4 EARLY MANAGEMENT OF SEPSIS, SEVERE SEPSIS, AND SEPTIC SHOCK IN THE SURGICAL PATIENT

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Sepsis continues to be a common and serious problem. It is currently the 10th leading cause of death in the United States and the leading cause of death in noncardiac intensive care units (ICUs).[1] The incidence of sepsis among hospitalized patients continues to increase as the population ages. The current incidence of severe sepsis among hospitalized patients in the United States is 208 cases/100,000 patients.[2] It was estimated that there would be nearly 1 million cases of sepsis in the United States in 2010, with an associated mortality rate of greater than 30% based on a projected 1.5% increase in incidence per year based on the growth and aging of the US population.[3] But subsequent studies have shown this estimate to be low, with increases in sepsis rates subsequently reported to be as high as 10% per year.[4,5] These epidemiologic studies document that severe sepsis remains a major challenge and an increasing burden on health care systems worldwide.

Among surgical patients, sepsis is a leading cause of morbidity and mortality. A large epidemiologic study from Angus and colleagues determined that surgical patients account for nearly one third of sepsis cases in the United States.[3] A recent analysis of the National Surgical Quality Improvement Project (NSQIP) database determined that sepsis and septic shock were 10 times more common than perioperative myocardial infarction and pulmonary embolism.[6] The incidence of sepsis was highest in patients requiring emergency surgery, and colon perforation was the predominant source of sepsis. The development of septic shock was associated with a 30% mortality rate among elective surgical patients and a 39% mortality rate among emergent surgical patients. Risk factors for both the development of sepsis and death from sepsis included age older than 60 years, the need for emergency surgery, and the presence of comorbid conditions.[7]

Definition of Sepsis, Severe Sepsis, and Septic Shock

A clear and accurate definition of sepsis is critical for clinicians and researchers. A standard definition allows us to identify patients, leads to a better understanding of the disease process, and facilitates clinical research. Sepsis syndrome was first defined in the literature by Balk and Bone in 1989.[8] This was followed by the American College of Chest Physicians and the Society of Critical Care Medicine's (ACCP/SCCM) Consensus Conference in 1991 that defined the systemic inflammatory response syndrome (SIRS) [*see Table 1*] and multiple organ dysfunction syndrome (MODS).[9] In response to ongoing criticism from experts in the field, a second consensus conference was convened in 2001 to revise the original definitions. The updated consensus conference definitions included an expanded list of the signs and symptoms of sepsis.[10] Although the definitions included in the 2001 update are widely accepted, they do not specifically define the concept of surgical sepsis. In addition, the consensus conference definitions remain nonspecific and allow for some variability, especially with regard to defining organ dysfunction.

In an attempt to better define the categories of sepsis, severe sepsis, and septic shock for the surgical patient, we modified the ACCP/SCCM consensus conference definitions. We defined surgical sepsis as SIRS plus an infection requiring surgical intervention for source control or SIRS plus an infection within 14 days of a major surgical procedure. A major surgical procedure is defined as any procedure requiring general anesthesia for more than 1 hour.

Severe sepsis is defined as SIRS plus infection plus acute organ dysfunction. The types of acute organ dysfunction are defined as follows:

1. Neurologic: a Glasgow Coma Scale (GCS) score less than 13 on recognition of sepsis or a deteriorating GCS score to less than 13 during the first 24 hours
2. Pulmonary: arterial oxygen tension (Pao_2) to fraction of inspired oxygen (F_IO_2) ratio less than 250 (< 200 if the lung is the primary site of infection) and pulmonary capillary wedge pressure (PCWP) (if available) not suggestive of fluid overload
3. Renal (one of the following): urine output less than 0.5 mL/kg for 1 hour or more despite adequate volume resuscitation, an increase in serum creatinine 0.5 mg/dL or

Table 1 **Systemic Inflammatory Response Syndrome (SIRS) Criteria**

Two or more of the following criteria must be present:

- Body temperature < 36°C or > 38°C
- Heart rate > 90 beats per minute
- Tachypnea, with > 20 breaths per minute, or an arterial partial pressure of carbon dioxide < 4.3 kPa (32 mm Hg)
- White blood cell count < 4,000 cells/μL (4×10^9 cells/L) or > 12,000 cells/μL (12×10^9 cells/L) or the presence of > 10% immature neutrophils (band forms)

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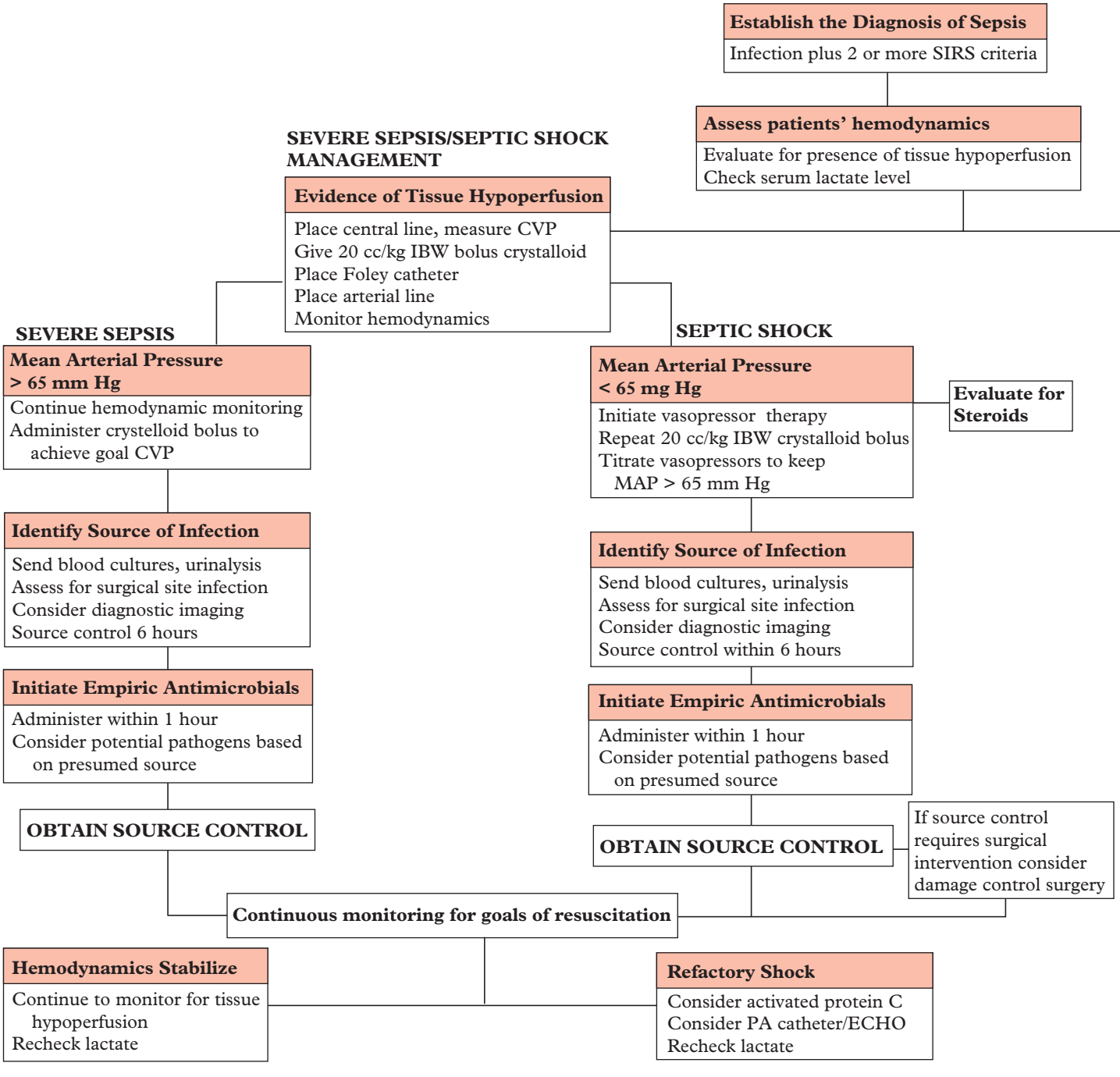
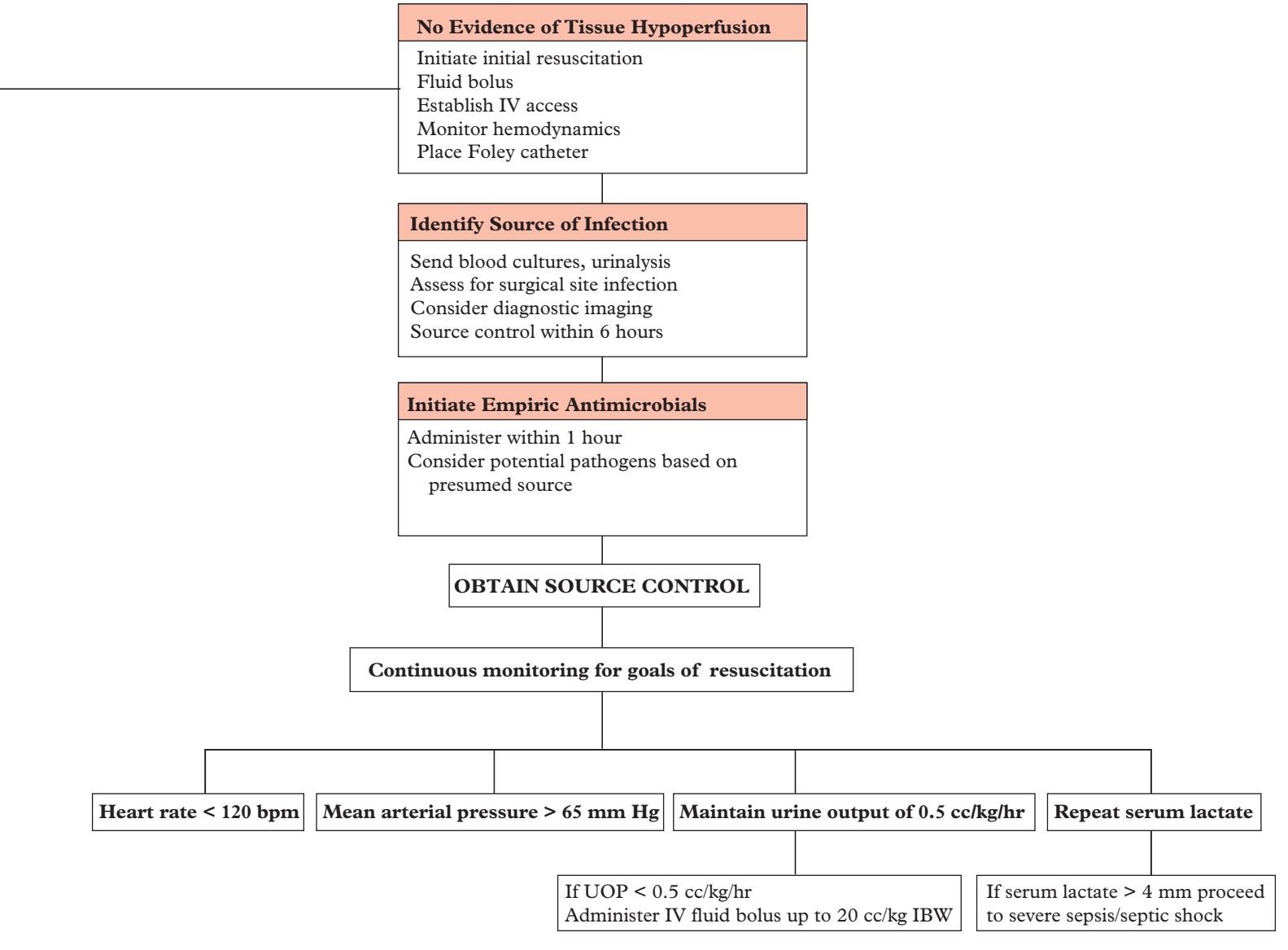
EARLY SEPSIS RESUSCITATION AND MANAGEMENT



SEPSIS MANAGEMENT



more from baseline (measured within 24 hours of starting sepsis resuscitation) despite adequate volume resuscitation or an increase in serum creatinine 0.5 mg/dL or more during the first 24 hours of sepsis management despite adequate volume resuscitation. Adequate volume resuscitation is defined as a minimum intravenous (IV) fluid infusion of 20 mL/kg/ideal body weight (IBW) or central venous pressure (CVP) 8 mm Hg or greater or PCWP 12 mm Hg or greater.

4. Coagulation (one of following): international normalized ratio (INR) greater than 1.5, platelet count less than 80,000 μL, or 50% or greater decreased platelet count compared to 24 hours before instituting sepsis resuscitation or in the 24 hours after starting sepsis resuscitation in the absence of chronic liver disease
5. Hypoperfusion: lactate level less than 4 mmol/L

Septic shock is defined as SIRS plus infection plus acute cardiac dysfunction, which is defined by the following (must meet both criteria): (1) intravenous fluid challenge greater than or equal to 20 mL/kg/IBW of isotonic crystalloid infusion or CVP greater than or equal to 8 mm Hg or PCWP greater than or equal to 12 mm Hg and (2) requires vasopressors to increase mean arterial pressure (MAP) to greater than or equal to 65 mm Hg.

Initial Assessment and Evaluation of the Septic Patient

EARLY IDENTIFICATION OF SEPSIS

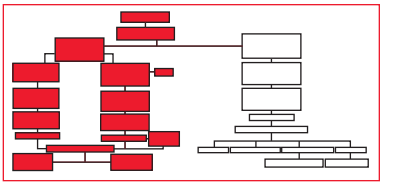
At our institution, we identified sepsis as a major cause of morbidity and mortality in our general surgery patients. As bedside nurses and other team members focus on multiple priorities and tasks, early signs of sepsis were often missed and interventions were delayed. In addition, many of the early signs and symptoms of sepsis may be subtle and in the surgical population are often attributed to other problems. For example, oliguria is commonly seen in surgical patients and is often attributed to underresuscitation in the operating room or volume loss from the gastrointestinal tract. However, oliguria can also be an early finding in patients with sepsis. Altered mental status, which is often attributed to narcotic administration or ICU psychosis, can also be an early warning sign of sepsis. Likewise, acute hypoxia on the surgical wards spurs a workup for pulmonary embolism, but acute hypoxia may herald the onset of severe sepsis or septic shock.

Identifying patients in the early stages of sepsis is imperative. If patients are allowed to progress into septic shock, their mortality is prohibitively high (> 30%) despite aggressive interventions. When you consider these factors, the benefit of routine, accurate screening of patients for sepsis quickly becomes apparent. In an attempt to increase the early identification of sepsis, we developed a sepsis screening tool in our surgical intensive care unit (SICU) [*see Figure 1*].[11] Our initial experience with this mandatory sepsis screening tool in our SICU showed promising results. The screening tool yielded a sensitivity of 96.5%, a specificity of 96.7%, a positive predictive value of 80.2%, and a negative predictive value of 99.5%. In addition, sepsis-related mortality decreased from 35.1% to 23.3%. Subsequent expansion and statistical validation of the screening on the surgical floor yielded similar results.[12] Since implementing mandatory sepsis screening, we have seen a significant decline in our severe sepsis and septic shock–related mortality. Regardless of the method used to screen patients, all members of the patient care team must be aware of the early signs and symptoms of sepsis.

INITIAL ASSESSMENT

A clinical suspicion for the presence of sepsis should prompt further evaluation of the patient. The initial evaluation should focus on determining the degree of physiologic derangement that the patient is experiencing. Specifically, it is important to assess for the presence of tissue hypoperfusion. Several clinical and laboratory variables can be used to evaluate tissue perfusion status. The following variables are indicators that the patient is experiencing tissue hypoperfusion: (1) urine output less than 0.5 mL/kg of IBW, (2) MAP less than 65 mm Hg, (3) GCS score less than 12, and (4) serum lactate greater than or equal to 4 mmol/L. The presence of tissue hypoperfusion should prompt aggressive resuscitative measures that are focused on restoring tissue perfusion. Based on the definitions outlined above, those patients who do not have evidence of tissue hypoperfusion would fall into the category of sepsis. Those patients who do have evidence of tissue hypoperfusion would be categorized as having severe sepsis or septic shock. The initial resuscitation and management of these patients are discussed below.

INITIAL RESUSCITATION OF SEPSIS



The initial resuscitation phase of sepsis should begin immediately on recognition of sepsis. The goals of the resuscitation phase include restoring intravascular volume, diagnosing the source of infection, initiation of broad-spectrum antimicrobial therapy, and source control. Many institutions have developed order sets that specifically address each of these issues. The use of standardized protocols for the initial management of sepsis has been demonstrated to improve patient outcomes in multiple settings.[13–18]

The major tenets of initial resuscitation can be initiated in any area of the hospital and should not be delayed pending arrival in the ICU. Establishing IV access is a critical first step as this allows for the administration of IV fluid and antimicrobials. For those patients without evidence of tissue hypoperfusion, a large-bore peripheral IV line should be sufficient. In the event that peripheral IV access is not attainable, a central venous line should be inserted in a timely fashion.

The initial resuscitation fluid of choice still remains extremely controversial. There are no prospective, randomized, controlled trials evaluating crystalloid versus colloid resuscitation in surgical patients with sepsis. If colloids are given, the initial fluid bolus should be 300 to 500 mL of colloid over 30 minutes. If crystalloids are given, the initial fluid challenge should be 1,000 cc of crystalloid over 30 minutes. Additional fluid boluses should be repeated based on the patient's response. Fluid resuscitation should be initiated with the following goals in mind: (1) a target CVP (if available) of 8 to 12 mm Hg in nonintubated patients and a target CVP of 12 to 15 mm Hg in mechanically ventilated patients[19];

Bedside Nurse SIRS score

patient label

10232007

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		34 – 35.9	32 – 33.9	30 – 31.9	≤29.9
max	36 – 38.4	38.5 – 38.9		39 – 40.9	≥ 41
T (°F) min		93.1 – 96.6	89.6 – 93.0	86 – 89.5	≤ 85.9
max	96.8 – 101.1	101.2 – 102.0		102.1 – 105.6	≥105.7
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 Nurse Practitioner to complete sepsis screening form.

Completed by: _____, RN Date / time: _____

Performance improvement review by PHYSICIAN:

sepsis (Phase 1) **severe sepsis (Phase 2)** **septic shock (Phase 2)**

Start sepsis management protocol **Yes** **No**

Comments:

_____
_____
_____

Signature: _____, MD Date / time: _____

Figure 1 **(a) Secondary Screening form to identify source of infection.**

Nurse Practitioner/Resident Physician Sepsis Screening

1. Vascular access? **Yes** **No** **Suspicion of:**

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

line infection?
Yes **No**

2. Clinical pulmonary infection score (CPIS)

Variable	**points**	**score**
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	

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**

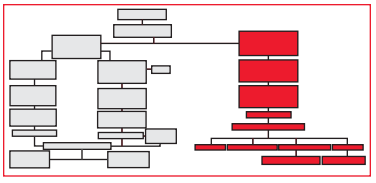
Completed by: _____, NP_____ Date / time: _____

Figure 1 **(b) Bedside Nurse SIRS Score.**

(2) a MAP of 65 mm Hg or greater[20]; (3) urine output of 0.5 mL/kg/hour or greater; and (4) central venous oxygen saturation ($Scvo_2$) of 70% or greater or mixed venous oxygen saturation (Svo_2) of 65% or greater (if available).[21] These goals of resuscitation should be achieved within 6 hours of the recognition of sepsis. In addition, a baseline serum lactate should be sent on the identification of sepsis. A repeat serum lactate level should be sent 4 hours later to monitor the progress of the initial resuscitation.

The Saline versus Albumin Fluid Evaluation (SAFE) study randomized nearly 7,000 critically ill patients who required fluid resuscitation to receive albumin or normal saline, and no difference in mortality was identified. Interestingly, in the SAFE study, a subgroup analysis of the 1,218 patients with severe sepsis documented that albumin was associated with a trend toward reduced mortality (relative risk of death 0.87; 95% confidence interval 0.74 to 1.02).[22] Two randomized clinical trials are ongoing to further investigate this finding: (1) Volume Replacement with Albumin in Severe Sepsis (ALBIOS)[23] (Italy) and (2) Early Albumin Resuscitation during Septic Shock (France).[24]

INITIAL RESUSCIATION OF SEVERE SEPSIS AND SEPTIC SHOCK



For those patients presenting with severe sepsis and septic shock, the timely restoration of tissue perfusion is critical. The concept of early goal-directed therapy (EGDT) in severe sepsis and septic shock [*see Figure 2*] was initially developed and validated in the emergency department (ED) setting in a single-center trial.[21] The ED is frequently the point of entry into the hospital for many septic patients. Unfortunately, many of these patients may wait for prolonged periods of time in the ED. The end result is often a delay in the implementation of early sepsis resuscitation.

The use of EGDT has been shown to improve survival in patients presenting with severe sepsis and septic shock.[16,21,25,26] The basic tenets of EGDT are to identify tissue hypoperfusion and institute therapies to reverse global tissue hypoxia by optimizing oxygen delivery. Tissue perfusion can be monitored by measuring Svo_2, $Scvo_2$, or peripheral muscle hemoglobin oxygen saturation (Sto_2). An Svo_2 of 65% or less, an $Scvo_2$ of 70% or less, and an Sto_2 of 75% or less can all be considered indicators of tissue hypoperfusion. Once tissue perfusion has been identified, specific therapies should be instituted to reverse tissue hypoxia by restoring adequate perfusion. The determinants of oxygen delivery are cardiac output, hemoglobin, and percent arterial hemoglobin oxygen saturation (Sao_2). EGDT attempts to restore tissue hypoperfusion by addressing these variables. The evidence-based sepsis resuscitation bundle was established with the goal of performing all indicated tasks 100% of the time within the first 6 hours after the diagnosis of sepsis was established and is used to assist with the provision of prompt resuscitation efforts in the treatment of sepsis [*see Table 2*].

To restore intravascular volume and enhance cardiac output, an initial crystalloid fluid bolus of 20 mL/kg of IBW is recommended. This fluid bolus can be initially administered through existing peripheral IV lines; however, placement of a central venous line for monitoring of CVP is recommended. In addition, an arterial line should be placed in those patients presenting with hypotension who do not rapidly respond to volume loading. The use of noninvasive blood pressure monitoring for patients in septic shock often produces inaccurate measurements and should not be used for titrating vasoactive medications. A Foley catheter should also be inserted to allow for close monitoring of urine output, and bladder pressures should be monitored in patients requiring vigorous volume loading.

The goals of resuscitation remain the same as those listed above: (1) a target CVP (if available) of 8 to 12 mm Hg in nonintubated patients and a target CVP of 12 to 15 mm Hg in mechanically ventilated patients[19]; (2) a MAP of 65 mm Hg or greater[20]; (3) urine output of 0.5 mL/kg/hour or greater; and (4) $Scvo_2$ of 70% or greater or Svo_2 of 65% or greater.[21] In the event that an $Scvo_2$ of 70% or greater or an Svo_2 of 65% or greater cannot be achieved with restoration of intravascular volume and MAP of 65 to 90 mm Hg, red blood cells should be transfused to achieve of hematocrit of 30% or greater.

Multiple international randomized, controlled trials of EGDT for patients with severe sepsis are under way to validate the findings of the single-center Rivers trial.[21] These include Protocolized Care for Early Septic Shock (ProCESS), Australian Resuscitation in Sepsis Evaluation (ARISE), and Protocolized Management in Sepsis (ProMISe). The ProCESS trial will randomize 1,950 patients who present to the ED in septic shock to three arms: (1) the EGDT Rivers protocol described above, (2) a simpler, less invasive protocol using an esophageal Doppler monitor and no blood transfusion, and (3) usual care.[27] The ARISE trial will randomize 1,600 patients to EGDT versus standard care and assess 90-day mortality in patients presenting to the ED with severe sepsis.[28] The ProMISe trial will randomize 1,260 patients to EGDT versus standard care and assess 90-day mortality in patients presenting to the ED with septic shock.[29] Furthermore, an individual, patient data meta-analysis will be performed across the three trials.

If the goal CVP, the goal MAP, and the goal hematocrit are all reached but there is still evidence of tissue hypoperfusion, inotropic agents should be initiated to improve cardiac output. In patients presenting with septic shock, the initial fluid bolus may not restore their MAP to 65 mm Hg or greater. A repeat fluid bolus of 20 mL/kg of IBW can be given to correct hypovolemia. However, transient vasopressor therapy may need to be initiated, even if volume resuscitation is still ongoing.

VASOPRESSOR THERAPY

Septic shock is primarily a vasodilatory shock, associated with a high cardiac output and a low systemic vascular resistance. Therefore, initial vasopressors therapy should be targeted at restoring vascular tone. Both norepinephrine and dopamine are acceptable first-line agents for treatment of septic shock. These agents should be administered through a central venous catheter. Norepinephrine is primarily a alpha-receptor agonist that promotes widespread vasoconstriction

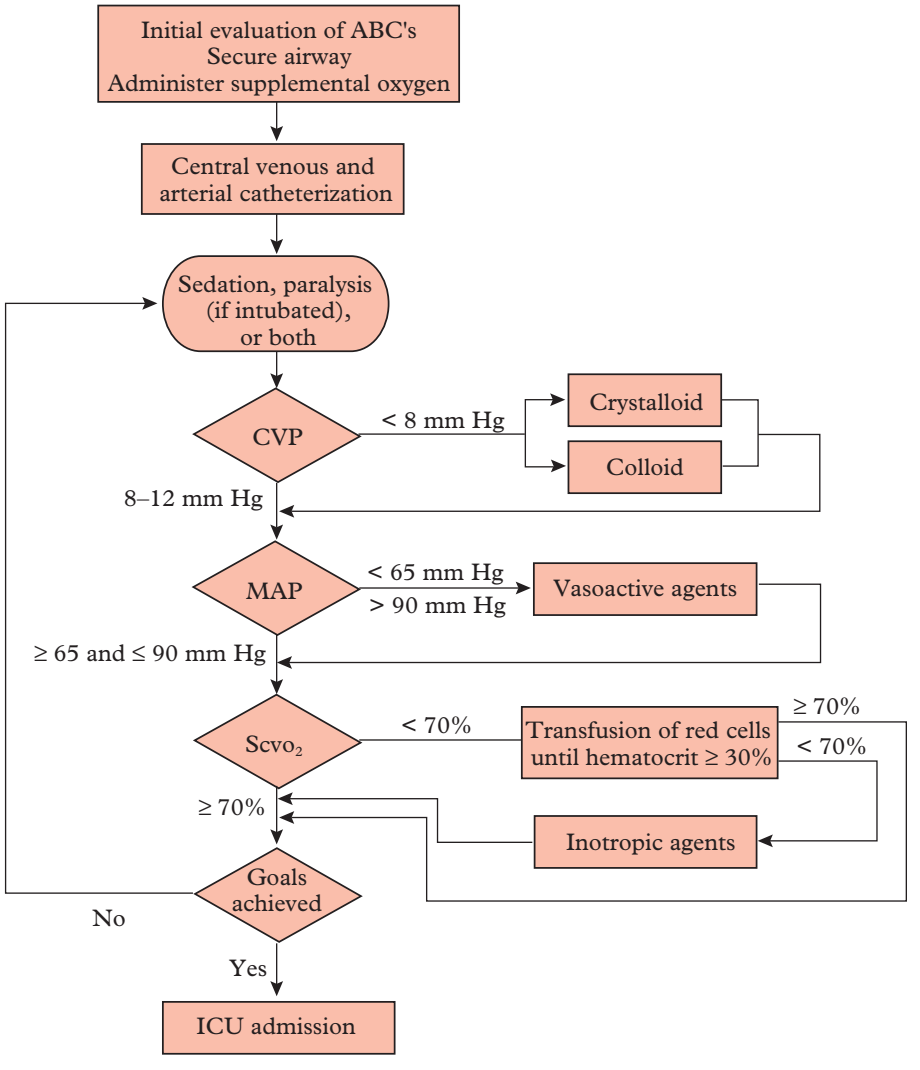


Figure 2 **Protocol for early goal-directed therapy (EGDT). Adapted from Rivers E et al.[21] CVP = central venous pressure; MAP = mean arterial pressure; $Scvo_2$ = central venous oxygen saturation.**

and has little effect on heart rate or stroke volume. Dopamine has dose dependent effects on alpha, beta, and dopaminergic receptors. The initial increase in blood pressure seen with dopamine is related to increasing cardiac output. At higher doses (> 7.5 μg/kg/min), dopamine does activate alpha receptors, with resultant vasoconstriction.

In those patients with septic shock that is refractory to first-line vasopressors, the addition of vasopressin may be beneficial. Vasopressin is a stress hormone that has vasoactive effects. Recent work by Landry and colleagues suggested that in septic shock states, there is a relative deficiency of vasopressin.[30] The administration of vasopressin in this patient population has been shown to improve responsiveness to catecholamines and potentially reduce the dose of catecholamine needed to maintain blood pressure.[31]

The Vasopressin and Septic Shock Trial (VASST) randomized 779 patients in septic shock requiring norepinephrine (5 μg/min) for at least 6 hours and at least one organ system dysfunction present for less than 24 hours to vasopressin (0.01 to 0.03 U/min) versus norepinephrine at a higher dose (5 to 15 μg/min).[32] No difference in 28-day or 90-day mortality was identified. In the prospectively defined stratum of less severe septic shock, the mortality rate was lower in the vasopressin group than in the norepinephrine group at 28 days (26.5% versus 35.7%; $p = .05$), which persisted to 90-day mortality (35.8% versus 46.1%; $p = .04$). A post hoc analysis of the VASST identified that the combination of low-dose vasopressin and corticosteroids was associated with decreased mortality and organ dysfunction compared with norepinephrine and corticosteroids.[33] Based on the results of studies to date, clinicians should consider the addition of low-dose (up to 0.03 U/min) continuous infusion vasopressin in individual septic shock patients who are adequately resuscitated and still require high doses of vasopressors.

Our current practice is to initiate a vasopressin drip at a rate 0.04 U/min in those patients requiring norepinephrine infusion at 15 μg/min or greater. The dose of vasopressin should not exceed 0.04 U/min because of the possibility of myocardial ischemia and decreased cardiac output at higher doses.[34] The evidence-based Surviving Sepsis Campaign

Table 2 Sepsis Bundles*

Sepsis Resuscitation Bundle (to be started immediately and completed within 6 hours)

- Serum lactate measured
- Blood cultures obtained prior to antibiotic administration
- Broad-spectrum antibiotics administered within 3 hours for ED admissions and 1 hour for non-ED ICU admissions
- In the event of hypotension and/or lactate > 4 mmol/L:
  - Deliver a minimum of 20 mL/kg of crystalloid (or colloid equivalent)
  - Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) ≥65 mm Hg
- In the event of persistent arterial hypotension despite volume resuscitation (septic shock) and/or initial lactate > 4 mmol/L (36 mg/dL):
  - Achieve central venous pressure (CVP) of ≥8 mm Hg
  - Achieve central venous oxygen saturation ($Scvo_2$) of ≥70% (achieving a mixed venous oxygen saturation of 65% is an acceptable alternative)

Sepsis Management Bundle (to be started immediately and completed within 24 hours)

- Low-dose steroids administered for septic shock in accordance with a standardized ICU policy
- Drotrecogin alfa (activated) administered in accordance with a standardized ICU policy
- Glucose control maintained ≥ lower limit of normal, but < 150 mg/dL (8.3 mmol/L)
- For mechanically ventilated patients, inspiratory plateau pressures maintained < 30 cm H_2O

ED = emergency department; ICU = intensive care unit.
*The goal is to perform all indicated tasks 100% of the time within the first 6 hours (sepsis resuscitation bundle) or first 24 hours (sepsis management bundle) of the diagnosis of severe sepsis.

guidelines regarding vasopressor use in sepsis are provided in Table 3.

Although most patients with sepsis initially present with increased cardiac output, a subset of patients will develop myocardial depression from sepsis. The exact mechanism for this reversible myocardial dysfunction is still under investigation. B-type natriuretic peptide (BNP) is secreted in response to stretching of myocardium and has been used clinically to assess volume overload and predict death in acute congestive heart failure. More recently, BNP has been shown to be elevated in early septic shock and likewise predict death. We recently showed that BNP increases with initial sepsis severity and is associated with early left ventricular dysfunction, which in turn is associated with later death.[35] Monitoring BNP in early sepsis to identify occult left ventricular dysfunction might prompt earlier use of inotropes, which are not commonly used in early sepsis resuscitation.

Table 3 Surviving Sepsis Campaign Guidelines Recommendations regarding Vasopressors[70]

- Maintain MAP ≥ 65 mm Hg (1C).
- Norepinephrine and dopamine centrally administered are the initial vasopressors of choice (1C).
- Epinephrine, phenylephrine, and vasopressin should not be administered as the initial vasopressor in septic shock (2C).
- Vasopressin 0.03 U/min may be subsequently added to norepinephrine with anticipation of an effect equivalent to norepinephrine alone.
- Use epinephrine as the first alternative agent in septic shock when blood pressure is poorly responsive to norepinephrine or dopamine (2B).
- Do not use low-dose dopamine for renal protection (1A).
- In patients requiring vasopressors, insert an arterial catheter as soon as practical (1D).

MAP = mean arterial pressure. Parens represent level of evidence for the recommendation.

For those patients with suspected or documented cardiac dysfunction, the addition of inotropic therapy is recommended. Dobutamine is the first-line agent for treatment of cardiac dysfunction in patients with sepsis. The management of patients with a cardiac component to their shock state presents a unique challenge to the managing clinician because they require the titration of vasopressors and inotropic agents. In this subset of patients, a pulmonary artery catheter can be extremely useful. This allows for the specific titration of vasopressors based on systemic vascular resistance and inotropic agents based on cardiac output. There is no evidence to support increasing cardiac index to predetermined supranormal levels.

STEROIDS IN SEPTIC SHOCK

The use of steroids for the management of septic shock has been debated for several decades. In recent years, the concept of relative adrenal insufficiency in septic shock has received renewed attention. In spite of several large clinical trials addressing the issue of steroid use in patients with septic shock, the topic remains controversial. Much of the ongoing debate surrounds the definition of relative adrenal insufficiency in critically ill patients and the "gold standard" for diagnosing adrenal insufficiency in this population.

It had previously been a common practice to perform a low-dose adrenocorticotropic hormone (ACTH; cosyntropin) stimulation test on all patients with septic shock as a means to identify those patients with relative adrenal insufficiency. To perform the cosyntropin stimulation test, a baseline serum cortisol is drawn that represents time zero (T_0). The patient is then given 250 μg of IV cosyntropin. Subsequent serum cortisol levels are measured at 30 (T_{30}) and 60 (T_{60}) minutes after the cosyntropin. If the delta cortisol is 9 μg/dL or less, then the patient is considered to have relative adrenal insufficiency and steroids are initiated. Based on the current evidence to date, we now recognize that the ACTH stimulation test is not recommended to identify the subset of adults with septic shock who should receive hydrocortisone. A number of factors interfere with the ACTH stimulation test, and our current diagnostic tests are not accurate. The administration of etomidate causes a temporary suppression of the hypothalamic-pituitary-adrenal axis, resulting in transient adrenal insufficiency. In addition, patients who have received steroids at any time during the 6 months preceding the presentation of septic shock should not undergo testing of their adrenal function. These patients should be empirically initiated on steroid therapy. The current edition (2008) of the Surviving Sepsis Campaign guidelines recommends that intravenous hydrocortisone be considered for adult septic shock when hypotension responds poorly to adequate fluid resuscitation and vasopressors [*see Table 4*]. The literature indicates that low-dose corticosteroids decrease the time to cessation of vasopressors,[36] increase the systemic vascular resistance and MAP,[37] and decrease the risk of death.[38] The dose of hydrocortisone should be 300 mg/day or less. We currently give hydrocortisone 50 mg IV every 6 hours. The

Table 4 Surviving Sepsis Campaign Guidelines regarding Steroids[70]

- Consider intravenous hydrocortisone for adult septic shock when hypotension responds poorly to adequate fluid resuscitation and vasopressors (2C).
- ACTH stimulation test is not recommended to identify the subset of adults with septic shock who should receive hydrocortisone (2B).
- Hydrocortisone is preferred to dexamethasone (2B).
- Fludrocortisone (50 μg orally once a day) may be included if an alternative to hydrocortisone is being used that lacks significant mineralocorticoid activity. Fludrocortisone is optional if hydrocortisone is used (2C).
- Steroid therapy may be weaned once vasopressors are no longer required (2D).
- Hydrocortisone dose should be ≤300 mg/day (1A).
- Do not use corticosteroids to treat sepsis in the absence of shock unless the patient's endocrine or corticosteroid history warrants it (1D).

ACTH = adrenocorticotropic hormone. Parens represent level of evidence for the recommendation.

duration of steroid administration also remains controversial. The current recommendation is that steroids be discontinued once vasopressors are no longer required.

IDENTIFYING THE SOURCE OF INFECTION

Identifying the source of infection is a key element to the initial management of sepsis. Whenever possible, cultures should be obtained prior to initiation of empirical antimicrobial therapy. Current recommendations include obtaining a minimum of two blood cultures, including one blood culture from each vascular access device and one blood culture from a peripheral puncture. Additional cultures from other sites (respiratory system, urinary tract) and radiographic imaging should be dictated by clinical suspicion. In the surgical population, this may include obtaining cultures from surgical drains and performing pertinent imaging to identify an undrained abscess.

To improve the chances of detecting bacteremia, it is crucial to obtain the appropriate volume of blood for the culture medium. Several studies have demonstrated that the volume of blood cultured is the single most important factor in the detection of bacteremia.[39–41] The recommended volume of blood per culture tube is 10 mL or greater. Obtaining blood cultures from all vascular access devices, along with simultaneous collection of blood cultures from a peripheral site, is beneficial in diagnosing catheter-related infections. This concept of differential time to positivity has been well described in the literature.[42,43] The differential time to positivity is defined as the difference in time necessary for the blood culture drawn simultaneously from a peripheral site and a central venous catheter to become positive. A differential time to positivity is considered to be positive if the blood culture that is drawn through the vascular access device becomes positive at least 120 minutes before the peripheral culture. If a patient has an indwelling vascular access device and the cultures drawn from that device become positive at least 120 minutes before the peripheral cultures become positive, it is recommended that the device be removed as it is likely infected.[42]

INITIATION OF EMPIRICAL ANTIMICROBIAL THERAPY

Another key component of the initial resuscitation of the septic patient is the administration of IV antimicrobial therapy. Antimicrobials should be administered after appropriate cultures have been sent but within 1 hour of sepsis recognition. The time to antimicrobial administration has been identified as a critical determinant of survival in patients presenting with sepsis. A recent study by Kumar and colleagues found that each hour in delay of antimicrobials was associated with an average decrease in survival of 7.6%.[44] Delayed administration of antifungal therapy in patients with *Candida* bloodstream infections was an independent predictor of hospital mortality.[45] Maintaining an adequate supply of commonly used antimicrobial agents in the ED and ICU can aid in the timely administration of these agents. The Surviving Sepsis Campaign guidelines recommend initiation of IV broad-spectrum antibiotics within the first hour of recognizing severe sepsis and septic shock [*see Table 5*].

The choice of antimicrobial therapy should take into account the patient's history (including drug allergies and recent antimicrobial exposure), suspected source of infection, and hospital-specific antibiograms. Within our SICU, our multidisciplinary sepsis team has developed antimicrobial regimens based on the suspected source of infection and the current antibiogram for our institution [*see Table 6*]. When selecting empirical antimicrobial therapy, a few general rules should be applied. The initial antimicrobial coverage should be broad enough to cover all potential pathogens. There is substantial evidence that administering inadequate antimicrobial coverage is associated with increased morbidity and mortality.[46–49] Any antimicrobial that the patient has recently received should be avoided. Vigilant monitoring of culture data and de-escalation of the antimicrobial regimen based on culture results and sensitivities will reduce the risk of superinfection and the emergence of resistant organisms.

OBTAINING SOURCE CONTROL

The final component of the initial resuscitation bundle is identifying and controlling the source of infection. This can be as simple as removing an infected vascular access device. However, in our experience, in surgical patients, the abdomen is the site of infection in ≥50% of cases. These patients frequently require diagnostic imaging to identify the source and an operative procedure for source control. This includes

Table 5 Surviving Sepsis Campaign Guidelines regarding Antimicrobial Therapy

- Begin intravenous antibiotics as early as possible and always within the first hour of recognizing severe sepsis (1D) and septic shock (1B).
- Broad spectrum: one or more agents active against likely bacterial/fungal pathogens and with good penetration into presumed source (1B).
- Reassess antimicrobial regimen daily to optimize efficacy, prevent resistance, avoid toxicity, and minimize costs (1C).
- Consider combination therapy in *Pseudomonas* infections (2D).
- Consider combination empirical therapy in neutropenic patients (2D).
- Combination therapy not more than 3–5 days and de-escalation following susceptibilities (2D).
- Duration of therapy typically limited to 7–10 days—longer if response slow or there is undrainable foci of infection or immunologic deficiencies (1D).
- Stop antimicrobial therapy if cause is found to be noninfectious (1D).

Parentheses represent level of evidence for the recommendation.

Table 6 **Recommendations for Source-Specific Empirical Antibiotic Selection**

Source of Infection	Antibiotic Drug	Regimen
Indication	If vancomycin allergy (not intolerance), then use linezolid	600 mg IV q. 12 hr
	1. Preferred therapy 2. Severe β-lactamase allergy	Monitor; adjust if renal dysfunction* Kinetic monitoring†
Pneumonia		
Community acquired (CAP)	1. Ceftriaxone and Levofloxacin	1 g IV q. 24 hr 750 mg IV q. 24 hr*
	2. Aztreonam and Levofloxacin	2 g IV q. 8 hr* 750 mg IV q. 24 hr*
Aspiration (not chemical pneumonitis)	Piperacillin-tazobactam	4.5 g IV q. 6 hr*
Ventilator associated (VAP)		
Early VAP (< 5 days)	1. Cefepime	2 g IV q. 12 hr*
	2. Ciprofloxacin	400 mg IV q. 12 hr*
Late VAP (≥ 5 days; *Pseudomonas* risk: previous hospital or broad-spectrum antibiotic exposure; positive *Pseudomonas* culture)	1. Cefepime and Vancomycin and Tobramycin	2 g IV q. 8 hr* 15 mg/kg IV q. 12 hr* 7 mg/kg IV*†
	2. Ciprofloxacin and Vancomycin and Tobramycin	400 mg IV q. 8 hr* 15 mg/kg IV q. 12 hr* 7 mg/kg IV*†
Catheter-related infections		
Catheter-associated urinary tract infection (CAUTI)	1. Cefepime	1 g IV q. 12 hr*
	2. Ciprofloxacin	400 mg IV q. 12 hr*
IV, arterial catheter; bloodstream	Vancomycin	1 g IV q. 12 hr*
Candidemia high risk (TPN, steroid therapy, diabetes, hepatic failure)	Fluconazole	800 mg IV q. 24 hr*
Wound/soft tissue infections		
Necrotizing soft tissue infection (NSTI)	1. Piperacillin-tazobactam and Vancomycin and Clindamycin	4.5 g IV q. 6 hr* 15 mg/kg IV q. 12 hr* 900 mg IV q. 8 hr
	2. Ciprofloxacin and Vancomycin and Clindamycin	400 mg IV q. 8 hr* 15 mg/kg IV q. 12 hr* 900 mg IV q. 8 hr
Surgical site infection (SSI)	1. Ertapenem and Vancomycin	1 g IV q. 24 hr* 15 mg/kg IV q. 12 hr*
	2. Ciprofloxacin and Vancomycin	400 mg IV q. 12 hr* 15 mg/kg IV q. 12 hr*
Intra-abdominal infections		
Pseudomonas low risk	1. Ertapenem and Vancomycin	1 g IV q. 24 hr* 15 mg/kg IV q. 12 hr*
	2. Ciprofloxacin and Metronidazole and Vancomycin	400 mg IV q. 8 hr* 500 mg IV q. 8 hr 15 mg/kg IV q. 12 hr*
Pseudomonas high risk (previous hospitalization or broad-spectrum antibiotic exposure; positive *Pseudomonas* culture)	1. Imipenem-cilastatin and Vancomycin	500 mg IV q. 6 hr* 15 mg/kg IV q. 12 hr*
	2. Ciprofloxacin and Metronidazole and Vancomycin	400 mg IV q. 8 hr* 500 mg IV q. 8 hr 15 mg/kg IV q. 12 hr*
Candidiasis high risk (TPN, steroid treatment, diabetes, hepatic failure, upper GI perforation + H_2 blocker, age ≥75 yr, prolonged antibiotic, long-term care)	Consider fluconazole	800 mg IV q. 24 hr*

GI = gastrointestinal; TPN = total parenteral nutrition.

emergent débridement of necrotic tissues, abscess drainage, removal of infected vascular access devices, and exploratory laparotomy. In the setting of septic shock, these procedures, although necessary, can present a unique challenge to the surgical team.

The concept of damage control laparotomy (DCL) was first used for the care of critically injured trauma patients.[50–52] Damage control is defined as initial control of hemorrhage and contamination followed by intraperitoneal packing as needed and rapid, temporary abdominal closure. This concept was employed on those patients who presented with severe physiologic derangements such as coagulopathy, acidosis, and hypothermia. Rather than persist for hours performing definitive surgery in the operating room, a patient's critical surgical needs should be addressed in an abbreviated fashion so that the patient may be taken to the ICU for further resuscitation. Once their physiologic derangements have been corrected, they are taken back to the operating room for a definitive surgical procedure. The decision to use DCL should not be viewed as a bailout. Instead, it is a deliberate decision to truncate the surgical procedure to minimize the time away from the ICU. The decision to perform DCL is often made prior to arriving in the operating room and is based on the severity of the patient's physiologic derangements at the time of presentation.

The concept of DCL has now evolved to include critically ill patients with surgical sepsis. Much like the trauma patient with the lethal triad of acidosis, hypothermia, and coagulopathy, many patients with septic shock present in a similar fashion. For those patients presenting with septic shock and a source of infection that requires surgical intervention, the use of DCL can be lifesaving.

The first priority is to initiate resuscitation. The patient needs to undergo preoperative optimization, during which time the airway is secured, central venous and arterial lines are placed, volume resuscitation and broad-spectrum antimicrobial agents are administered, and vasopressors are titrated to the appropriate end points. Within 6 hours, the patient is taken to the operating room for emergency laparotomy and potential damage control. The surgeon needs to assess the degree of physiologic derangement early in the operation, and if severe physiologic derangements exist, then the operative interventions need to be truncated. The primary aim is to control the source of infection (e.g., resect dead bowel, manage bowel perforations [resection versus primary closure], drain abscesses, and wash out the abdomen). We do not create ostomies, and bowel may be left in discontinuity at this first operation. The abdomen is then managed with a temporary abdominal closure device (via a variety of techniques), and the patient is rapidly returned to the ICU, where he or she undergoes postoperative optimization. This includes optimizing volume resuscitation and mechanical ventilation, correction of coagulopathy and hypothermia, and monitoring for abdominal compartment syndrome (ACS). Over the next 24 to 48 hours, abnormal physiology is corrected so that the patient can safely return to the operating room for a definitive operation and abdominal closure. Septic shock is a tremendous metabolic insult, and it is very important to provide optimal nutritional support (this often requires combined enteral and parenteral nutrition) and early mobilization to prevent the loss of lean body mass, which impairs recovery.

One of the problems with this "damage control" strategy is that in some patients, the midline abdominal fascia cannot be closed at the second operation because of bowel distention and edema, and they require multiple additional laparotomies for definitive abdominal wall closure. The midline fascia is progressively closed with the use of a vacuum-assisted closure (VAC) device. For this technique to work, it is important that the bowel not become adherent to peritoneum of the anterior abdominal wall lateral to the paracolic gutters; otherwise, the abdomen becomes "frozen" and the fascia cannot be brought to midline. The VAC device actively removes fluid and decreases edema; provides medial tension, which helps minimize fascial retraction and loss of domain; and protects the abdominal contents by providing separation between the abdominal wall and viscera, with no fascial damage because it does not require fascial suture placement. Traditionally, abdominal wall defects in these "frozen" abdomens were closed by mobilizing skin or subcutaneous tissue flaps to cover the defect (i.e., accepting a large hernia defect and the need for delayed reconstruction) or by bridging the defect with mesh with later split-thickness skin grafting once granulation tissue has developed. This is associated with a 20% gastrointestinal fistula rate, which is a terrible complication. Additionally, many of these patients required delayed complex abdominal wall reconstructions. Recently, there has been a lot of enthusiasm for acute reconstruction with biologic mesh. However, long-term follow-up studies show that many of these patients require delayed hernia repairs of large defects.[53] In our published experience of treating the open abdomen with the VAC device, we achieved primary fascia closure in 87% at a mean of 7 days with a 2% fistula rate and no intra-abdominal abscess.[54,55] These results are nearly identical to the results reported by Miller and colleagues from Wake Forest University, who taught us how to do this type of closure.[56] More recently, Cothren and colleagues reported a 100% primary fascial closure rate using a modified VAC device technique.[57] The long-term outcomes are not known, but in short-term follow-up (mean 180 days), ventral hernia was 2.3%. However, as is true with all emergency laparotomies, this rate will increase with time, but the hernia defects will be small and more easily repaired.

In addition to damage control scenarios, there are other reasons for leaving the abdomen open and planning a staged relaparotomy:

1. Patients with ischemic bowel who have undergone a resection will be taken back the next day to assess the viability of the remaining bowel before we attempt an anastomosis or ostomy. We have been quite successful in completing the small bowel to colon anastomosis at the second operation; thus, these patients have avoided the need for a temporary ileostomy.
2. Patients who have massive bowel distention that cannot be closed without causing significant intra-abdominal hypertension (IAH) will undergo temporary abdominal closure. Intra-abdominal hypertension sets the stage of ACS, which occurs with subsequent ICU resuscitation.[58] Avoiding ACS significantly improves survival.
3. In patients with necrotizing pancreatitis, we try very hard to avoid operative interventions but are occasionally forced to do so.
4. Patients who develop ACS will require a decompressive laparotomy and temporary abdominal closure. As a result

of advances in trauma care starting in the 1980s, this entity emerged as an epidemic in the mid-1990s in trauma centers worldwide. As we began to understand this new entity, it has been increasingly recognized to occur in nontrauma ICU patients.[59–61] Unfortunately, if you do not look for ACS by monitoring bladder pressures, you will not find it, and these patients will die of refractory shock.

Within our SICU, we have been using DCL for our patients with septic shock. Over 2 years, we had 22 patients who underwent DCL for source control. Sources of intra-abdominal infection were the colon (11 patients), small bowel (four patients), stomach (two patients), and pancreas (one patient). Four patients had peritonitis with no identified source. Of the 22 patients, six died from multiple organ failure, for an actual mortality rate of 27%. The mean P-POSSUM predicted mortality was significantly higher at 69.4% ($p < .02$), as was the predicted mortality of 76% based on a mean Acute Physiology and Chronic Health Evaluation (APACHE) II score of 31.8 ($p < .02$).[62] These data suggest that the use of DCL for patients with surgical sepsis is saving lives and is a viable option for patients with septic shock and the need for immediate operative source control.

ACTIVATED PROTEIN C FOR SEVERE SEPSIS AND SEPTIC SHOCK

In the normal physiologic state, anticoagulation predominates. The major anticoagulant factors are protein C, protein S, antithrombin, and tissue factor (TF) pathway inhibitor. Protein C is activated by the binding of thrombin to thrombomodulin on the surface of the endothelium. Once activated, protein C directly inhibits factor Va and factor VIIIa in the clotting cascade. In patients with severe sepsis and septic shock, there is a decreased expression of thrombomodulin on the vascular endothelium. As a result, there is decreased production of activated protein C (APC). This results in a shift toward the procoagulant state. This shift to a procoagulant state results in microvascular thrombosis, impaired fibrinolysis, and endothelial dysfunction. The microvasculature becomes occluded with resultant tissue hypoxia and direct tissue damage, which ultimately results in organ dysfunction or failure. The extent of coagulation disturbance ranges from mild laboratory abnormalities to disseminated intravascular coagulation (DIC). This underlying disruption of the intrinsic production of APC served as the physiologic impetus for the administration of APC as a means to reverse the procoagulant state seen in severe sepsis and septic shock.

As a result of the expense and potential bleeding complications associated with APC, its use should be restricted to patients meeting specific criteria. The administration of APC is currently recommended in those patients who are at highest risk of death from sepsis. This includes patients with an APACHE II score of 25 or greater, multiple organ failure (two or more organs), septic shock, or acute respiratory distress syndrome (ARDS) from sepsis. Because of the inherent risk of bleeding from the administration of APC, its use in surgical patients must be carefully considered. Current absolute contraindications to the use of APC include active internal bleeding, hemorrhagic stroke within the preceding 3 months, severe head trauma or intracranial surgery in the preceding 2 months, trauma patients with an increased risk of life-threatening hemorrhage, the presence of an epidural catheter, the presence of an intracranial neoplasm, a platelet count less than 30,000/μL, an INR less than 3, or administration of other anticoagulant therapies (warfarin, heparin). The current guidelines for the use of APC in surgical patients include discontinuing the agent 2 hours prior to an invasive surgical procedure and restarting infusion 12 hours after an invasive surgical procedure. The use of APC has been shown to improve survival in surgical patients with a high risk of death. A recent review of current literature by Barie and colleagues revealed a significant reduction in mortality (odds ratio 0.66; 95% confidence interval 0.45 to 0.97) with the administration of APC in surgical patients with an APACHE II score of 25 or greater.[63] Although there is an increased risk of bleeding in surgical patients who receive APC, this survival benefit afforded by the administration of APC is believed to outweigh the risk. However, in those patients with a lower risk of death from sepsis, the administration of APC outweighs the potential benefits because of the increased risk of bleeding complications. The 2008 Surviving Sepsis Campaign guidelines recommend consideration of APC in adult patients with sepsis-induced organ dysfunction with clinical assessment of high risk of death (typically APACHE II > 25 or multiple organ failure) if there are no contraindications (grade 2B; grade 2C for postoperative patients). They recommend that adult patients with severe sepsis and a low risk of death (e.g., APACHE II < 20 or one organ failure) should not receive APC.

Discussion

PATHOPHYSIOLOGY OF SEPSIS: A COMPLEX PROCESS

The clinical manifestations of sepsis are the result of a complex series of interactions between the inciting organism and the host's innate immune response. This intricate cellular interaction involves numerous signaling pathways as well as the production of cytokines and chemokines. A detailed discussion of each of these pathways is beyond the scope of this text. However, a few key elements are discussed.

Characteristics of the Pathogen

The host response to infection can be triggered by bacterial, viral, and/or fungal infection. The specific characteristics of the inciting organism play a role in the body's response to the infectious stimuli. Each organism has specific virulence factors that enable the organism to evade the host's defenses. These virulence factors include antigenic variation of surface molecules, inhibition of complement activation, resistance to phagocytosis, production of exotoxins, and scavenging of reactive oxygen intermediates.[64] Cell-to-cell communication between organisms allows for signaling and upregulation of virulence factors. Perhaps one of the best described virulence factors is lipopolysaccharide (LPS), also known as endotoxin, which is a component of the outer cell wall of all gram-negative bacteria. The presence of LPS provokes local and systemic inflammation, including proliferation of cytokines and activation of macrophages. The presence of LPS is essential to maintaining the integrity of the outer membrane of gram-negative bacteria, acting as a protective barrier against lysozymes, antimicrobial agents, and host phagocytic cells.

Characteristics of the Host

The human body is equipped with a variety of defense mechanisms against microorganisms. These include physical barriers such as the skin and mucosal surfaces, the innate immune response, and the adaptive immune response. Dysfunction of any of these components can lead to the development of sepsis. The recognition of pathogens by the innate immune response initiates a complex cascade of events that are intended to remove the pathogen from the host. This includes the release of reactive oxygen metabolites to destroy the pathogen, the release of chemokines to recruit additional lymphocytes, and the generation of a variety of systemic cytokines to further activate the host immune response. We are just beginning to understand the potential impact of genetic polymorphisms and the impact these may have on patient survival.[65,66]

Effect of Sepsis on Coagulation

Proper function of the coagulation system is of critical importance, particularly in the surgical patient as it plays an important role in hemostasis. Extensive laboratory research has furthered our understanding of the relationship between inflammation and coagulation. In the septic patient, dysregulation of the coagulation system can result in derangements in laboratory tests of coagulation, increased bleeding risk, and DIC. A basic understanding of this relationship is essential to understanding the pathophysiology of sepsis.

A key factor in the interaction between coagulation and inflammation is TF expression. Under normal circumstances, TF is found only on adventitial structures, myocytes, and fibroblasts. When tissue injury occurs, these subendothelial structures that express TF are exposed and the clotting cascade is initiated when TF binds with circulating factor VII. During sepsis, proinflammatory mediators induce the expression of TF on the endothelium. The expression of TF by the endothelium not only activates the coagulation cascade but also is a potent stimulus for excess thrombin generation. Thrombin is a procoagulant molecule that converts fibrinogen to fibrin and promotes platelet activation. The formation of fibrin is followed by consumption of clotting factors and the formation of fibrin clots in the microcirculation. These fibrin clots serve as filters, trapping platelets to form larger clots. All of these actions combined shift the coagulation system into a procoagulant state. In addition, there is a loss of anticoagulant factors, such as thrombomodulin. Proinflammatory cytokines downregulate the production of thrombomodulin on the surface of the endothelial cells. Thrombomodulin is an essential cofactor in the conversion of protein C into APC. Clinically, this imbalance in the coagulation system is reflected as tissue hypoxia secondary to microvascular thrombosis. This disruption in the coagulation system and the resulting microvascular thrombosis have been the target of potential pharmacologic interventions, including APC.

SEPSIS SCREENING: INCREASING AWARENESS AND IMPROVING OUTCOMES

The early identification and management of sepsis remain a significant challenge to health care providers. In the recent past, multiple organizations have focused their efforts on providing evidence-based guidelines (EBGs) in an attempt to decrease the morbidity and mortality associated with sepsis. Several recent studies in the literature have highlighted the correlation between early sepsis intervention and patient survival. The use of EGDT as described by Rivers and colleagues has emphasized the importance of early intervention during the "golden hours" of sepsis.[21] A recently published study by Kumar and colleagues demonstrated a significant correlation between time to appropriate antimicrobial administration and patient survival.[44] In this study of 2,154 patients with septic shock, administration of effective antimicrobial therapy within the first hour of documented hypotension was associated with a survival rate of 79.9%. Each hour of delay in administration of effective antimicrobial therapy was associated with an average decrease in survival of 7.6%.

In spite of strong evidence that the early implementation of evidence-based, sepsis-specific therapies saves lives, the early identification of sepsis remains challenging. The signs and symptoms of sepsis are nonspecific, particularly in the early phases of sepsis. As bedside nurses and other health care providers focus on multiple priorities and tasks, early signs of sepsis are often missed and time-critical interventions are delayed. Lack of awareness of the signs and symptoms of impending sepsis may contribute to the problem. In the surgical patient, some of the early signs of sepsis are often attributed to other common problems seen in the postoperative period. A recent audit of ward nurses' knowledge of sepsis demonstrated a lack of awareness of the standard definitions of sepsis, severe sepsis, and septic shock; the significance of increased blood lactate concentration as an indicator of severe sepsis; and the basic tenets of EGDT.[67] The conclusion of this audit was that these deficits could result in missed or delayed diagnosis of severe sepsis or septic shock and seriously delayed therapy. Physicians also struggle with the early identification and evidence-based management of sepsis. A recent international survey of physicians regarding their knowledge about sepsis reported that 83% of physicians surveyed had missed the diagnosis of sepsis.[68] The reasons listed for missing the diagnosis of sepsis included a lack of monitoring, a lack of a common definition for sepsis, and a lack of knowledge. Of the 1,058 physicians surveyed, only 140 (13.2%) were able to give the definition of sepsis from the ACCP/SCCM consensus statement.

Our experience with the sepsis screening tool in the SICU prompted us to further evaluate sepsis in general surgery patients within our own institution. We conducted a quality improvement review of patients admitted to our SICU over a 5-month period with an admitting diagnosis of sepsis, severe sepsis, or septic shock. Of the 55 patients with sepsis, severe sepsis, or septic shock, 26 (47%) were admitted to the SICU from an inpatient surgical ward. Of these 26 patients admitted from the surgical ward, 15 (58%) presented to the SICU with severe sepsis or septic shock. Of the 15 patients who presented to the SICU in severe sepsis or septic shock, six died (40%). There were no deaths among the 11 patients who presented with sepsis. For each of these 26 patients, the first step of our sepsis screening tool was performed in a retrospective fashion. Of the 26 patients, 20 (77%) had a positive retrospective SIRS screen (SIRS score ≥ 4). On average, the screen became positive 25 hours before the diagnosis of sepsis was made (range 30 minutes to 114.75 hours, SD 35.8, interquartile range 33.75). The Surviving Sepsis Campaign guidelines place great emphasis on the speed with

which sepsis-specific interventions are initiated and the impact this has on sepsis-related mortality. The average delay of 25 hours between the initial recognition of sepsis using this screening tool and the initiation of appropriate therapy is well beyond the recommended time for intervention. This would indicate that the use of this nurse-initiated sepsis screening tool could significantly improve sepsis recognition on the inpatient surgical floor.

We subsequently implemented and validated our sepsis screening tool on the inpatient surgical ward.[12] The screening tool yielded a sensitivity of 99.9%, a specificity of 91.3%, a positive predictive value of 16.3%, and a negative predictive value of 99.9%. The sepsis-related mortality in those patients who screened positive for sepsis was 6.3%. Of the 16 patients who developed sepsis, four (25%) required transfer to the SICU. Of the 16 true positive screens, 14 (87.5%) had sepsis and two (12.5%) had severe sepsis at the time of the screen. These results emphasize the importance of sepsis screening for the identification of sepsis before the patient progresses into septic shock.

IMPLEMENTING EVIDENCE-BASED GUIDELINES: USE OF COMPUTERIZED CLINICAL DECISION SUPPORT

In the recent past, multiple organizations have focused on providing EBGs in an attempt to decrease the morbidity and mortality associated with sepsis.[69–71] These EBGs provide a comprehensive list of therapies and include several time-sensitive interventions. In spite of strong evidence that the early implementation of evidence-based, sepsis-specific therapies saves lives, the complexity of these recommendations makes bedside implementation difficult and subsequent compliance poor. A recent study by McGlyn and colleagues evaluating compliance with implementation of evidence-based care in a variety of acute and chronic health conditions found that only 55% of patients currently receive appropriate evidence-based care.[72] This failure of health care providers to consistently implement evidence-based care is multifactorial. Busy clinicians struggle to keep up with the information overload that has resulted from the recent explosion in health care–related guidelines. As a result, it often takes 15 or 20 years for a newly proven therapy to become standard of care.[73] In addition, guidelines are often difficult to implement at the local level because they are not patient specific and rarely provide explicit directions for use at the bedside. All of these factors result in a significant hurdle that clinicians must overcome to provide up-to-date, evidence-based care.

In the case of EBGs for sepsis management, the number and complexity of the recommendations make it difficult to consistently implement these interventions. In addition, many of the interventions are time sensitive and need to be prioritized. Patients with an intra-abdominal source of surgical sepsis are at particularly high risk because of the severity of illness and treatment complexity. These patients often require emergent operation for source control, with damage control techniques employed for the most severely ill. Integration of surgical intervention with ICU resuscitation introduces even more variables in sepsis management. This necessitates having a system that ensures adequate timely resuscitation and adherence to EBGs for sepsis.

Our previous experience with computerized clinical decision support (CCDS) has proven valuable in implementing other complex EBGs for critically ill patients.[74] A computer-based algorithm has the ability to accurately and precisely manage clinical interventions, often more consistently than the bedside clinician. Previous studies evaluating the use of CCDS to implement EBGs for ARDS management and hemorrhagic shock resuscitation have demonstrated that the use of CCDS improves compliance with EBGs at the bedside.[75–78] Based on this experience, we developed a CCDS protocol for the management of sepsis. This bedside CCDS program includes an algorithm for goal-directed volume resuscitation, with subsequent real-time prompts for specific therapies such as antimicrobials, vasopressors, and further modalities within the initial 24 hours after sepsis identification. Acknowledgment of administered therapies allows the computer logic to proceed to the next step, ensuring compliance with all aspects of the EBGs.

Implementation of CCDS for the management of sepsis has significantly improved our ability to consistently implement EBGs in our SICU. Since implementing our CCDS sepsis management protocol, we have increased our compliance with all components of the 6-hour resuscitation bundle from 29 to 79%. In addition, our overall severe sepsis/septic shock mortality has declined from 24% to 12%. We attribute this significant decrease in sepsis-related mortality to increased compliance with the EBGs, a finding that is consistent with other reports in the literature.[21,44,79–81]

FLUID RESUSCITATION: CRYSTALLOID VERSUS COLLOID

Since the early 1940s, the restoration of intravascular volume has been embraced as a pivotal intervention in shock resuscitation. However, considerable controversy has persisted concerning the optimal resuscitation fluid to use. This is largely attributable to conflicting evidence within the literature. Because of a lack of large, randomized trials addressing the issue, a number of meta-analyses have been performed. One large meta-analysis of 1,419 patients by the Cochrane Injuries Group Albumin Reviewers revealed an increased risk of death in those patients resuscitated with albumin compared with those resuscitated with crystalloid.[82] Another large meta-analysis of by Wilkes and Navickis revealed no difference in mortality between patients who were resuscitated with albumin compared with those resuscitated with crystalloid.[83]

The SAFE trial was a large, multicenter, randomized, controlled trial that compared the effect of colloid versus crystalloid fluid resuscitation on mortality in patients admitted to the ICU.[84] The results of the study revealed similar outcomes for patients in the colloid and crystalloid groups, suggesting that there is no advantage to the use of either resuscitation fluid. A subgroup analysis of patients with severe sepsis showed a slight improvement in survival among patients who received albumin, but this difference was not statistically significant as this study was not specifically designed to evaluate patients with sepsis.

There are several basic differences between crystalloid (lactated Ringer solution, normal saline) and colloid (albumin, hydroxyethyl starch, hypertonic saline) as resuscitation fluid. The volume of distribution of crystalloids is significantly larger than that of colloids. Therefore, the ratio of crystalloid to colloid infusion is approximately 3 to 1. Proponents of the crystalloid resuscitation cite improved expansion of the

extracellular compartment, minimal risk of anaphylactoid reaction, replacement of volume loss with physiologically balanced solution, and decreased costs. Proponents of colloid resuscitation cite faster time to restoration of intravascular volume because of the decrease in fluid required and reduced risk of interstitial edema secondary to the high oncotic pressure. If colloids are used for resuscitation, one must be particularly vigilant about monitoring cardiac filling pressures and avoiding fluid overload. In addition, the expense and availability of albumin may be factors in some settings. The use of hydroxyethyl starch solutions is associated with alterations of the coagulation cascade and therefore should be used with caution in surgical patients. In addition, hydroxyethyl starch solutions have been associated with renal dysfunction and higher rates of acute renal failure in sepsis.[85]

USE OF STEROIDS IN SEPTIC SHOCK

The administration of steroids in septic shock has been debated for decades. In the 1960s, high-dose steroid replacement therapy was found to improve survival in animal models of septic shock. However, a clinical study by Bennet and colleagues found no benefit to the use of steroids in sepsis, and the practice was largely abandoned.[86] In the 1970s, high-dose steroids were widely used for patients with septic shock. Schumer and colleagues demonstrated significant improvement in survival among patients who received high-dose steroids.[87] This practice continued into the 1980s, at which time new evidence emerged that high-dose steroids were associated with an increased risk of death and a higher frequency of secondary infections. However, because of the discrepancies in the medical literature regarding the use of steroids in sepsis, there was no clear consensus. The 1990s produced several meta-analyses evaluating the use of high-dose steroids in septic shock. The consensus of these studies was that high-dose steroids provided no survival benefit and, in fact, were associated with increased mortality. As a result of these studies, the use of high-dose steroids for patients with septic shock has been largely abandoned. However, the use of low-dose steroids for the management of septic shock remains a topic of intense discussion.

The concept of relative adrenal insufficiency in septic shock has been the focus of several recent clinical studies. To better understand the debate, a basic understanding of the role of the adrenal glands is required. The adrenal gland produces several substances, including sympathetic hormones and glucocorticoids, including cortisol. Cortisol has immunologic and antiinflammatory effects, including inhibition of many proinflammatory cytokines (interleukin-1 [IL-1], IL-2, IL-3, IL-6, interferon gamma, and tumor necrosis factor–α). It also stimulates the production of antiinflammatory mediators such as IL-10 and decreases the local inflammatory reaction. Cortisol also plays a vital role in maintaining vascular tone and endothelial integrity. In addition, cortisol potentiates the vasoconstrictor effects of catecholamines. During critical illness, the normal physiologic response results in the stimulation of the adrenal glands and an increase in cortisol production by up to sixfold. During sepsis, the adrenal glands' ability to increase cortisol production may be impaired. Multiple factors contribute to this, including high levels of circulating inflammatory cytokines, decreased glucocorticoid sensitivity of receptors, and suppression of the hypothalamic-pituitary-adrenal axis by various medications. The end result is a state of relative adrenal insufficiency.

In the recent past, numerous trials have been undertaken to evaluate the use of low-dose steroids in sepsis. Low-dose steroid use is defined as 300 mg or less of hydrocortisone (or an equivalent steroid) over 5 days or less. In 2002, Annane published the results of a multicenter, randomized, double-blind, placebo-controlled trial evaluating the use of low-dose steroids in patients with septic shock.[38] All patients with septic shock were randomized within 3 hours of the onset of septic shock to either the treatment arm or the placebo arm. Patients underwent a low-dose cosyntropin stimulation test, and relative adrenal insufficiency was defined as a delta cortisol of 9 μg/dL or less. Patients in the treatment arm received hydrocortisone 50 mg IV every 6 hours and 50 μg of fludrocortisone orally daily or matching placebos. Patients who received low-dose steroids showed a decreased time to shock reversal and a decreased mortality compared with patients who received placebo. Subsequently, two smaller trials and two meta-analyses demonstrated similar results.[88,89] The findings of these studies suggest that low-dose steroid use in patients with relative adrenal insufficiency significantly improves time to shock reversal and 28-day mortality. However, a follow-up study published in 2008 brought the use of low-dose steroids in septic shock back into question. The Corticosteroid Therapy of Septic Shock (CORTICUS) trial was a multicenter, randomized, double-blind, placebo-controlled trial that also evaluated the use of low-dose steroids in patients with septic shock.[90] Patients with septic shock underwent a low-dose cosyntropin stimulation test with a delta cortisol of 9 μg/dL used to define relative adrenal insufficiency. Unlike the Annane study, patients in the CORTICUS trial were randomized up to 72 hours after the diagnosis of septic shock to receive either hydrocortisone 50 mg IV every 6 hours or placebo. No difference in 28-day all-cause mortality was identified, but earlier shock resolution was confirmed in the steroid group (median time to reverse shock 3.1 versus 5.7 days; $p = .003$). However, it is important to note that the patients enrolled in this trial had a lower placebo group mortality (63% in the Annane study; 31% in the CORTICUS trial). The Annane study enrolled only patients with vasopressor-dependent septic shock, whereas the CORTICUS trial enrolled all patients with septic shock. In the Annane study, patients were randomized within 3 hours of the onset of septic shock. In the CORTICUS trial, patients were randomized up to 72 hours after the onset of septic shock. In addition, patients in the Annane study received both hydrocortisone and fludrocortisones as opposed to only hydrocortisone in the CORTICUS trial. The CORTICUS trial patients were different as well, with more abdominal sepsis and more surgical patients and fewer pneumonia patients. The CORTICUS trial documented that 46.7% of patients did not have a response to the corticotropin stimulation test, and these patients had a higher mortality rate. CORTICUS was underpowered for the primary outcome measure, death within 28 days in patients who did not respond to corticotropin. Therefore, considerable controversy still remains. An important contribution of the CORTICUS trial was the identification that hospital-based immunoassays are not accurate for cortisol measurements in critically ill patients.

Despite the ongoing debate over the optimal use of low-dose steroids in patients with septic shock, the Surviving Sepsis Campaign guidelines still recommend that hydrocortisone be considered in patients with septic shock who are not responsive to volume resuscitation and vasopressor therapy. The dose of hyrdrocortisone given should not exceed 300 mg/day and should be administered in divided doses. The use of fludrocortisone is still considered to be optional. Although the optimal duration of steroids also remains in question, most would agree that steroid administration should continue until the patient is off vasopressor therapy.

IMPORTANCE OF EARLY BROAD-SPECTRUM ANTIMICROBIALS

The timely administration of empirical antimicrobial therapy is perhaps the most beneficial pharmacologic intervention in patients with sepsis. Although antimicrobial therapy has always been a mainstay in the treatment of infection, only recently has the importance of antimicrobial choice and rapid administration been demonstrated to significantly impact patient mortality. In a landmark study by Kumar and colleagues, the relationship between time to antimicrobial administration and patient mortality was clearly documented.[44] This multicenter, retrospective study evaluated 2,154 patients with septic shock over a 15-year period. The primary objective was to determine the prevalence and impact on mortality of delays in antimicrobial administration from the initial onset of septic shock. The results of this study demonstrated a 7.6% decrease in survival for each hour of delay in antimicrobial administration after the onset of shock. In addition, patients who received effective antimicrobial therapy within 1 hour of the onset of septic shock had the highest survival rate at 79.9%. The results of this study have subsequently been corroborated by other studies.[91,92]

In spite of convincing evidence that early antimicrobial administration significantly improves outcomes in patients with sepsis, compliance with this recommendation remains problematic. In Kumar and colleagues' study, more than 50% of septic shock patients experienced a delay in antimicrobial administration of at least 6 hours.[44] A recent multicenter prospective analysis of compliance with antimicrobial administration revealed that only 60% of patients were receiving antimicrobials within 1 hour.[93] After a 2-year educational campaign and focused programs for performance improvement, compliance reached only 67%. Clearly, there must be some significant clinical hurdles that we must overcome to implement this seemingly simple intervention.

Several barriers to the timely administration of antimicrobials have been identified. One critical issue is the rapid availability of IV access. During active sepsis resuscitation, IV access is needed for fluid administration and antimicrobial therapy. In addition, appropriate cultures, often from various sites, must be sent prior to antimicrobial administration. Many antimicrobials are not readily available in patient care areas and must be transported from the pharmacy to the bedside. Most patients receive at least two empirical antimicrobials, which can result in additional delays if adequate IV access is not available. Performing this multitude of tasks, particularly in an unstable septic shock patient, can quickly overwhelm the clinical team. The end result is a delay in antimicrobial administration.

Although each institution has its own barriers to implementation, it is important to recognize the importance of administering IV antimicrobials within 1 hour. This simple task of administering an antimicrobial can significantly improve patient survival. To minimize the time to antimicrobial administration, a few basic clinical practices can be implemented to help overcome these barriers. Rapidly establishing IV access is critical to the success of the resuscitation. If peripheral IV access is not easily attainable, central venous access should be secured promptly. Central venous access has the benefit of providing the clinical team with multiple infusion ports and a way to monitor CVP. Working in conjunction with Pharmacy to establish a rapidly available, premixed supply of commonly administered antimicrobials will also help minimize delays. Many institutions have developed a "sepsis toolbox" containing IV fluids, culture materials, blood tubes for measuring serum lactate, and a premixed supply of antimicrobials. This toolbox can be taken to the bedside of the sepsis patient at any location in the hospital, avoiding potential delays in the initiation of resuscitation.

The choice of empirical antimicrobial therapy is as important as administering antimicrobials within 1 hour. 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. Failure to provide effective antimicrobial coverage for the causative organism significantly increases the risk of death from sepsis. The best practice is to provide broad coverage initially and de-escalate antimicrobial therapy based on culture data.

PLANNED LAPAROTOMY FOR ESTABLISHED PERITONITIS IS NOT DAMAGE CONTROL

The treatment strategy for patients with established peritonitis has been debated for three decades. After an initial emergency laparotomy, relaparotomy is frequently necessary to eliminate persistent peritonitis or a new infectious focus. There are two widely used relaparotomy strategies: relaparotomy when the patient's condition demands it ("on demand") and "planned" relaparotomy. In the planned strategy, a relaparotomy is performed every 48 hours for inspection, drainage, and peritoneal lavage of the abdominal cavity until the findings are negative for ongoing peritonitis. The planned strategy may lead to early detection of persistent peritonitis or a new infectious focus that reduces the risk of multiorgan failure but harbors the risk of potentially unnecessary reexplorations in critically ill patients, whereas the on-demand strategy harbors the risk of a potentially harmful delay in the detection of intra-abdominal infection with increased risk of multiorgan failure and the need for a delayed laparotomy at a time when intra-abdominal adhesions (days 10 to 14) create a hostile operative environment. Over the years, a number of case series have offered conflicting results. The consensus and meta-analysis conclusion is that for the non–critically ill patient (APACHE II < 10), use the on-demand strategy. Newer computed tomographic scan technology can accurately detect intra-abdominal infections in patients who clinically deteriorate or fail to improve, and with aggressive interventional radiology, greater than 95% of the

infections can be successfully treated without a repeat laparotomy. More recently, van Ruler and colleagues performed a prospective, randomized, controlled trial (PRCT) in patients with severe peritonitis (defined as APACHE II > 10) that confirmed that the practice of planned relaparotomy was associated with no difference in outcome compared with on-demand laparotomy and was associated with increased expenditure of hospital resources and length of hospital stay.[94] It is important to emphasize that this recent PRCT is not relevant to the previous discussion of "damage control" in patients with septic shock. Patients randomized into this PRCT had a mean APACHE II score of 15 (with predicted mortality of < 25%), whereas the patients we described had a mean APACHE II score of 32 (with a predicted mortality of > 75%). We use damage control in patients in the "persistent septic shock cycle." Its rationale is to appropriately time and limit the duration of source control to break the cycle and then optimize resuscitation in the ICU.

Conclusion

Sepsis continues to be a common and potentially lethal problem for surgical patients. The early identification and management of surgical patients with sepsis present a significant challenge to the surgical team. The implementation of rapid, evidence-based care in conjunction with timely surgical source control improves survival.

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