The Decision-Making Process in Sepsis and Septic Shock

7

Michelle H. Scerbo and Laura J. Moore

Introduction

Despite increased attention, research, and dedicated task forces, sepsis continues to be problematic in surgical patients. Severe sepsis and septic shock are the leading cause of death in non-cardiac Intensive Care Units (ICUs), costing $24.3 billion [1] and contributing to 17 % of all hospital deaths per year in the United States [2]. A recent analysis of the American College of Surgeons National Surgical Quality Improvement Project (NSQIP) Database demonstrated that sepsis and septic shock are ten times more frequent and have a higher associated mortality in surgical patients compared with perioperative myocardial infarction and pulmonary embolism [3]. Further, surgical patients account for nearly a third of all sepsis patients [4].

This is particularly concerning in the elderly patients, who have prolonged hospital stays, more diagnoses upon discharge, and higher mortalities from sepsis compared with younger patients [2, 4]. With an anticipated increase in the incidence of sepsis of 1.5 % per year and the projected growth of the elderly population in the United States, this is expected to increase the number of estimated cases from 934,000 in 2010 to 1.1 million in 2020.

Risk factors for death from sepsis in the general surgery population include age greater than 60, the need for emergency surgery, and the presence of comorbid diseases [5]. When septic shock occurs in surgical patients, it has an associated mortality of 39 % in emergent cases and 30 % in elective cases [5].

Despite these harrowing figures and increasing rates of hospitalization and mortality, recent evidence-based advancement in critical care practices have led to a decrease in case fatality rate for severe sepsis [6].

The tenets to successfully treating a patient with sepsis rely on early recognition, early interventions, and the implementation of the proper evidence-based care. However, early recognition and consistent implementation of evidence-based care are not consistently accomplished.

M.H. Scerbo, M.D.
Department of General Surgery, The University of Texas Health Science Center at Houston, 6431 Fannin Street, MSB 4.331, Houston, TX 77030, USA
e-mail: Michelle.l.scerbo@uth.tmc.edu

L.J. Moore, M.D. (✉)
Department of General Surgery, The University of Texas Health Science Center at Houston, 6431 Fannin Street, MSB 4.331, Houston, TX 77030, USA

Texas Trauma Institute, Memorial Hermann Hospital, 6431 Fannin Street, MSB 4.292, Houston, TX 77030, USA
e-mail: Laura.j.moore@uth.tmc.edu

R. Latifi, *Surgical Decision Making*, DOI 10.1007/978-3-319-29824-5_7

Definitions of Systemic Inflammatory Response Syndrome, Sepsis, Severe Sepsis, Septic Shock, and Surgical Sepsis

Balk and Bone originally defined sepsis syndrome as the systemic response to infection [7]. The American College of Chest Physicians and the Society of Critical Care Medicine (ACCP/SCCM) held a consensus conference in 1991 to define the systemic inflammatory response syndrome (SIRS), sepsis, septic shock, and multiple organ dysfunction syndrome (MODS) [8]. The goal was to provide definitions in order to facilitate the ease of early detection, implementation of early therapeutic intervention, and the standardization of research in order to compare protocols and therapeutic interventions. Subsequently, the terms septicemia and septic syndrome were recommended to be dropped from the lexicon of those describing SIRs, sepsis, severe sepsis, septic shock, and MODS. A decade later, these terms were revisited to expand the list of signs and symptoms of sepsis [9].

SIRS and Sepsis

SIRS is the clinical manifestation of the innate immune system. It is intentionally nonspecific and can be a result of infectious or noninfectious pathology, including pancreatitis, traumatic injury, hemorrhagic shock, or ischemia. Sepsis is SIRS in response to an infection. The definitions of SIRS, sepsis, severe sepsis, and surgical sepsis are outlined in Table 7.1.

Table 7.1 Definitions of SIRS, sepsis, severe sepsis, septic shock, and MODS

		Criteria
SIRS	*Two or more of the following*	
	Body temperature	<36 °C (96.8 °F) or >38 °C (100.4 °F)
	Heart rate	>90 beats per minute
	Respiratory rate	>20 breaths per minute
	OR	
	Hyperventilation	Arterial carbon dioxide tension ($PaCO_2$) <32 mmHg
	Leukocyte count	<4000 cells/μL
		OR >12,000 cells/μL OR
		The presence of >10 % immature neutrophils (bands)
Sepsis	SIRS as a result of an infection	
Severe sepsis	Sepsis associated with:	
	Organ dysfunction	See Table 7.2
	OR	
	Hypoperfusion	*One of the following*:
		1. Urine output < 0.5 mg/kg of IBW
		2. MAP < 65 mmHg
		3. GCS < 14
		4. Serum lactate ≥ 4 mmol/L
	OR	
	Hypotension	Systolic blood pressure <90 mmHg or a reduction of >40 mmHg from baseline in the absence of other causes of hypotension
Septic shock	Sepsis with acute cardiac dysfunction	Acute cardiac dysfunction (must meet both criteria):
		1. IV fluid challenge ≥ 20 mL/kg of IBW, CVP ≥ 8 mmHg, or PCWP ≥ 12 mmHg
		2. Requires, vasopressors to increase MAP to ≥ 65 mmHg
MODS	Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention	

MAP mean arterial pressure, *IV* intravenous, *IBW* ideal body weight, *CVP* central venous pressure, *PCWP* pulmonary capillary wedge pressure

Table 7.2 Criteria for organ function for defining severe sepsis

Organ system	Criteria	Caveat
Neurologic	Glasgow Coma Scale (GCS) < 13	Upon recognition of sepsis
	OR	
	Deteriorating GCS to <13	Within recognition of sepsis
Pulmonary	Ratio of Arterial oxygen tension (PaO_2) to fraction of inspired oxygen (F_IO_2) < 250	<200 if the lung is the primary site of infection and PCWP is not suggestive of fluid overload (<18 mmHg)
Renal	*One of the following*:	Cutoffs are despite adequate volume resuscitation, which is defined as one of the following:
	1. Urine output < 0.5 mL/kg for ≥1 h	• Minimum IV fluid infusion of 20 mL/kg of IBW
	2. Increase in serum creatinine at least 0.5 mg/dL from in baseline within 24 h of starting resuscitation	• CVP ≥8 mmHg or greater
	3. Increase in serum creatinine ≥0.5 mg/dL during the first 24 h of sepsis management	• PCWP ≥12 mmHg
Hematologic	*One of the following*:	Coagulation abnormalities must be in the absence of chronic liver disease
	1. INR > 1.5	
	2. Platelet count < 80,000 μL	
	3. ≥50 % decrease in platelet count in the first 24 h of instituting sepsis resuscitation	
Tissue hypoperfusion	Lactate > 4 mmol/L	

IV intravenous fluid, *IBW* ideal body weight, *CVP* central venous pressure, *PCWP* pulmonary capillary wedge pressure, *INR* international normalized ratio

Severe Sepsis

Severe sepsis is defined as SIRS with the presence of an infection and evidence of acute organ dysfunction. Criteria for organ dysfunction by system are listed in Table 7.2.

Septic Shock

Septic shock is the progression of severe sepsis to include acute cardiac dysfunction. The criteria for acute cardiac dysfunction includes vasopressor requirement for maintenance of MAP above 65 mmHg despite adequate volume resuscitation. These parameters are more specifically defined in Table 7.1.

Surgical Sepsis

The most recent conference of the ACCP/SCCM did not define surgical sepsis [9]. The authors of this text define surgical sepsis as (1) SIRS plus an infection within 14 days or a major surgical procedure or (2) SIRS plus an infection requiring surgical intervention for source control. A major surgical procedure is any procedure requiring general anesthesia for more than 1 h.

Management of the Septic Patient

The work of Rivers and Colleagues over a decade prior to the publication of this text has largely changed the way that sepsis is identified and managed. The original trial consisted of 263 patients in the emergency department who were randomized to standard therapy or early (within 6 h) goal-directed therapy. Implementation of this early goal-directed therapy (EGDT) showed a decrease in 28 day (49 % compared to 33 %) and 60 day (57 % compared to 44 %) mortality ($p < 0.05$). This study coined the terms "golden hours of resuscitation," referred to as the first 6 h for the

Table 7.3 Early goal-directed therapy sepsis bundles

Sepsis bundles
Sepsis resuscitation bundle (initiate immediately and complete within 6 h)
Measure serum lactate
Obtain blood cultures prior to administering antibiotics
Administer broad-spectrum antibiotics within
• 3 h (ED admission)
• 1 h (non-ED ICU admission)
If hypotensive (SBP <90 mmHg) and/or lactate >4 mmol/L
• Infuse a minimum of 20 mL/kg crystalloid or colloid equivalent
• Include vasopressors if initial fluid resuscitation does not maintain a MAP ≥65 mmHg
If septic shock and/or initial lactate >4 mmol/L
• Goal CVP ≥ 8 mmHg
• Goal $ScvO_2 \geq 70$ % or $SvO_2 \geq 65$ %
Sepsis management bundle (initiate immediately and complete within 24 h)
Administer low-dose steroids for septic shock
Maintain inspiratory plateau pressures <30 cm H_2O
Maintain glucose ≥ lower limit of normal but <150 mg/dL (8.3 mmol/L)

Used with permission from Kreiner LA. Early management of sepsis, severe sepsis, and septic shock in the surgical patient. In Common Problems in Acute Care Surgery. Moore LJ, Turner KL, Todd SR, eds. New York: Springer Science+Business Media; 2013

"resuscitation bundle" and first 24 h for the "management bundle." The goal is to perform all indicated tasks 100 % of the time within the first 6 h for the sepsis resuscitation bundle or first 24 h for the sepsis management bundle upon the diagnosis of severe sepsis. The components of these bundles are outlined in Table 7.3.

Management Goals for Sepsis, Severe Sepsis, and Septic Shock

The goals for managing a patient with sepsis, severe sepsis, or septic shock are on a continuum that is reflective of the critical status of the patient. Concordantly, all patients will need the initial steps, but the latter will only apply to the more critically ill.

Goal 1: Screen for Sepsis and Identify Sepsis Early

Sepsis Screening

Rivers et al. emphasized the importance of early intervention during the "golden hours" of sepsis [10]. Early recognition of sepsis is paramount to preventing patient morbidity and mortality; however, surveys of ward nurses and physicians reveal this to be a difficult task [11, 12]. Rivers et al. was further corroborated by Kumar and colleagues, who demonstrated that administration of appropriate antimicrobial therapy within the first hour of documented hypotension was associated with a survival rate of 80 % from septic shock. The authors additionally revealed that each additional hour delay in therapy was associated with an average decrease in survival by 7.6 % [13]. These interventions cannot be expeditiously employed without first identifying sepsis. Therefore, the Surviving Sepsis Campaign advocates the routine screening for sepsis to facilitate early identification of sepsis and early implementation of sepsis therapy (Grade 1C) [14]. A shorter time to implementation of evidence-based therapies has been shown to improve outcomes and decrease sepsis-related mortality [15]. Of note, the ideal screening interval has not been determined. Using SIRS criteria to screen for sepsis has proven impractical and insensitive [16, 17], and it is even more challenging in a perioperative patient. The early signs and symptoms, including tachycardia, tachypnea, and hyper- or hypothermia are nonspecific, particularly in a postoperative patient who is also subject to pain, perioperative fluid shifts, sensible fluid losses, and narcotic administration. Additional indicators of sepsis, including oliguria and altered mental status, are also often attributed to volume imbalance or narcotic administration. When these signs are misinterpreted, this causes delays in the implementation of early therapy, which can lead to increased (>30 %) likelihood of mortality.

A sepsis screening tool has been developed by the author of this text for screening specifically in a surgical population (Fig. 7.1). Validation in nearly 5000 surgical ICU patients has demonstrated

SICU Bedside Nurse SIRS score

patient label

04162007

current heart rate _____ time _____
T min _____ time _____
T max _____ time _____
current resp rate _____ time _____
latest WBC count _____ date, time _____

points	0	1	2	3	4
heart rate (bpm)	70 - 109		55 – 69 110 – 139	40 - 54 140 - 179	≤ 39 ≥ 180
T (°C) min max	36 – 38.4	34 – 35.9 38.5 – 38.9	32 – 33.9	30 – 31.9 39 – 40.9	≤ 29.9 ≥ 41
resp rate (br / min)	12 - 24	10 – 11 25 - 34	6 - 9	35 – 49	≤ 5 ≥ 50
latest WBC (kcell / mm^3)	3 – 14.9	15 – 19.9	1 – 2.9 20 – 39.9		≤ 1 ≥ 40
score (total points)					

If SIRS score ≥ 4, then notify SICU Nurse Practitioner to complete sepsis screening form.

□ SICU
□ overflow □ MICU □ NICU □ CCU

Completed by: _____.RN Date / time: _____

Fig. 7.1 Sepsis screening tool. *SICU* surgical intensive care unit, *SIRS* systemic inflammatory response syndrome, *resp* respiratory, *WBC* white blood cell count, *MICU* medical intensive care unit, *NICU* neuro intensive care unit, *CCU* cardiac care unit. (Used with permission from Moore LJ, Jones SL, Kreiner LA, et al. Validation of a screening tool for the early identification of sepsis. J Trauma. 2009;66(6):1539–1546; discussion 1546–1547)

a sensitivity of 96.5 %, specificity of 96.7 %, positive predictive value of 80.2 %, and a negative predictive value of 99.5 %. This has been similarly validated in general surgical floor patients as well as trauma patients [18, 19]. The sepsis screening tool has been implemented in a three step tool which includes (1) initial score calculation of sepsis screening score by the bedside nurse, (2) notification of the mid-level provider for a score of four or greater for investigation of the physiologic derangements (Fig. 7.2), and (3) notification of the surgical intensivist and implementation of a sepsis management protocol in the case that sepsis is suspected. Implementation of this three step tool has been demonstrated to decrease mortality from 35.1 to 23.3 % in surgical patients [18].

Goal 2: Initiate Resuscitation Immediately Upon Recognition of Sepsis and Prior to Transfer to Higher Level of Care

Monitoring and Invasive Devices

Establish Intravenous (IV) Access

Upon the identification of sepsis, two large-bore peripheral IV catheters should be placed for initiation of fluid resuscitation and administration of antibiotics. If the patient has merely sepsis (i.e., no evidence of tissue hypoperfusion or end-organ dysfunction), a large-bore peripheral IV is appropriate. In the case that the patient has evidence of tissue hypoperfusion, end-organ dysfunction, or a peripheral IV cannot easily be obtained, a

SICU Nurse Practitioner/Resident Physician Sepsis Screening

1. Vascular access?

Yes No

type	dialysis	triple / quad	PICC	port	tunneled	other (IV, art)
date placed						
site						
local finding						
blood culture finding						

Suspicion of:

line infection?

Yes No

2. Clinical pulmonary infection score (CPIS)

Variable		points
temperature (°C)	time (hhmm)	
36.5 – 38.4		0
38.5 – 38.9		1
>39.0 or <36.0		2
blood leukocyte count (# per mm^3)	time (hhmm)	
4,000 – 11,000		0
<4,000 or >11,000		1
tracheal secretions	time (hhmm)	
small		0
moderate		1
large		2
purulent (add 1 point if purulent)		+1
oxygenation (PaO_2/FiO_2)	time (hhmm)	
≥240 or presence of ARDS		0
<240 and absence of ARDS		2
chest radiograph	time (hhmm)	
no infiltrate		0
patchy or diffuse infiltrate		1
localized infiltrate		2

score

Intubated / mech vent support?

Yes No

date intubated:

pneumonia?

Yes No

3. Abdomen

recent abdominal surgery?	Yes	No
abdominal pain?	Yes	No
abdominal distention?	Yes	No
purulent drainage from surgical drains?	Yes	No
intolerance to enteral nutrition?	Yes	No

abdominal infection?

Yes No

4. Skin / soft tissue

erythema / drainage from other surgical site?	Yes	No
site		

cellulitis / soft tissue infection?

Yes No

5.Urinary tract

urinary catheter?	Yes	No
date placed		
latest urinalysis / urine culture results		

UTI?

Yes No

6. other site

site	

other infection?

Yes No

Completed by: _____ Date / time: _____

Fig. 7.2 Two-part Sepsis screening tool. *SICU* surgical intensive care unit, *SIRS* systemic inflammatory response syndrome, *resp* respiratory, *WBC* white blood cell count, *PICC* peripherally inserted central catheter, *IV* intravenous, *art* arterial, *ARDS* acute respiratory distress syndrome, *UTI* urinary tract infection. (Used with permission from Moore LJ, Jones SL, Kreiner LA, et al. Validation of a screening tool for the early identification of sepsis. J Trauma. 2009;66(6):1539–1546; discussion 1546–1547)

central venous catheter (CVC) should be placed in order to expeditiously administer fluid.

Establish a Baseline

If it has not been done already, a complete blood count should be obtained to assess changing white blood cell (WBC) and platelet count. A baseline serum lactate should be sent upon the identification of sepsis, with a repeat measurement drawn 4 h later to monitor the progress of resuscitation. In addition, a baseline Creatinine should be drawn to assess for kidney injury and an INR should be assessed to determine if the patient has evidence of coagulation dysfunction.

Monitor Hemodynamic Parameters

CVCs can be used to monitor central venous pressure (CVP) and central venous oxygen saturation ($ScvO_2$). These measurements can be used to guide the administration of intravenous fluids, vasopressors, blood products and inotropes to target mean arterial pressure (MAP), CVP, and $ScvO_2$. CVCs placed into the subclavian vein have been demonstrated to have fewer infectious complications compared to the internal jugular and femoral veins [20].

If the vasopressors are required to maintain an adequate blood pressure, then an arterial line should be place to allow for titration of drips. The routine use of a pulmonary artery catheter is not always needed as there are less invasive and more dynamic measurements, such as stroke volume variation (SVV) or continuous transesophageal doppler, that can provide the practitioner with similar information in regards to preload. SVV has limited interpretation in the case of arrhythmias or in patients on mechanical ventilation with either low tidal volume ventilation or spontaneous respirations [21–23].

Monitor Urine Output

Strict measurement of urinary output should always occur when sepsis is suspect or recognized. In severe sepsis and septic shock, a Foley catheter should be inserted to reliably measure urinary output and guide fluid resuscitation. Persistence of acidosis, electrolyte imbalances, or oliguria is an indication for renal replacement therapy. If a patient needs renal replacement therapy, placement of dialysis catheters in the subclavian vein should be avoided as it has been demonstrated to be associated with stenosis and preclude the placement of permanent dialysis access in the future [24]. The Stuivenberg Hospital Acute Renal Failure (SHARF) study demonstrated that continuous and intermittent renal replacement therapies for treatment of acute kidney injury had similar effects on mortality (62.5 % intermittent, 58.1 % continuous, $p=0.430$) [25]. A patient with labile blood pressures will tolerate continuous renal replacement therapy better than intermittent therapy.

Therapy (Sepsis, Severe Sepsis, and Septic Shock)

Fluid Resuscitation

The goal of initial resuscitation is to restore intravascular volume. According to the Frank-Starling curve, administering fluid increases the stroke volume until an optimal preload is obtained. The endpoints of fluid resuscitation are list in Table 7.4.

Initial fluid resuscitation should begin with a 30 cm^3/kg (ideal body weight, IBW) bolus of crystalloid. There are no randomized controlled trials demonstrating the superiority of crystalloids or colloids in surgical patients with sepsis. The Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) trial randomized 2857 medical (~70 %) and sur-

Table 7.4 Endpoints of fluid resuscitation

	Endpoint	Caveat
Central venous pressure (CVP)	8–12 mmHg	Nonintubated
	12–15 mmHg	Mechanically ventilated [26]
Mean arterial pressure (MAP)	≥65 mmHg [27]	
Urine output	≥0.5 mL/kg/h	
Central venous oxygen saturation ($ScvO_2$)	≥70 %	
OR		
Mixed venous oxygen saturation (SvO_2)	≥65 % [10]	

gical ICU patients with hypovolemic shock secondary to sepsis (54 %), trauma, or neither, to volume resuscitation with either colloids or crystalloids. There was no difference in the primary outcome of all-cause 28-day mortality between the two groups. Colloids were associated with a reduction in the all-cause 90-day mortality (30.7 % vs. 34.2 %; number needed to treat = 29). Although this suggests a lack of harm with the use of colloids as the resuscitation fluid in septic shock, the authors caution interpreting this findings as anything other than exploratory, mainly because of the null findings at 28 days [28]. These findings were additionally found in the Effects of Voluven on Hemodynamics and Tolerability of Enteral Nutrition in Patients with Severe Sepsis (CRYSTMAS) trial, conducted in patients with septic shock, which demonstrated no difference in mortality with hydroxyethyl starch (HES) compared with 0.9 % Normal Saline (NS) (31 % vs. 25.3 %, $p = 0.37$); however, this study was underpowered to detect the 6 % difference in absolute mortality observed [29].

The Saline versus Albumin Fluid Evaluation (SAFE) study randomized 6997 ICU patients (18 % with severe sepsis) to receive either albumin or normal saline for fluid resuscitation. No difference in mortality was identified between the two groups (20.9 % vs. 21.1 %, Relative Risk 0.99, 95 % Confidence Interval 0.91–1.09). Evaluation of the patients with severe sepsis revealed a non-significant trend towards reduced mortality in the albumin group (Relative Risk of death 0.87, 95 % Confidence Interval 0.74–1.02) [30].

The trend of improved mortality with the use of albumin as a resuscitation fluid has been subsequently investigated in two trials. In the Volume Replacement with Albumin in Severe Sepsis (ALBIOS) trial, 1818 patients in 100 Italian ICUs with severe sepsis or septic shock were randomized to receive both 20 % albumin and crystalloid or crystalloid alone. The patients receiving albumin continued to receive daily IV albumin to maintain a goal serum albumin of ≥3 g/dL while both groups received crystalloid for further volume expansion as necessary. The authors found no difference in all-cause 28- or 90-day mortality with the administration of albumin to maintain target serum levels; however, the patients receiving albumin had a shorter duration of vasopressors or inotropes by 1 day ($p = 0.007$) [31]. The Early Albumin Resuscitation during Septic Shock study (France) has been completed as of 2011, but had not yet reported outcomes at the time of publication of this text. [32].

While the benefit of colloids or crystalloids continues to be investigated, it is well understood that the use of hydroxyethyl starch (HES) solutions should be avoided. The 6S Trial is a multicenter, parallel-group, blinded trial in which 804 patients with severe sepsis were randomized to receive either 6 % HES 130/0.42 (Tetraspan) or Ringer's acetate. The 6 % HES group had increased 90-day mortality (51 % vs. 43 % $p = 0.03$) and renal replacement requirements (22 % vs. 16 % $p = 0.04$). The increased need for renal replacement therapy in patients that received 6 % HES was further demonstrated in a trial randomizing 7000 patients to 6 % HES vs. (7.0 % vs. 5.8 %; Relative Risk 1.21; 95 % Confidence Interval 1.00 – 1.45; $p = 0.04$) [33]. Finally, a Cochrane Review of 42 studies including 11,399 patients concluded that HES solutions increase the risk of acute kidney injury and the need for renal replacement therapy [34].

Therefore, initial fluid resuscitation of a patient with severe sepsis or septic shock should begin with a bolus of 30 mL/kg (IBW) of crystalloid. Albumin may be considered if the patient continues to have high volume requirements for resuscitation. HES should not be used for fluid resuscitation in severe sepsis and septic shock as it has been demonstrated to have an increased risk of death and the need for renal replacement therapy. A summary of the results of these trials and resulting Surviving Sepsis Campaign (2012) recommendations are outlined in Table 7.5.

Therapy (Septic Shock)

Vasopressors

The goal for administering vasopressors is to target an MAP of 65 mmHg (Grade IC); however, the comorbidities of the patient should be considered when assessing this target. For example, a

Table 7.5 Surviving sepsis campaign 2012 fluid therapy guidelines

Surviving sepsis campaign 2012 fluid therapy guidelines
Crystalloids should be used as the initial fluid of choice for the resuscitation of severe sepsis and septic shock (Grade 1B)
HES should not be used for fluid resuscitation of severe sepsis and septic shock (Grade 1B)
Albumin should be used in the fluid resuscitation of severe sepsis and septic shock when patients require substantial volume of crystalloid (Grade 2C)

Data from Dellinger, R. P. et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 2013; 39:165–228

patient with atherosclerosis and uncontrolled hypertension may require a higher MAP to achieve end-organ perfusion, and this can be assessed by using other indicators of end-organ perfusion, such as mental status and urinary output [15].

Septic shock causes an initial increase in cardiac output and decreased systemic vascular resistance, resulting in decreased blood pressure. The treatment for refractory hypotension despite adequate fluid resuscitation should therefore focus on restoring vascular tone.

First-Line Therapy

It has long been the consensus that either norepinephrine or dopamine was acceptable first-line vasopressor agents for septic shock. However, recent evidence has demonstrated that norepinephrine is superior to dopamine in the treatment of shock because of a decreased incidence of cardiac arrhythmias. Norepinephrine is an α-adrenergic receptor agonist; it increases contraction of smooth muscle cells, increasing vascular resistance and consequently blood pressure. Little effect is appreciated in heart rate and stroke volume. In contrast, dopamine has dose-dependent effects on α-, β- and dopaminergic receptors. Dopamine initially acts on β1-receptors to increase heart rate and stroke volume, causing an increase in cardiac output and blood pressure. At higher doses, dopamine activates α-receptors and causes vasoconstriction. A 2011 Cochrane Review of ten randomized controlled trials additionally concluded that while there was not sufficient evidence to show that norepinephrine compared to dopamine or epinephrine was superior in terms of mortality, dopamine was shown to be more associated with arrhythmias [35].

More recently, a meta-analysis of 2811 patients from 14 randomized clinical trials (nine comparing four different vasopressors and five examining the effects of two different inotropes) demonstrated improved 28-day mortality with norepinephrine alone compared to dopamine for the treatment of hypotension in septic shock (Odds Ratio 0.8, 95 % Confidence Interval 0.65–0.99). Additionally, adjunctive therapy of low-dose vasopressin with norepinephrine reduced mortality (Odds Ratio 0.69, 95 % Confidence Interval 0.48–0.98) compared with dopamine [36]. This effect was not appreciated with the use of epinephrine or the addition of an ionotropic agent such as dopexamine or dobutamine.

The beneficial adjunctive effect of vasopressin was challenged in the Vasopressin and Septic Shock Trial (VASST). The VASST trial randomized 779 subjects in septic shock on 5 μg/min of norepinephrine for at least 6 h to receive either a higher dose of norepinephrine (5–15 μg/min) or adjunctive vasopressin (0.01–0.03 U/min). The overall cohort did not show a difference in 28- or 90-day mortality; however, when the patients were stratified into severity of septic shock, the less severe strata showed decreased 28-day (26.5 % vs 35.7 %, $p=0.05$) and 90-day (35.8 % vs 46.1 %, $p=0.04$) mortality in the vasopressin group compared to the escalating norepinephrine group.

Therefore, it is recommended to start with norepinephrine (5 μg/min) as a first-line vasopressor and add vasopressin in patients that continue to be hypotensive despite maximum doses of norepinephrine (15 μg/min). Vasopressin can be started at a dose of 0.03 U/min and should not exceed 0.04 U/min due to the risk of decreased cardiac output and myocardial ischemia [37].

Phenylephrine, a central α-adrenergic vasoconstrictor, has been demonstrated to decrease stroke volume. For this reason, phenylephrine is only recommended when norepinephrine has caused serious arrhythmias or when target blood pressure is not maintained despite first-line vasopressor and

inotrope therapy and the patient has maintained their cardiac output [15].

Inotropic Therapy: Severe sepsis and septic shock result in defective cellular oxygen utilization rather than impaired tissue oxygenation [38]. Therefore, there is no benefit to using inotropic agents to raise oxygen delivery to supranormal targets in patients with severe sepsis or septic shock [14]. Conversely, patients with known or suspected cardiac dysfunction should be started on inotropic therapy. Dobutamine (20 μg/kg/min) is the first-line agent for management of cardiac dysfunction in these patients. Dobutamine is a β1-receptor agonist and weak β2-receptor agonist. The β1 stimulation increases stroke volume while the β2 stimulation results in peripheral vasodilation. Heart rate may be increased or decreased depending on the response in sympathetic tone to the change in cardiac output.

Later stages of sepsis can progress to myocardial depression, which is characterized by non-ischemic, reversible depression of the left and right ventricles [39, 40]. As the myocardium stretches, B-type natriuretic peptide (BNP) is secreted. A retrospective review on 231 surgical sepsis patients demonstrated a correlation between increasing BNP and sepsis severity, early systolic dysfunction and death [41]. This supports the monitoring of BNP in early sepsis in order to identify occult left ventricular dysfunction and possibly prompt an earlier administration of inotropes.

Steroids

The use of steroids, the definition of relative adrenal insufficiency, and the gold standard to diagnose adrenal insufficiency in patients with septic shock have been long debated and remain controversial [42, 43].

The Role of the Adrenal Gland in Sepsis: In response to a stressful trigger such as critical illness, the hypothalamic-pituitary-adrenal axis is stimulated to synthesize cortisol in the adrenal cortex. Cortisol then exerts metabolic, cardiovascular, and immune effects to restore homeostasis during illness. The immune effects include the inhibition of proinflammatory cytokines, stimulation of the production of anti-inflammatory cytokines, and locally acting to decrease inflammation. Cardiovascular effects include increasing blood pressure by increasing vascular smooth muscle sensitivity to catecholamines and angiotensin II. Metabolic effects are appreciated as an increase in blood glucose through potentiation of gluconeogenesis and lipolysis, as well as through upregulation of epinephrine and glucagon [44].

In response to critical illness and stress, cortisol production increases sixfold. In septic shock, relative adrenal insufficiency has been noted to be as prevalent as in 60 % of patients [45]. Increased levels of circulating inflammatory cytokines, decreased receptor sensitivity to cortisol, and hypothalamic-pituitary-adrenal axis suppression all contribute to this adrenal insufficiency. The result is a catecholamine-dependent patient who is no longer able to maintain his or her own vascular tone via endogenous cortisol.

Diagnosis of Adrenal Insufficiency: Traditionally, adrenal insufficiency in critically ill patients is best diagnosed by either (1) random total cortisol level of <10 μg/dL or (2) delta cortisol of <9 μg/dL after administering 250 μg of cosyntropin (ACTH) (Grade 2B). Additionally, a low random cortisol level (<18 μg/dL) in a patient with shock should be regarded as an indication for initiating steroid therapy [14].

Due to limited accuracy [46] and potential interfering therapies in the patient with septic shock, current guidelines recommend against performing a low-dose ACTH stimulation test to identify patients who should receive glucocorticoids. For instance, etomidate is an induction agent commonly used for rapid-sequence intubation in patients that decompensate quickly. Etomidate is known to cause a transient suppression of the hypothalamus-pituitary-adrenal axis and resultant adrenal insufficiency for approximately 24 h [47]. However, the impact of this adrenal insufficiency on mortality is not well understood [48–50]. In addition, patients who have received steroids in the 6 months prior to their episode of septic shock will have inconsistent results when testing their adrenal function. Therefore, in these patients with known alterations of their hypothalamic-pituitary-adrenal axis, empiric steroid therapy should be initiated

regardless of the baseline adrenal function as demonstrated by the ACTH stimulation test.

Evidence of the Benefit of Steroid Therapy in Septic Shock: After the abandonment of the use of high-dose steroids for septic shock, the use of low-dose steroids has been intensely studied. In 2002, Annane and colleagues conducted a multicenter randomized, double-blind, placebo-controlled parallel-group trial of 300 patients with septic shock receiving either placebo or 50 mg of hydrocortisone IV every 6 h and 50 μg of oral fludrocortisone. The authors concluded that the patients receiving steroids had decreased mortality (Hazard Ratio 0.67, 95 % Confidence Interval 0.47–0.92, $p=0.02$) as well as decreased duration of vasopressor therapy [51].

A systematic review of 17 randomized and quasi-randomized trials comparing corticosteroids to placebo in patients with severe sepsis or septic shock found that corticosteroids did not affect 28-day mortality. However, a subgroup of 12 trials with prolonged (≥5 days) low-dose (<300 mg hydrocortisone or equivalent) treatment suggested a favorable effect on all-cause mortality [52]. This benefit of low-dose hydrocortisone or equivalent was corroborated by an additional meta-analysis of eight (six randomized) studies [53].

Conversely, the Corticosteroid Therapy of Septic Shock (CORTICUS) trial was another multicenter, randomized, double-blind, placebo-controlled trial that evaluated the use of low-dose steroids in septic shock [46]. The results from this study failed to show a difference in 28-day mortality between the two groups; however, it was again displayed that the steroid group had a decreased time to shock resolution by approximately 2 days.

Differences between the results of the two studies have been largely attributed to time to randomization, placebo group mortalities, patient baseline characteristics, and power. The study by Annane and colleagues randomized patients within 3 h of the onset of septic shock, enrolled only patients with vasopressor-dependent septic shock, and had a placebo group mortality of 63 %. The CORTICUS trial randomized up to 72 h after the diagnosis of septic shock, included all patients with septic shock, and had a placebo mortality of over half of that of the Annane and colleagues study. Finally, the CORTICUS study was underpowered for their primary outcome.

Therefore, low-dose steroids (≤200 mg/day hydrocortisone or equivalent) have been demonstrated to be beneficial in septic shock by increasing both systemic vascular resistance and MAP, resulting in a decrease in the duration of vasopressor use and a decrease in the risk of death. Low-dose steroids should only be used in patients with septic shock who cannot maintain hemodynamic parameters with fluid resuscitation and vasopressors [14]. Steroids should be tapered to discontinuance if vasopressor dependency has not improved within 48 h of glucocorticoids or in patients who are no longer vasopressor dependent [44].

Goal 3: Reverse Hypoperfusion

According to the ACCP/SCCM definitions, tissue hypoperfusion indicates that a patient has progressed from sepsis to severe sepsis [9]. The presence and degree of tissue hypoperfusion can be assessed via the blood pressure, urine output, mental status, or serum lactate. The specific parameters for defining tissue hypoperfusion are outlined in Table 7.6.

Goal 4: Diagnose the Source of Infection

Immediately following the initiation of fluid resuscitation, the source of infection should be identified. Cultures should be drawn prior to, but without delaying, initiation of empiric antimicrobial therapy. Blood cultures should be obtained in all patients with sepsis; current recommendations include obtaining a minimum of two blood cultures. A blood culture should be obtained from each vascular access device (i.e., indwelling

Table 7.6 Indicators of tissue hypoperfusion

Parameter	Cutoff value
Mean arterial pressure (MAP)	<65 mmHg
Urine output	<0.5 mg/kg of IBW
Glasgow coma score	<12
Serum lactate	≥4 mmol/L

IBW ideal body weight

CVC, dialysis catheter) as well as from peripheral puncture. If there are no vascular access devices in place upon the recognition of sepsis, two peripheral cultures should be obtained. A vascular access device can be identified as a site of infection if there is a differential time to positivity of at least 120 min from the vascular access device prior to positivity from a peripheral puncture [54, 55]. In this case, it is recommended that the device is removed and a new, distant site is accessed for continual vascular access. Furthermore, if the site of the vascular access device displays clinical signs of infection (cellulitis, purulence), then it should be removed. Recent evidence recommends against the routine replacement of CVCs for the prevention of catheter-related infections [24, 56].

Blood culture and gram stain is the current standard for diagnosing bacteremia, yet this has an estimated overall positivity of 60 % despite application in the correct clinical context, standardized procedures, and optimal volume of blood collection [13, 57–59]. For instance, failure to collect at least 10 mL of blood significantly compromises the ability to detect bacteremia when present. The use of molecular methods to detect bacteremia may have advantages in comparison to the traditional blood culture and gram stain analysis as they are more rapid, can identify and quantitate pathogens directly from clinical samples, and have reduced variability associated with organism-specific growth requirements. Molecular pathogen detection techniques have been developed that rely on mass spectroscopy, microscopy, or nucleic acid testing such as polymerase chain reaction. The clinical application of these techniques is still under investigation [60].

Additional cultures from other sites (respiratory, urinary tract, surgical wound) and radiographic imaging should be guided by clinical suspicion. In the surgical population, this may include obtaining cultures from surgical drains and performing pertinent imaging to identify an undrained abscess.

Goal 5: Initiate Broad-Spectrum Antimicrobial Therapy

Early administration of empiric antibiotic therapy has been demonstrated to improve mortality from sepsis [15, 61]. Current guidelines from the Surviving Sepsis Campaign recommend the initiation of empiric antimicrobial therapy within the first hour of the recognition of sepsis [14]. Empiric therapy is defined as the inclusion of antimicrobials that have activity against all likely pathogens while considering local antibiotic susceptibility patterns [14]. It should be emphasized that the expeditious administration of the correct antibiotics has a profound impact on survival; Kumar and colleagues demonstrated that every hour delay in administration of antimicrobials from the observation of hypotension was associated with a 7.6 % increase in mortality [13]. Failure to administer correct antimicrobials also contributes to a five-fold increase in risk of death [58]. This is further highlighted in a prospective cohort study in 2000 medical and surgical patients which demonstrated the association between inadequate antimicrobial therapy and hospital mortality (Odds Ratio 4.27, 95 % Confidence Interval 3.35–5.44) [62]. Antimicrobial selection can be a complex process and should take into account the patient's history and comorbid conditions, recent antimicrobial exposure, and probable source of infection. With the recent emergence of several virulent, drug-resistant pathogens, the length of the patient's hospital course and the potential for infection with such organisms should be taken into consideration. Empiric antibiotic protocols have been developed in order to improve mortality by administering appropriate antibiotics (Table 7.7). Compliance with such empiric antibiotic protocols was demonstrated to decrease ICU length of stay by 6 days (14.5 versus 8.4, $p=0.014$) in a single-center study of patients with surgical sepsis [63]. The best practice is to provide broad coverage initially and de-escalate antimicrobial therapy based upon culture data.

Goal 6: Obtain Source Control

Soft Tissue Infections

Necrotizing Soft Tissue Infections

Necrotizing soft tissue infections include necrotizing cellulitis, myositis, and fasciitis. Early recognition and source control of a necrotizing

Table 7.7 Sample empiric antibiotic protocol, assuming normal renal and hepatic function

Suspected site of infection	First-line drug regimen	Second-line drug regimen
CAP	Ceftriaxone 1 g IV every 24 h azithromycin 500 mg IV/PO every 24 h	Levofloxacin 750 mg IV every 24 h
Suspected aspiration	CAP regimen + clindamycin 600 mg IV every 8 h	Ceftriaxone to piperacillin/tazobactam 4.5 g IV every 6 h
Early VAP (<5 days)	Cefepime 2 g IV every 24 h	
Late VAP (pseudomonal risk)	Cefepime 2 g IV every 24 h vancomycin 15 mg/kg IV every 12 h tobramycin 7 mg/ kg IV	Ciprofloxacin 400 mg IV every 12 h vancomycin 15 mg/kg IV every 12 h tobramycin 7 mg/kg IV
UTI/urosepsis	Piperacillin/tazobactam 4.5 g IV every 6 h	Ciprofloxacin 400 mg IV every 12 h
Line infection	Remove line + vancomycin 1 g IV every 12 h + fluconazole 800 mg IV every 24 h (if risk for candidemia)	
Necrotizing fasciitis	Piperacillin/tazobactam 4.5 g IV every 6 h vancomycin 15 mg/kg IV every 12 h clindamycin 900 mg IV every 8 h	Ciprofloxacin 400 mg IV every 12 h vancomycin 15 mg/kg IV every 12 h clindamycin 900 mg IV every 8 h
Surgical site infections	Piperacillin/tazobactam 4.5 g IV every 6 h vancomycin 15 mg/kg IV every 12 h	Ciprofloxacin 400 mg IV every 12 h vancomycin 15 mg/kg IV every 12 h
Intra-abdominal	Imipenem/cilastatin 500 mg IV every 6 h vancomycin 15 mg/kg IV every 12 h fluconazole 800 mg IV every 24 h	Ciprofloxacin 400 mg IV every 12 h metronidazole 500 mg IV every 8 h vancomycin 15 mg/kg IV

infection are imperative to avoid multiple organ failure, potential loss of limb(s), and death. Risk factors for developing a necrotizing soft tissue infection include obesity, diabetes, peripheral vascular disease, immunosuppression, recent trauma or surgery, and intravenous drug use. In necrotizing fasciitis, the infection spreads along the fascia due to its poor blood supply; overlying muscle and soft tissue appear unaffected, making necrotizing fasciitis difficult to diagnose without surgical investigation [64]. Therefore, surgical exploration should be considered for any concern of a necrotizing infection.

Type I Necrotizing Fasciitis: Type I infections are polymicrobial, usually due to a mixed infection of anaerobic species, facultative anaerobic streptococci (not group A), and Enterobacteriaceae [65].

Type II Necrotizing Soft Tissue Infections: Type II necrotizing fasciitis is monomicrobic. The most common offending pathogen is beta-hemolytic streptococci (group A streptococcus); however, cases of Aeromonas hydrophila [66] and Vibrio vulnificus [67, 68] have been associated with injuries occurring in fresh water and seawater, respectively. Community-acquired methicillin-resistant Staphylococcus aureus has also been implicated in cases of necrotizing fasciitis [69].

Diagnostic Considerations: Typical physical exam findings of a necrotizing soft tissue infection may be difficult for the novice to appreciate, but include cellulitis/ecchymosis, crepitus, bullae, skin necrosis, local anesthesia, or pain out of proportion to physical exam [65].

The presence of gas declares the need for surgical debridement. Obligate anaerobes, such as *Clostridial* species, flourish in oxygen-poor environments. Similarly, facultative anaerobes, such as *Staphylococcus* spp. and *Streptococcus* spp., are capable of utilizing nonoxidative metabolic pathways when stressed by their environment. In anaerobic respiration, these pathogens rely on denitrification, fermentation, or deamination to produce hydrogen and nitrogen [70]. Unlike CO_2, which is the waste product of oxidative metabolic pathways, hydrogen and oxygen are relatively insoluble and collect in the tissue. This is appreciated as crepitus on physical exam or gas on diagnostic imaging. Therefore, the finding of gas implies the existence of tissue without oxygen, that is, it is non-perfused, devitalized, or dead, and warrants debridement.

The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) was developed to aid the clinician in distinguishing necrotizing fasciitis from non-necrotizing infections. The score considers total white cell count, hemoglobin, sodium, glucose, serum Creatinine, and C-reactive protein. A score greater than or equal to 6 has a positive predictive value of 92.0 % and negative predictive value of 96.0 % for predicting the presence of a necrotizing infection [71]. The score, however, should never replace the surgical investigation of a concerning lesion. In addition, the LRINEC score should not be interpreted as a dynamic score. Improvements in the LRINEC score after resuscitation do not obviate the need for surgical investigation and/or intervention. Rather, this should be regarded as perioperative optimization of a patient that is more likely to tolerate necessary operative intervention.

Treatment: Surgical source control is the hallmark of therapy. Delay to achieving source control has an associated mortality as high as 30 %. Debridement should be aggressive, removing all devitalized tissue and extending into healthy tissue [70]. The wound should be continually reassessed for repeat debridement. Antibiotic therapy should initially be broad and should continue until no further debridement is needed. Appropriate regimens include (1) a carbapenem or beta-lactam-beta-lactamase inhibitor plus, (2) Clindamycin, and (3) coverage against MRSA.

Intra-abdominal Infections

The abdomen is the site of infection in nearly half of the patients with surgical sepsis. This is usually due to hepatobiliary disease, appendicitis, diverticulitis, inflammatory bowel disease, infected pancreatic necrosis, perforation of a gastric or duodenal ulcer, or large or small bowel perforation from obstructive carcinoma. Additionally, intra-abdominal infections can occur postoperatively due to injury to the bowel, anastomotic leak, or contamination of the peritoneal cavity. A postoperative intra-abdominal infection is considered an organ/space surgical site infection if it occurs within 30 days of the procedure [72].

When patients present with diffuse peritonitis and severe sepsis, careful consideration, planning, and coordination of care should occur to ensure that all necessary diagnostic imaging, resuscitation, and operative intervention are performed as expeditiously as possible.

In the case of septic shock, operative intervention should not precede resuscitation if feasible and should only take as long as necessary for source control. It is currently our practice to admit the patient to the ICU, implement the sepsis resuscitation bundle, and once the patient has received antibiotics, appropriate volume resuscitation, and placement of central venous access (typically 3 or 4 h), the patient is taken to the operating room for an abbreviated laparotomy. The goal at the time of laparotomy is to address the intra-abdominal source of infection (i.e., dead or perforated bowel) followed by temporary abdominal closure. The patient should then be returned to the ICU for continued resuscitation and stabilization prior to any subsequent operative procedures. For intra-abdominal sepsis, this is referred to as performing a damage control, or abbreviated, laparotomy. This technique has been recently regarded as an alternative treatment for definitive surgical care for a patient in extremis.

The Abbreviated Laparotomy

An abbreviated laparotomy was first introduced into the surgical theater as a means to control hemorrhagic shock in patients that were traumatically injured [73–75]. This method includes controlling hemorrhage and contamination followed by intra-peritoneal packing and rapid, temporary abdominal closure in patients with severe physiological derangements such as coagulopathy, acidosis, and hypothermia. The concept of abbreviated laparotomy has now evolved to include critically ill patients with surgical sepsis. Much like the patients with trauma having severe physiological compromise, many patients with septic shock present in a similar fashion.

Assessing the Need for an Abbreviated Laparotomy: For those patients presenting with septic shock due to an intra-abdominal infection, the utilization of an abbreviated laparotomy can

be lifesaving. The decision to utilize an abbreviated laparotomy is not a bailout, rather it is a deliberate decision to truncate the surgical procedure in order to minimize the time away from the ICU. The decision to pursue an abbreviated laparotomy is often made prior to arriving in the OR and is based on the combination of the patient's medical and surgical history, severity of the patient's physiologic derangements at the time of presentation, and type of definitive surgery required. To date, there are no specific, validated physiologic cutoffs that define a patient appropriate for an abbreviated laparotomy. However, the presence of hypothermia (<35 °C), acidosis (base deficit <8, pH < 7.20), or the laboratory and clinical evidence of coagulopathy is commonly regarded as indicators [76].

Preoperative Optimization: The first priority is to initiate resuscitation. The tenets to sepsis survival still apply to this patient; they need to undergo preoperative optimization during which time the airway is secured, central venous and arterial lines are placed, volume resuscitation and broad-spectrum antimicrobials are : administered, and vasopressors are titrated to the appropriate end points. Once the patient displays restoration of cardiac contractility, and optimization of preload and afterload, he or she is taken to the OR for emergency laparotomy.

Operative Procedure and Repeat Assessment: The surgeon needs to assess the degree of physiologic derangement early in the operation and if the severe derangements exist, then the operative interventions need to be truncated. The primary aim in the operating room is to control the source of infection, resect nonviable bowel, close bowel perforations, and wash out the abdomen. No definitive procedures should occur during this operation, including anastomosis and abdominal closure. An anastomosis is likely to fail in the setting of extreme physiological derangements and it is unlikely that the patient appropriate for this abbreviated laparotomy will tolerate such a failure. The abdomen is then quickly and temporarily closed, with the goal to contain the viscera, avoid potential injury and contamination, and control the peritoneal effluent [77]. The patient is then rapidly returned to the ICU for continued resuscitation.

Postoperative Optimization and Considerations: Postoperatively, volume resuscitation should continue, as well as correction of other physiological derangements. Patients should be continually assessed for their restoration of these physiological parameters. Additional operative procedures should be considered as necessary. During this phase, consideration and planning for eventual abdominal closure should occur.

Planned Staged Laparotomy: It should be mentioned that abbreviated laparotomy for the management of intra-abdominal sepsis is not the same as a planned, staged laparotomy. Patients with established peritonitis frequently require repeat laparotomy for washout of persistent peritonitis and/or new foci of infection. In these cases, two approaches can be considered. The first approach is to perform a repeat laparotomy to lavage, drain, and inspect the peritoneal cavity every 48 h; this is considered the planned approach. The planned approach theoretically reduces the risk of progression to multi-organ failure; however, it may also cause multiple unnecessary procedures in a patient that is already critically ill. The alternative approach is to wait until the patient's condition necessitates it; this is considered "on demand." With the combination of advances in computer tomographic scan technology to detect intra-abdominal infections with improved sensitivity and the ability of interventional radiologists to access these foci of infection, it is reasonable to expect that the majority of residual infections can be successfully treated without repeat laparotomy. Thus, repeat and excessive laparotomies can be avoided unless it is again a true surgical emergency. This may also reduce healthcare utilization and cost. [78] There are disadvantages to this approach as well. Entering the abdomen within 6 weeks of the original operation is challenging as dense adhesions are being formed during this time; this increases the risk of additional enterotomies and the sequelae that can follow. Both of these methods are reasonable to consider in a patient that is not in septic shock; however, they do not constitute the definition of a damage control, or abbreviated, laparotomy.

Other reasons for a planned, staged laparotomy include:

1. Reassessment of bowel viability. Patients that undergo resection of ischemic bowel should be left in discontinuity and reassessed 24 h later. The viability of the remaining bowel should be assessed during this repeat procedure, and if viable, an anastomosis should be performed at this time. Allowing a "second look" operation affords these patients the chance to have restoration of intestinal continuity and avoids their need for a temporary ostomy and an additional (future) procedure for reversal. In the case that an anastomosis is not feasible, an ostomy should be created in order to resume alimentary nutrition.
2. Avoidance of abdominal hypertension. In patients with massive bowel distension, premature closure of the abdomen can cause abdominal hypertension which can lead to abdominal compartment syndrome (ACS), an incredibly morbid complication. Abdominal hypertension is defined as sustained intra-abdominal pressure of ≥12 mmHg.
3. Abdominal Compartment Syndrome. The Eastern Association for the Surgery of Trauma (EAST) recommends the patients who develop ACS to receive a decompressive laparotomy (level I), with temporary abdominal closure and continued monitoring.
4. Necrotizing pancreatitis. EAST recommends an abbreviated laparotomy and open abdomen technique for the management of infected pancreatic necrosis [78].

Abdominal Compartment Syndrome: While the patient is in the postoperative optimization phase, judicious monitoring for abdominal compartment syndrome should occur via bladder pressure measurements.

The presence of a temporary abdominal closure should not eliminate the possibility of abdominal compartment syndrome [79]. In these critically ill patients that are heavily volume resuscitated, abdominal hypertension and abdominal compartment syndrome is a morbid complication that can result in Acute Respiratory Distress Syndrome (ARDS) or multiple organ failure. The World Society of the Abdominal Compartment Syndrome 2004 defined ACS as sustained intra-abdominal hypertension >20 mmHg associated with new organ dysfunction or failure, such as hypotension, increased ventilator pressures, or oliguria [80].

Achieving Abdominal Closure: Once source control has been achieved and the patient has received restoration of bowel continuity, the midline fascia can be definitively closed. Unfortunately, bowel distension from aggressive fluid resuscitation and multiple subsequent laparotomies commonly causes lateral migration of the fascia and proves abdominal closure to be difficult. In addition, if the bowel becomes adherent to the peritoneum of the anterior abdominal wall and into the lateral gutters, the abdomen will become "frozen," preventing the ability to bring the fascia back to the midline. Therefore, gentle blunt lysis of adhesions, or finger dissection, is imperative during each laparotomy to prevent the formation of a "frozen" abdomen and facilitate future abdominal closure. If the abdomen remains "frozen," the traditional method for closure includes mobilizing skin flaps to cover the defect, creating a large hernia to be repaired at a later date. This procedure is considerably comorbid, with a rate of enterocutaneous fistula in nearly a third of patients, development of additional intra-abdominal abscesses, deep soft tissue infections, persistent ventral incisional hernia requiring delayed complex abdominal wall reconstruction and future risk of hernia recurrence [66].

The use of biological mesh and vacuum-assisted devices has been separately investigated for achieving abdominal closure; however, this is beyond the scope of this text.

Discussion

Activated Protein C

Following the 2001 Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study, recombinant human activated protein C was used for the treatment of severe sepsis and was advocated by the Surviving Sepsis Campaign. The PROWESS study was a phase 3 international, randomized controlled trial that was stopped

early (after enrolling 1690 patients with severe sepsis) due to its efficacy; absolute mortality in the intention-to-treat population was reduced by 6.1 % [81]. Following the results of this study, the Food and Drug Administration approved the use in patients with a high risk of death. This was due to a subgroup analysis that suggested the mortality benefit was limited to patients with an APACHE II score >24 or with at least one organ system dysfunction. Subsequent placebo-controlled trials were unable to produce the same results as the PROWESS trial [82]. Therefore, a decade later, the Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis and Septic Shock (PROWESS-SHOCK) was undertaken to evaluate the efficacy of recombinant human activated protein C specifically in patients with septic shock. There was no benefit in mortality in the drug group compared with placebo [83]. Following the results of this study, recombinant human activated protein C was removed from the market and is no longer included in the Surviving Sepsis Guidelines [14].

Disputes of Early Goal-Directed Therapy

Despite the successes demonstrated by Rivers et al. with early goal-directed therapy (EDGT) lowering mortality from septic shock at a single center from 46.5 to 30.5 %, there have been challenges to both the necessity and safety of EGDT. A retrospective, cohort study of 405 medical ICU patients with severe sepsis or septic shock suggested that EGDT may increase the risk of fluid overload, the need for subsequent medical inventions (thoracentesis and diuresis), and mortality [84].

ProCESS Trial

The objectives of the Protocolized Care for Early Septic Shock (ProCESS) trial were to determine if EGDT therapy is generalizable and which components of the protocol are necessary [85]. The multicenter trial randomized 1341 adult patients presenting to academic emergency departments with septic shock. The patients were randomized to three arms: early goal-directed therapy, protocol-based standard therapy without a CVC or arterial line, and usual care. The protocol-based therapy group was administered intravenous fluids to goal systolic blood pressure and shock index (ratio or heart rate to systolic blood pressure); there was no $ScvO_2$ goal, as it was not measured. The usual care group was at the varied discretion of the bedside physician. There were no significant differences between either groups with respect to 60- or 90-day mortality; however, the EGDT group did receive more vasopressors, inotropes, and blood transfusions [86]. This led to the conclusion that perhaps, in academic emergency departments in the United States, patients presenting with septic shock can be safely managed with an approach that focuses on patient response to resuscitation, early antibiotic use, and continued observation [12]. Of note in this study, randomization occurred after the initiation of volume resuscitation, making the "6 h" initial resuscitation bundle of EGDT [10] longer than 6 h. Additionally, most (>75 %) patients received antibiotics prior to randomization.

ARISE

In a similar effort, the Australasian Resuscitation in Sepsis Evaluation (ARISE) randomized 1600 patients with severe sepsis or septic shock in both academic and community centers throughout Australia, New Zealand, Finland, Hong Kong, and Ireland to EGDT therapy or variable physician-guided care. Like the ProCESS trial, no survival benefit at 90 days was appreciated (Relative Risk 0.98, 95 % Confidence Interval 0.80–1.21, $p = 0.90$). Additionally, no differences in ICU length of stay, in-hospital mortality, need for renal replacement therapy, or duration of vasopressor support were appreciated [87]. In this study, the mortality was only approximately 18 % in both groups, which is considerably lower than the overall mortality from sepsis. Also, due

to the wide-spread acceptance of EGDT, it was difficult to ascertain how different the usual care was from the EGDT protocol.

ProMISe Trial

Finally, the Protocolised Management in Sepsis (ProMISe) Trial randomized 1260 patients in 56 hospitals in England to early goal-directed therapy or usual care. There was no difference in all-cause 90-day mortality (Odds Ratio 0.95, 95 % Confidence Interval 0.74–1.24, $p=0.73$). Additionally, this trial demonstrated a greater mean Sequential Organ Failure Assessment (SOFA) score at 6 h, a greater proportion of patients receiving cardiovascular support, and a greater median length of stay in the early goal-directed therapy group [88]. Comparable to the ProCESS trial, all patients did receive antibiotics prior to randomization.

The ProCESS, ARISE, and ProMISe trials all attempted to compared EGDT to usual care in academic, community, and National Health Service (England) settings, respectively. Differences between the trial by Rivers et al., the ProCESS, ARISE, and ProMISe trials are outlined in Table 7.8. This highlights the difficulty in comparing these new trials to the original study by Rivers et al. The Rivers et al. trial had a higher mortality that is reflective of the expected mortality from sepsis, despite having similar APACHE II scores and baseline lactate values. In addition, while the ProCESS, ARISE, and ProMISe trials appear to be more IV-fluid conservative, each group was administered nearly 2 l of fluid prior to randomization. This was not included in the 6-h resuscitation bundle.

Meta-Analysis of EGDT Compared to Usual Care

A meta-analysis of ten randomized controlled trials comparing EGDT to usual care over 10 years (2004–2014) including 4157 patients found that EGDT did not show a survival benefit in patients with severe sepsis or septic shock (Relative Risk 0.91, 95 % Confidence Interval 0.79–1.04, $p=0.17$). In addition, patients receiving EGDT compared to their controls received more inotropic agents, and a greater volume of fluid, including red cell transfusion. EGDT did not benefit patients by decreasing vasopressor support, ICU length of stay, hospital-free days, or ventilator-free days [89].

Table 7.8 Comparison of Rivers et al. with ProCESS [85], ARISE [87] and ProMISe [88] study characteristics

	Rivers EGDT (2001)	ProCESS (2014)	ARISE (2014)	ProMISe (2015)
APACHE II				
Usual Care	20.4 ± 7.4	20.8 ± 8.1	15.8 ± 6.5	18.0 ± 7.1
EGDT	21.4 ± 6.9	20.7 ± 7.5	15.4 ± 6.5	18.7 ± 7.1
Serum lactate mmol/L (Baseline)				
Usual care	6.9 ± 4.5	5.0 ± 3.6	6.6 ± 2.8	6.8 ± 3.2
EGDT	7.7 ± 4.7	4.8 ± 3.1	6.7 ± 3.3	7.0 ± 3.5
IV fluids (mL) in first 6 h				
Usual care	3499 ± 2438	2279 ± 1881[a]	1713 ± 1401[b]	1784 (1075, 2775)[c]
EGDT	4981 ± 4984	2805 ± 1957[a]	1964 ± 1415[b]	2000 (1150, 3000)[c]
28-day Mortality				
Usual care (%)	49	18.9[d]	15.9	24.8
EGDT (%)	33	21[d]	14.8	24.5

Plus-minus values are means ± standard deviation. Patients in the ProMISe trial received an additional 1790 (1000, 2500) mL in the usual care group and 1600 (1000, 2500) mL in the EGDT group prior to randomization.

[a]Patients in the ProCESS trial received 2083 ± 1405 mL in the usual care group and 2254 ± 1472 mL in the EGDT group prior to randomization

[b]Patients in the ARISE trial received an additional 2591 ± 1331 mL in the usual care group and 2515 ± 1244 mL in the EDGT group prior to randomization

[c]Values are expressed as median (interquartile range)

[d]60-day mortality

Finally, a meta-analysis including 13 trials with 2525 patients revealed that the mortality benefit of goal-directed therapy was only appreciated when applied early (within 6 h, Relative Risk 0.77; 95 % Confidence Interval, 0.67–0.89; $p = 0.0004$; $I^2 = 40$ %) and not when the timing was outside of the 6 h or unclear (Relative Risk 0.92; 95 % Confidence Interval, 0.69–1.24; $p = 0.59$; $I^2 = 56$ %) [89].

There have not yet been updates to the Surviving Sepsis Guidelines in light of these new studies. What these studies do emphasize is that while all components of EDGT may not be necessary, they do not definitively display any harm. This could be a limitation of only assessing mortality as an outcome. The work of Rivers and colleagues over a decade ago revolutionized the way that sepsis is considered, leading to increased awareness, earlier identification, and earlier administration of therapies. Perhaps the biggest contribution of EDGT is the earlier recognition of sepsis and earlier administration of antimicrobial therapy.

Conclusion

Sepsis continues to be a frequent cause of mortality in surgical patients. Early identification through the use of screening tools designed specifically for surgical patients, early administration of antimicrobials, and source control are all essential for survival from surgical sepsis. For patients with severe physiological derangements, planned, staged, and abbreviated procedures may improve patient survival.

Acknowledgment There are no identifiable conflicts of interests to report.

The authors have no financial or proprietary interest in the subject matter or materials discussed in the manuscript.

References

1. Lagu T, et al. Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007. Crit Care Med. 2012;40:754–61.
2. Hall MJ, Williams SN, DeFrances CJ, Golosinskiy A. Inpatient care for septicemia or sepsis: a challenge for patients and hospitals. NCHS Data Brief. 2011;(62):1–8.
3. Moore LJ, et al. Sepsis in general surgery: the 2005–2007 national surgical quality improvement program perspective. Arch Surg. 2010;145:695–700.
4. Angus DC, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29:1303–10.
5. Moore LJ, Moore FA, Jones SL, Xu J, Bass BL. Sepsis in general surgery: a deadly complication. Am J Surg. 2009;198:868–74.
6. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Facing the challenge: decreasing case fatality rates in severe sepsis despite increasing hospitalizations. Crit Care Med. 2005;33:2555–62.
7. Balk RA, Bone RC. The septic syndrome. Definition and clinical implications. Crit Care Clin. 1989;5:1–8.
8. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med. 1992;20:864–874.
9. Levy MM, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med. 2003;31:1250–6.
10. Rivers E, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345:1368–77.
11. Robson W, Beavis S, Spittle N. An audit of ward nurses' knowledge of sepsis. Nurs Crit Care. 2007;12:86–92.
12. Assunção M, et al. Survey on physicians' knowledge of sepsis: do they recognize it promptly? J Crit Care. 2010;25:545–52.
13. Kumar A, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34:1589–96.
14. Dellinger RP, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med. 2013;39:165–228.
15. Levy MM, et al. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. Intensive Care Med. 2010;36:222–31.
16. Lai NA, Kruger P. The predictive ability of a weighted systemic inflammatory response syndrome score for microbiologically confirmed infection in hospitalised patients with suspected sepsis. Crit Care Resusc J Australas Acad Crit Care Med. 2011;13:146–50.
17. Churpek MM, Zadravecz FJ, Winslow C, Howell M, Edelson DP. Incidence and prognostic value of the systemic inflammatory response syndrome and organ dysfunctions in ward patients. Am J Respir Crit Care Med. 2015;192(8):958–64.
18. Moore LJ, et al. Validation of a screening tool for the early identification of sepsis. J Trauma. 2009;66:1539–46; discussion 1546–7.
19. Moore L, et al. 8: Simple, reliable sepsis screening tool improves mortality in trauma patients. Crit Care Med. 2014;42:A1370.

20. Merrer J, De Jonghe B, Golliot F, et al. Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. JAMA. 2001;286:700–7.
21. Guerin L, Monnet X, Teboul J-L. Monitoring volume and fluid responsiveness: from static to dynamic indicators. Best Pract Res Clin Anaesthesiol. 2013;27:177–85.
22. Teboul J-L, Monnet X. Prediction of volume responsiveness in critically ill patients with spontaneous breathing activity. Curr Opin Crit Care. 2008;14:334–9.
23. Marik PE, Monnet X, Teboul J-L. Hemodynamic parameters to guide fluid therapy. Ann Intensive Care. 2011;1:1.
24. O'Grady NP, et al. Guidelines for the prevention of intravascular catheter-related infections. Centers for Disease Control and Prevention. MMWR Recomm Rep. 2002;51:1–29.
25. Lins RL, et al. Intermittent versus continuous renal replacement therapy for acute kidney injury patients admitted to the intensive care unit: results of a randomized clinical trial. Nephrol Dial Transplant. 2009;24:512–8.
26. Bendjelid K, Romand J-A. Fluid responsiveness in mechanically ventilated patients: a review of indices used in intensive care. Intensive Care Med. 2003;29:352–60.
27. Varpula M, Tallgren M, Saukkonen K, Voipio-Pulkki L-M, Pettilä V. Hemodynamic variables related to outcome in septic shock. Intensive Care Med. 2005;31:1066–71.
28. Annane D, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. JAMA. 2013;310:1809–17.
29. Guidet B, et al. Assessment of hemodynamic efficacy and safety of 6% hydroxyethyl starch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: the CRYSTMAS study. Crit Care. 2012;16:R94.
30. Finfer S, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350:2247–56.
31. Caironi P, et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med. 2014;370:1412–21.
32. Early Albumin Resuscitation During Septic Shock—Full Text View—ClinicalTrials.gov. (n.d.). https://clinicaltrials.gov/ct2/show/NCT00327704. Accessed 7 Mar 2016.
33. Myburgh JA, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367:1901–11.
34. Mutter TC, Ruth CA, Dart AB. Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. Cochrane Database Syst Rev. 2013;7:CD007594.
35. Havel C, Arrich J, Losert H, Gamper G, Müllner M, Herkner H. Vasopressors for hypotensive shock. Cochrane Database Syst Rev. 2011;5, CD003709. 10.1002/14651858.CD003709.pub3.
36. Oba Y, Lone NA. Mortality benefit of vasopressor and inotropic agents in septic shock: a Bayesian network meta-analysis of randomized controlled trials. J Crit Care. 2014;29:706–10.
37. Holmes CL, Walley KR, Chittock DR, Lehman T, Russell JA. The effects of vasopressin on hemodynamics and renal function in severe septic shock: a case series. Intensive Care Med. 2001;27:1416–21.
38. Fink MP. Cytopathic hypoxia. Is oxygen use impaired in sepsis as a result of an acquired intrinsic derangement in cellular respiration? Crit Care Clin. 2002;18:165–75.
39. Parker MM, et al. Profound but reversible myocardial depression in patients with septic shock. Ann Intern Med. 1984;100:483–90.
40. Jardin F, Brun-Ney D, Auvert B, Beauchet A, Bourdarias JP. Sepsis-related cardiogenic shock. Crit Care Med. 1990;18:1055–60.
41. Turner KL, et al. Identification of cardiac dysfunction in sepsis with B-type natriuretic peptide. J Am Coll Surg. 2011;213:139–46; discussion 146–7.
42. Toma A, Stone A, Green RS, Gray S. Steroids for patients in septic shock: the results of the CORTICUS trial. CJEM. 2011;13:273–6.
43. Groeneveld ABJ, Molenaar N, Beishuizen B. Should we abandon corticosteroids during septic shock? No. Curr Opin Crit Care. 2008;14:384–9.
44. Marik PE, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. Crit Care Med. 2008;36:1937–49.
45. Annane D, et al. Diagnosis of adrenal insufficiency in severe sepsis and septic shock. Am J Respir Crit Care Med. 2006;174:1319–26.
46. Sprung CL, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med. 2008;358:111–24.
47. Vinclair M, et al. Duration of adrenal inhibition following a single dose of etomidate in critically ill patients. Intensive Care Med. 2008;34:714–9.
48. Alday NJ, et al. Effects of etomidate on vasopressor use in patients with sepsis or severe sepsis: a propensity-matched analysis. J Crit Care. 2014;29:517–22.
49. Bruder EA, Ball IM, Ridi S, Pickett W, Hohl C. Single induction dose of etomidate versus other induction agents for endotracheal intubation in critically ill patients. Cochrane Database Syst Rev. 2015;1:CD010225.
50. Chan CM, Mitchell AL, Shorr AF. Etomidate is associated with mortality and adrenal insufficiency in sepsis: a meta-analysis*. Crit Care Med. 2012;40:2945–53.
51. Annane D, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA. 2002;288:862–71.
52. Annane D, Bellissant E, Bollaert P, et al. Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. JAMA. 2009;301:2362–75.
53. Sligl WI, Milner DA, Sundar S, Mphatswe W, Majumdar SR. Safety and efficacy of corticosteroids for the treatment of septic shock: a systematic review and meta-analysis. Clin Infect Dis. 2009;49:93–101.
54. Blot F, et al. Earlier positivity of central-venous- versus peripheral-blood cultures is highly predictive of catheter-related sepsis. J Clin Microbiol. 1998;36:105–9.

55. Blot F, et al. Diagnosis of catheter-related bacteraemia: a prospective comparison of the time to positivity of hub-blood versus peripheral-blood cultures. Lancet. 1999;354:1071–7.
56. Cook D, et al. Central venous catheter replacement strategies: a systematic review of the literature. Crit Care Med. 1997;25:1417–24.
57. Vincent J-L, et al. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med. 2006;34:344–53.
58. Kumar A, et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. Chest. 2009;136:1237–48.
59. Fenollar F, Raoult D. Molecular diagnosis of bloodstream infections caused by non-cultivable bacteria. Int J Antimicrob Agents. 2007;30 Suppl 1:S7–15.
60. Scerbo MH, Kaplan HB, Dua A, Litwin DB, Ambrose CG, Moore LJ, Murray CK, Wade CE, Holcomb JB. Beyond blood culture and gram stain analysis: a review of molecular techniques for the early detection of bacteremia in surgical patients. Surg Infect. 2016. doi: 10.1089/sur.2015.099.
61. Ferrer R, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med. 2014;42:1749–55.
62. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest. 1999;115:462–74.
63. Fitousis K, Moore LJ, Hall J, Moore FA, Pass S. Evaluation of empiric antibiotic use in surgical sepsis. Am J Surg. 2010;200:776–82; discussion 782.
64. Gozal D, Ziser A, Shupak A, Ariel A, Melamed Y. Necrotizing fasciitis. Arch Surg. 1986;121:233–5.
65. Brook I, Frazier EH. Clinical and microbiological features of necrotizing fasciitis. J Clin Microbiol. 1995;33:2382–7.
66. Monaghan SF, Anjaria D, Mohr A, Livingston DH. Necrotizing fasciitis and sepsis caused by Aeromonas hydrophila after crush injury of the lower extremity. Surg Infect. 2008;9:459–67.
67. Hsu J-C, et al. Necrotizing fasciitis and sepsis caused by Vibrio vulnificus and Klebsiella pneumoniae in diabetic patients. Biomed J. 2015;38:136–42.
68. Kuo Y-L, Shieh S-J, Chiu H-Y, Lee J-W. Necrotizing fasciitis caused by Vibrio vulnificus: epidemiology, clinical findings, treatment and prevention. Eur J Clin Microbiol Infect Dis. 2007;26:785–92.
69. Young LM, Price CS. Community-acquired methicillin-resistant Staphylococcus aureus emerging as an important cause of necrotizing fasciitis. Surg Infect. 2008;9:469–74.
70. Dellinger EP. Severe necrotizing soft-tissue infections. Multiple disease entities requiring a common approach. JAMA. 1981;246:1717–21.
71. Wong C-H, Khin L-W, Heng K-S, Tan K-C, Low C-O. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med. 2004;32:1535–41.
72. Centers for Disease Control and Prevention (CDC). Surgical site infection (SSI) event. (2015).
73. Cué JI, Cryer HG, Miller FB, Richardson JD, Polk HC. Packing and planned reexploration for hepatic and retroperitoneal hemorrhage: critical refinements of a useful technique. J Trauma. 1990;30:1007–11; discussion 1011–3.
74. Rotondo MF, et al. 'Damage control': an approach for improved survival in exsanguinating penetrating abdominal injury. J Trauma. 1993;35:375–82; discussion 382–3.
75. Burch JM, et al. Abbreviated laparotomy and planned reoperation for critically injured patients. Ann Surg. 1992;215:476–83; discussion 483–4.
76. Aoki N, et al. Predictive model for survival at the conclusion of a damage control laparotomy. Am J Surg. 2000;180:540–4; discussion 544–5.
77. Waibel BH, Rotondo MF. Damage control for intra-abdominal sepsis. Surg Clin North Am. 2012;92:243–57.
78. Diaz JJ, et al. The management of the open abdomen in trauma and emergency general surgery: part 1-damage control. J Trauma. 2010;68:1425–38.
79. Offner PJ, et al. Avoidance of abdominal compartment syndrome in damage-control laparotomy after trauma. Arch Surg. 2001;136:676–81.
80. Malbrain MLNG, et al. Results from the international conference of experts on intra-abdominal hypertension and abdominal compartment syndrome. I. definitions. Intensive Care Med. 2006;32:1722–32.
81. Bernard GR, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med. 2001;344:699–709.
82. Martí-Carvajal A, Salanti G, Cardona AF. Human recombinant activated protein C for severe sepsis. Cochrane Database Syst Rev. 2008;1, CD004388. doi: 10.1002/14651858.CD004388.pub3.
83. Ranieri VM, et al. Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med. 2012;366:2055–64.
84. Kelm DJ, et al. Fluid overload in patients with severe sepsis and septic shock treated with early goal-directed therapy is associated with increased acute need for fluid-related medical interventions and hospital death. Shock. 2015;43:68–73.
85. Yealy DM, Kellum JA. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014;370:1683–93.
86. Cabrera JL, Pinsky MR. Management of septic shock: a protocol-less approach. Crit Care. 2015;19:260.
87. ARISE Investigators, et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014;371:1496–506.
88. Mouncey PR, et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med. 2015;372:1301–11.
89. Zhang L, Zhu G, Han L, Fu P. Early goal-directed therapy in the management of severe sepsis or septic shock in adults: a meta-analysis of randomized controlled trials. BMC Med. 2015;13:71.