the CHEST trial, all 7000 enrolled were critically ill patients, of whom 29% had sepsis and 45% were in shock; maximum potential septic shock accrual is estimated as 913 patients.

Several meta-analyses have found consistent results. A network meta-analysis using direct and indirect comparisons in severe sepsis found evidence of greater of mortality with hydroxyethyl starch vs crystalloid (RR, 1.13 [95% CI, 0.99-1.30]; high confidence), and no difference for albumin (RR, 0.83 [95% CI, 0.65-1.04]; moderate confidence) or gelatin vs crystalloids (RR, 1.24 [95% CI, 0.61-2.55]; very low confidence). Comparison of albumin vs hydroxyethyl starch indirectly favored albumin

(RR, 0.73 [95%CI, 0.56-0.95]; moderate confidence).[8] Additional meta-analyses in sepsis have confirmed a greater rate of renal failure or all-cause mortality comparing hydroxylethyl starch to other solutions, although no meta-analysis evaluated patients strictly in shock (eTable 2 in the Supplement).[9]

Vasopressors

For shock that is persistent despite adequate circulating volume, vasopressors are recommended to maintain perfusion of vital organs. Vasopressors such as norepinephrine, epinephrine, dopamine, and phenylephrine differ in their half-life, β- and α-adrenergic stimulation, and dosing regimens. Recent evidence comes from the SOAP II trial (Sepsis Occurrence in Acutely Ill Patients), a double-blind RCT in 8 centers testing norepinephrine vs dopamine in 1679 undifferentiated ICU patients with shock, of whom 62% had sepsis (Table 3).[49] Although no difference was observed in 28-day mortality or in predefined septic shock subgroup, arrhythmias were significantly greater with dopamine. A meta-analysis of 6 trials in septic shock found a greater mortality with dopamine vs norepinephrine (RR, 1.12 [95% CI, 1.01-1.20]; eTable 3 in the Supplement).[56] As a result, expert opinion[26] and consensus guidelines[21] recommend norepinephrine as the first vasopressor choice in septic shock. Vasodilatory shock in sepsis can also be reversed with the endogenous hormone, vasopressin. The administration of vasopressin can reduce norepinephrine dose and has been found to be safe, albeit with no mortality benefit, in subsequent meta-analyses.[57,58] Consensus guidelines suggest vasopressin at a fixed dose (0.03-0.04 U/min) in patients without contraindication who are taking a norepinephrine dose of at least 0.15 μg/kg/minute. There may be select indications for alternative vasopressors such as when tachyarrythmias, limb ischemia, or other adverse effects dictate.[1]

Protocols

Current guidelines and an expert opinion recommend that clinicians incorporate a structured approach to resuscitation in septic shock.[21,30] The principles of initial management include rapid recognition, prompt antibiotics, obtainment of cultures, and control of the infection source. After these initial steps, new evidence suggests that protocol-based, early goal-directed therapy (EGDT) may confer little survival advantage compared with clinical assessments of organ perfusion and management without a protocol (Table 3).[35,50,51] The PROCESS (Protocol-Based Care for Early Septic Shock) trial found that 60-day in-hospital mortality for protocolized standard care (18.2%) was similar to usual care (18.9%) and protocolized early goal directed therapy (21%) among 1341 patients enrolled in 31 US emergency departments.[35] The ARISE (Australasian Resuscitation in Sepsis Evaluation) trial confirmed this finding, reporting that among 1600 early septic shock patients in 51 centers in Australia and New Zealand that 90-day mortality was similar between EGDT and usual care.[51] The PROMISE (Protocolized Management in Sepsis) trial enrolled 1260 patients in 56 hospitals in England, finding that EGDT offered no mortality benefit in early septic shock, but increased treatment intensity and cost.[50] These findings were consistent for multiple a priori subgroups—including those stratified by demographics, severity of illness, time to enrollment, and lactate. Multiple subsequent meta-analyses of PROCESS, ARISE, and PROMISE trials have confirmed that EGDT offers no mortality benefit while increasing health care utilization and ICU admission in well-resourced countries.[59-62] Notably, these studies enrolled patients with distinct physiology and improved preenrollment resuscitation than prior research.[63] Modified versions of EGDT were also tested in lower-resourced settings with no change in outcome.[53]

Given the challenge of studying multistep protocols,[64] the SepsisPAM (Sepsis and Mean Arterial Pressure) trial tested a single element in shock protocols—the mean arterial pressure target. Among 776 septic shock patients in France, a high mean arterial pressure target (80-85 mm Hg) conferred no survival advantage at 28 days (hazard ratio, 1.07 [95%CI, 0.84-1.38]; $P = .57$) compared with a low mean arterial pressure target (65-70 mm Hg).[52] Notably, the subgroup of patients with a history of hypertension had lower rates of acute kidney injury and renal replacement therapy in the high mean arterial pressure target group. Beyond this study, a meta-analysis confirmed the paucity of evidence to help guide blood pressure management in septic shock.[65] The original EGDT protocol also targeted a high hemoglobin threshold of greater than10 g/dL. The recent Scandinavian TRISS (Transfusion Requirements in Septic Shock) trial demonstrated in 1005 septic shock patients that a lower threshold (7 g/dL) resulted in similar 90-day mortality as a higher threshold (9 g/dL) and reduced transfusions by 50%.[54]

Adjuncts

Many adjunctive treatments in septic shock target perturbations in the innate immune response and coagulation cascade. Yet few trials demonstrate benefit, most notably those of activated protein C and the TLR4 antagonist, Eritoran.[66,67] However, specific adjuncts like corticosteroids in septic shock continued to be widely used.[68] A large negative clinical trial[69] and a conflicting systematic review in 2009 extended the debate about whether corticosteroids improve 28-day mortality or shock reversal.[70] A recent meta-analysis reported on 8 trials of approximately 1000 patients finding that hydrocortisone (≤300 mg/d) was associated with no significant change in 28-day mortality yet reduced the odds of shock over 7 and 28 days.[71] Consensus guidelines recommend low-dose glucocorticoid therapy only in patients with vasopressor-dependent septic shock and removal once vasopressors are no longer needed.[21] A more extensive discussion of the trade offs of corticosteroid therapy is found elsewhere.[68]

Areas of Uncertainty

The prompt administration of intravenous fluid is a ubiquitous therapy in septic shock, yet many aspects of this treatment are unknown. First, the timing (ie, prehospital vs emergency department) and effectiveness of fluid bolus therapy has come under question.[72] Second, no trial has directly compared balanced vs unbalanced crystalloids in early septic shock. Third, the ideal resuscitation target remains an important knowledge gap, particularly since recent evidence suggests there may be a disconnect between the augmentation of systemic hemodynamics and different measures of regional perfusion.[73] Additionally, the overuse of fluids in septic shock is common.[74] More work is needed to understand the optimal timing and method of fluid removal.

Discussion

The typology of shock is informed by classic animal experiments in specific physiologic states, such as crushing injury, hypovolemia, or profound hemorrhage. This has led to a clinical approach to shock based on aggressive fluid resuscitation and supported by evidence from small, single-center clinical trials.[63] The underlying heterogeneity of shock is now more apparent as modern pragmatic trials enroll large numbers of patients with complex physiology. Although unusual cases will always be difficult to define, the variety of enrollment criteria in recent trials highlights that experts lack consensus even about the core elements of shock.[75] This issue is magnified as clinicians and researchers attempt to treat shock at its earliest presentation. Ultimately, a simple strategy to promptly diagnose shock using easy-to-measure clinical features may help lower overall mortality in the majority of cases. However, those cases with complex physiology or occult presentations may require a more precise approach informed by biologic phenotypes and advanced hemodynamic monitoring.

This review has several limitations. First, we restricted our search to the past 5 years, and excluded articles prior to 2010. Second, we addressed the prompt diagnosis and treatment of shock, and various diagnostic tools or treatments will have different benefit or harm at later stages.[76] Third, guidelines for shock are infrequently updated—a process less nimble to new evidence and challenged by trials where usual care is equivalent to the intervention. Finally, many studies in this review enrolled patients without septic shock. These studies included patients with sepsis who did and did not have varying degrees of organ dysfunction. Thus, the rate of shock across studies ranged from 13% to 100% and few meta-analyses could focus entirely on septic shock due to trial heterogeneity.

Clinical Bottom Line

Diagnosis

- Septic shock is an emergency event requiring prompt clinical diagnosis.
- Focused ultrasonography may assist in early shock diagnosis and alert clinicians to underlying physiologic disturbance.
- Invasive (eg, pulmonary artery catheter) and noninvasive hemodynamic monitoring devices (eg, pulse contour analysis) are only recommended for use in select subgroups of septic shock.
- Lactate is widely used in shock assessment but deserves further evaluation of its specific role in diagnostic and treatment algorithms.

Treatment

- The first step in the treatment of septic shock is promptly addressing suspected or documented infection.
- Protocol-guided fluid resuscitation in septic shock is not superior to management by clinical assessment without a protocol.
- A variety of crystalloid fluids or albumin are recommended in septic shock, while hydroxyethyl starch solutions may be associated with worse outcomes.

Conclusions

Septic shock is a clinical emergency. A prompt diagnosis of septic shock begins with a focused history and physical examination for signs and symptoms of infection and may require focused ultrasonography to recognize complex physiologic manifestations of shock. Clinicians should understand the importance of prompt administration of intravenous fluids aimed at restoring adequate circulation, vasoactive medications, and the limitations of protocol-based therapy, as guided by recent evidence.

ARTICLE INFORMATION

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