Sepsis Management

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LEARNING OBJECTIVES

1. Assess the updates in guideline definitions and recommendations for managing sepsis and/or septic shock.
2. Evaluate recent literature regarding the management of sepsis and septic shock.
3. Design an evidence-based treatment regimen for a patient with sepsis and/or septic shock.
4. Justify pharmacist involvement in preventing, recognizing, and managing sepsis and/or septic shock.

ABBREVIATIONS IN THIS CHAPTER

AKI	Acute kidney injury
CVP	Central venous pressure
EGDT	Early goal-directed therapy
EN	Enteral nutrition
MAP	Mean arterial pressure
PLR	Passive leg raise
qSOFA	Quick Sequential Organ Failure Assessment
RRT	Renal replacement therapy
Scvo$_2$	Central venous oxygen saturation
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential Organ Failure Assessment
SSC	Surviving Sepsis Campaign
SUP	Stress ulcer prophylaxis
VTE	Venous thromboembolism

Table of other common abbreviations.

INTRODUCTION

Epidemiology

Sepsis is a multifaceted clinical syndrome involving the response of a host's immune system to an invading pathogen. The word "sepsis" was used in Greek literature and is derived from the Greek work "sepo," which translates to "I rot" (Funk 2009). Throughout history, understanding of the pathophysiology of sepsis has evolved and grown. However, much remains to be discovered about this disease process. A complex interaction between immunity (both innate and adaptive), inflammation, coagulation, and circulation often results in tissue damage and organ failure. Sepsis management aims to target each aspect of this pathophysiology to improve patient survival and outcomes.

Sepsis continues to be a leading cause of morbidity and mortality in the United States. Trends identified over the past 10 years show that the incidence of sepsis and septic shock is increasing (Kadri 2017). Using clinical data to identify septic shock, defined as a presumed infection with vasopressor use, the incidence of sepsis increased from 12.8 per 1000 hospitalizations in 2005 to 18.6 per 1000 hospitalizations in 2014, a 4.9% increase per year. Reports indicate a sepsis incidence of around 6% in hospitalized patients (Rhee 2017). Despite the rising occurrence of sepsis, mortality has decreased. The in-hospital mortality rate for septic shock, as identified by clinical criteria, decreased from 54.9% in 2005 to 50.7% in 2014 (Kadri 2017). Other reports indicate an in-hospital mortality rate of almost 16% for sepsis and greater than 40% for septic shock (Singer 2016).

In addition to the increase in morbidity and mortality, sepsis was the most expensive condition to treat in the U.S. health care system in 2013, accounting for almost $24 billion in annual costs (Torio 2016).

Potential reasons for the increased incidence of sepsis include increased age of the population, increased use of invasive procedures, and increased use of immunosuppressive therapies. The evolving sepsis definitions over time may have contributed to a greater sensitivity in identifying sepsis.

PATIENT ASSESSMENT AND MONITORING

Definitions and Classifications

Identifying and classifying patients with sepsis or septic shock has changed significantly over the past 2 years. Previously, the systemic inflammatory response syndrome (SIRS) criteria were important in identifying patients with sepsis/septic shock. However, with the publication of the Third International Consensus Definitions for Sepsis and Septic Shock guidelines (Sepsis-3) in 2016, the Sequential Organ Failure Assessment (SOFA) and quick SOFA (qSOFA) were recommended in place of the SIRS criteria (Singer 2016) (Figure 1). Controversy still exists regarding which criteria should be used to identify patients with sepsis. Therefore, the pharmacist should be familiar with the different standards and definitions.

The Society of Critical Care Medicine and the European Society of Intensive Care Medicine defined sepsis as "life-threatening organ dysfunction caused by dysregulated host response to infection" and septic shock as "subset of sepsis with circulatory and cellular/metabolic dysfunction associated with higher risk of mortality." The classification of severe sepsis as outlined in the 2012 iteration of the Surviving Sepsis Campaign (SSC) guidelines is no longer used in the 2016 update (Rhodes 2017).

To meet the Sepsis-3 sepsis definition, patients should have a suspected or documented infection and an acute increase of at least 2 SOFA points from baseline. If patients meet the sepsis criteria and require vasopressor therapy to meet the mean arterial pressure (MAP) of at least 65 mm Hg and their lactate concentration is greater than 2 mmol/L (18 mg/dL) despite adequate fluid resuscitation, their condition is classified as septic shock (Rhodes 2017; Singer 2016).

In Sepsis-3, qSOFA is suggested to identify patients with suspected infection who are likely to develop sepsis or septic shock. This tool can be used outside the ICU, and even outside the hospital, because it is easy to perform by clinical examination (Singer 2016).

Monitoring

To identify patients likely to develop sepsis or septic shock, the qSOFA criteria (includes mental status, systolic blood pressure, and respiratory rate) should be monitored in patients with a suspected or documented infection. Once patients meet at least two qSOFA criteria, organ dysfunction should be assessed using the SOFA score (see Table 1 for a list of the criteria). An increase in SOFA score of at least 2 points with suspected infection indicates sepsis. A SOFA score of 2 or more correlates with a mortality rate of 10% (Singer, 2016).

The 2018 SSC guideline update does not specifically address hemodynamic parameters as resuscitation goals. However, the update advocates measuring lactate to guide resuscitation therapy (Levy 2018).

Challenges Facing Critical Care Practitioners

Because of the complexity of sepsis, it is exceedingly difficult to develop a concrete set of criteria for identifying it. Although recent guidelines have tried to solidify definitions, controversy remains surrounding the suggested classifications, and previous sepsis definitions are still being used clinically. This ambiguity could hinder evaluating the incidence rates of this syndrome over time, as well as identifying the condition. Clinicians need to be familiar with proposed old and new definitions, clinical markers, and pathophysiology of sepsis in order to identify patients with this condition.

In the 2018 SSC guideline update, the 3- and 6-hour care bundles are combined into a 1-hour care bundle. Providers may find it difficult not only to meet care bundles, but also to distinguish between guideline recommendations and core measure criteria. Significant discrepancies exist between the Centers for Medicare & Medicaid (CMS) early management bundle, the Severe Sepsis/Septic Shock (SEP-1) core measure,

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BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the pathophysiology that leads to sepsis and septic shock.
- Hemodynamic assessment in septic shock.
- Pharmacology, pharmacokinetics, pharmacodynamics, and spectrum of activity of antimicrobial agents. (Review article provided in additional readings)

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources are available for readers wishing additional background information on this topic.

- Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med 2017;45:486-552.
- Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign bundle: 2018 update. Crit Care Med 2018;46:997-1000.
- Myburgh JA, Mythen MG. Resuscitation fluids. N Engl J Med 2013;369:1243-51.
- Varghese JM, Roberts JA, Lipman J. Antimicrobial pharmacokinetic and pharmacodynamics issues in the critically ill with severe sepsis and septic shock. Crit Care Clin 2011;27:19-34.

- Sepsis: Life-threatening organ dysfunction caused by dysregulated host response to infection (associated with > 10% of hospital mortality)

- Septic shock: Subset of sepsis with circulatory and cellular/metabolic dysfunction associated with higher risk of mortality (associated with > 40% of hospital mortality)

- qSOFA
  - Altered mental status = GCS score < 15
  - Systolic blood pressure (SBP) ≤ 100 mm Hg
  - Respiratory rate ≥ 22 breaths/min

SOFA Score

System	Score				
	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg	≥ 400	< 400	< 300	< 200 (with respiratory support	< 100 with respiratory support
Coagulation					
Plt, × 10^3/mm^3	≥ 150	< 150	< 100	< 50	< 20
Liver					
Bilirubin, mg/dL	< 1.2	1.2–1.9	2.0–5.9	6.0–11.9	≥ 12.0
Cardiovascular					
MAP ≥ 70 mm Hg	MAP < 70 mm Hg	Dopamine < 5 mcg/ kg/min or dobutamine	(any dose)	Dopamine 5.1–15 mcg/ kg/min or epinephrine ≤ 0.1 mcg/min or norepinephrine ≤ 0.1 mcg/kg/min	Dopamine > 15 mcg/ kg/min or epinephrine > 0.1 mcg/min or norepinephrine > 0.1 mcg/kg/min
Central nervous system					
GCS score	15	13–14	10–12	6–9	< 6
Renal					
SCr, mg/dL	< 1.2	1.2–1.9	2.0–3.4	3.5–4.9	> 5.0
Urinary output, mL/day				< 500	< 200

Figure 1. Sepsis definitions according to the 2016 SSC guidelines.

GCS = Glasgow Coma Scale (score); Pao_2/Fio_2 = arterial oxygen partial pressure to fractional inspired oxygen.

Information from: Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016 (SSC 2016). Crit Care Med 2017;45:486-552; Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801-10; and Ferreira FL, Bota DP, Bross A, et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 2001;286:1754-8.

Table 1. EGDT Literature

Study	Design and Population	Intervention	Results	Conclusion
Tuchschmidt 1992	RCT Patients with suspected septic shock (n=51)	Normal treatment (resuscitation goal of cardiac index ≥ 3 $L/min/m^2$ and SBP ≥ 90 mm Hg) Optimal treatment (resuscitation goal of cardiac index ≥ 6 $L/min/m^2$ and SBP ≥ 90 mm Hg)	Mortality 72% in normal treatment group vs. 50% in optimal treatment group (p=0.014)	Titration of therapy to increased concentrations of cardiac index and Do_2 may be associated with improved survival
Yu 1993	RCT Patients with sepsis/septic shock, ARDS, or hypovolemic shock with pulmonary arterial catheters (n=67)	Control group = no specific therapeutic goal Treatment group = Do_2I goal > 600 $mL/min/m^2$	No significant difference in mortality between groups Subgroup analysis of supranormal Do_2I vs. normal Do_2I mortality (14% vs. 56%, p=0.01)	Supranormal Do_2I values may be associated with increased survival in this disease state
Haynes 1994	RCT Patients with septic shock (n=109)	Treatment group = resuscitation goal of cardiac index > 4.5 $L/min/m^2$, Do_2 > 600 $mL/min/m^2$, and O2 consumption > 170 $mL/min/m^2$	No significant difference in ventilated days, ICU LOS, hospital LOS, or mortality	Overall outcomes in patients not improved using dobutamine to meet these hemodynamic goals
Gattinoni 1995	RCT Critically ill adults (n=762)	Normal cardiac index (cardiac index 2.5–3.5 $L/min/m^2$) Supranormal cardiac index (cardiac index > 4.5 $L/min/m^2$) Normal Svo_2 (> 70% or difference of < 20% between arterial oxygen saturation and Svo_2)	No significant differences in mortality or rate of organ dysfunction	Therapeutic goal of supranormal cardiac index or normal Svo_2 does not reduce morbidity or mortality in critically ill patients
Yu 1998	RCT Critically ill adults ≥ 50 with SIRS, sepsis, severe sepsis, septic shock, or ARDS unable to achieve Do_2 ≥ 600 $mL/min/m^2$ with fluid alone (n=105)	Control group = resuscitation goal of Do_2 450–550 $mL/min/m^2$ Treatment group = resuscitation goal of Do_2 ≥ 600 $mL/min/m^2$	In patients age 50–75, mortality was 21% in the treatment group vs. 52% in the control group (p=0.01) In those > 75, mortality was 57% in the treatment group vs. 61% in the control group (p=NS)	In patients age 50–75, a higher Do_2 goal improved survival. However, no benefit occurred in patients > 75
Alia 1999	RCT Patients with severe sepsis or septic shock (n=63)	Control group = normal targeted value of Do_2 Treatment group = targeted Do_2 > 600 $mL/min/m^2$	Mortality was 66% in the control group vs. 74% in the treatment group (p=0.46)	Maximizing Do_2 as a treatment goal did not reduce mortality

Table 1. EGDT Literature *(continued)*

Study	Design and Population	Intervention	Results	Conclusion
Rivers 2001	RCT Sepsis, severe sepsis, or septic shock (n=236)	Standard therapy = hemodynamic protocol at physician discretion EGDT group	In-hospital mortality higher in standard therapy group (p=0.009) 28-day mortality higher in standard group (p=0.03)	EGDT has significant short- and long-term benefits
Lin 2006	RCT Septic shock (n=224)	Standard therapy = clinician judgment GDT = algorithm-based treatment	Time to shock reversal lower in GDT (47 hr vs. 65.4 hr, p<0.001) In-hospital mortality lower in GDT (53.7% vs. 71.6%, p=0.006) ICU mortality lower in GDT (50% vs. 67.2%, p=0.009)	GDT resulted in faster shock reversal and mortality benefit than standard therapy
Wang 2006 [abstract]	RCT Patients with septic shock (n=16)	Conventional therapy GDT with CVP, MAP, and Svo$_2$ goals	7- and 14-day in-hospital mortality lower in GDT (p<0.05)	Efficacy of GDT better than conventional therapy
Chen 2007 [abstract]	RCT Early stages of septic shock (n=273)	Control group EGDT	Incidence of MODS lower in EGDT (p=0.002) MODS mortality rate lower in EGDT (p=0.007)	EGDT may decrease the incidence and severity of MODS and can decrease mortality of MODS in the presence of severe sepsis
He 2007 [abstract]	RCT Patients with septic shock (n=203)	Control group EGDT	Mortality in patients with mild organ dysfunction lower in EGDT (27.78% vs. 37.5%, p<0.05) No difference between groups among patients with moderate or severe organ dysfunction	In early periods of septic shock, EGDT can decrease mortality, but this benefit does not extend into advanced stages of septic shock
Yan 2010	RCT Patients with severe sepsis or septic shock (n=303)	Conventional therapy EGDT	28-day survival higher in EGDT (75.2% vs. 57.5%, p=0.001) ICU mortality higher in conventional therapy (35% vs. 50.7%, p=0.035)	EGDT improves 28-day survival in patients with severe sepsis and septic shock
Jones 2010	RCT Patients with severe sepsis and septic shock (n=300)	Scvo$_2$ group = resuscitated to normalize CVP, MAP, and Scvo$_2$ Lactate clearance group = resuscitated to normalize CVP, MAP, and lactate clearance of at least 10%	In-hospital mortality insignificantly lower with lactate clearance group (23% vs. 17%)	Adding lactate clearance to resuscitation goals did not decrease mortality

(continued)

Table 1. EGDT Literature (*continued*)

Study	Design and Population	Intervention	Results	Conclusion
Yealy 2014 (PROCESS)	RCT Patients with septic shock (n=1341)	Protocol-based EGDT Protocol-based standard therapy Usual care	No significant difference in 60- or 90-day mortality or 1-yr mortality	Protocol-based resuscitation did not improve outcomes
Andrews 2014	RCT Patients with sepsis within 24 hr of admission (n=109)	Protocol-based care Usual care	No difference between groups for in-hospital mortality (RR 1.05; 95% CI, 0.79–1.41)	Results are likely because of factors other than tissue hypoperfusion causing end organ failure, and future studies should amend inclusion criteria to control for this
Peake 2014 (ARISE)	RCT Patients with early septic shock (n=796)	Usual care EGDT	No difference in 90-day mortality (18.6% vs. 18.8%, p=0.90)	EGDT did not reduce mortality at 90 days
Mouncey 2015 (PROMISE)	RCT Patients with early septic shock (n=1260)	Usual care EGDT	No difference in 90-day mortality (RR 1.01; 95% CI, 0.85–1.20)	EGDT did not improve outcomes

ARDS = acute respiratory distress syndrome; CVP = central venous pressure; Do_2 = oxygen delivery; Do_2I = oxygen delivery indexed; EGDT = early goal-directed therapy; GDT = goal-directed therapy; LOS = length of stay; MODS = multiple organ dysfunction syndromes; RCT = randomized controlled trial; $Scvo_2$ = central venous oxygen saturation; SIRS = systemic inflammatory response syndrome.

Information from: Tuchschmidt J, Fried J, Astiz M, et al. Elevation of cardiac output and oxygen delivery improves outcome in septic shock. Chest 1992;102:216-20; Yu M, Mitchell L, Smith P, et al. Effect of maximizing oxygen delivery on morbidity and mortality rates in critically ill patients: a prospective, randomized, controlled study. Crit Care Med 1993;21:830-8; Hayes M, Timmins AC, Yau E, et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 1994;330:1717-22; Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. N Engl J Med 1995;333:1025-32; Yu M, Burchell S, Hasaniya N, et al. Relationship of mortality to increasing oxygen delivery in patients >or=to 50 years of age: a prospective, randomized trial. Crit Care Med 1998;26:1011-9; Alia I, Esteban A, Federico G, et al. A randomized and controlled trial of effect of treatment aimed at maximizing oxygen delivery in patients with severe sepsis or septic shock. Chest 1999;115:453-61; Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;344:1368-77; Lin SM, Huang CD, Lin HC, et al. A modified goal-directed protocol improves clinical outcomes in intensive care unit patients with septic shock: a randomized controlled trial. Shock 2006;26:551-7; Wang XZ, Lu CJ, Gao FQ, et al. Efficacy of goal-directed therapy in the treatment of septic shock. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 2006;18:661-4; Chen ZQ, Jin YH, Chen H, et al. Early goal-directed therapy lowers the incidence, severity and mortality of multiple organ dysfunction syndrome. Nan Fang Yi Ke Da Xue Xue Bao 2007;27:1892-5; He ZY, Gao Y, Wang XR, et al. Clinical evaluation for execution of early goal directed therapy in septic shock. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 2007;19:14-6; Early Goal-Directed Therapy Collaborative Group of Zhejiang Province. The effect of early goal-directed therapy on treatment of critical patients with severe sepsis/septic shock: a multi-center, prospective, randomized, controlled study. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 2010;22:331-4; Jones AE, Shapiro NI, Trzeciak S, et al. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. JAMA 2010;303:739-46; ProCESS Investigators, Yealy DM, Kellum JA, Huang DT, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med 2014;370:1683-93; Andrews B, Mechemwa L, Kelly P, et al. Simplified severe sepsis protocol: a randomized controlled trial of modified early goal-directed therapy in Zambia. Crit Care Med 2014;42:2315-24; ARISE Investigators, ANZICS Clinical Trials Group, Peake SL, Delaney A, Bailey M, et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med 2014;371:1496-506; and Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med 2015;372:1301-11.

and the newest SSC 1-hour bundle. Because the SEP-1 requirements have not been updated to reflect the newest guideline recommendations, practitioners may need to decide which of these to follow. The definitions and requirements outlined in the CMS SEP-1 core measure are shown in Box 1. To be considered compliant with SEP-1, all measures must be met.

Many barriers to accomplishing these tasks in the recommended time interval often exist. A study assessed adherence to the SSC guideline recommendations of 3- and 6-hour care bundles at one institution before and after implementing the SEP-1 core measure. The study found a 3-hour bundle compliance rate of 31.3% before SEP-1 implementation and 66.4% after implementation. The 6-hour compliance rate was 41.7%

before SEP-1 implementation and 75.5% afterward (Ramsdell 2017). Even after SEP-1 became a core measure, these results still indicate room for improvement with compliance rates.

New knowledge regarding sepsis is continually coming to light, indicating there is still much to learn. The evolving body of evidence for sepsis treatment presents the challenge of staying up to date. With the rapid dissemination of information, practitioners should familiarize themselves with the newest information available, assess the quality of any new evidence, and ultimately incorporate this into their patients' care plans to improve patient outcomes. This chapter focuses on updates in the literature regarding sepsis and septic shock management.

Box 1. SEP-1 Definitions and Requirements of CMS SEP-1 Core Measure vs. Sepsis-3 Definitions and SSC 1-Hr Bundle

CMS SEP-1 Definitions

Sepsis = 2 SIRS criteria + suspected infection

  SIRS criteria
- Temp > 101°F
- Temp < 96.8°F
- HR > 90 beats/min
- RR > 20 breaths/min
- WBC > 12 x 10^3 cells/mm^3
- WBC < 4 x 10^3 cells/mm^3
- > 10% bandemia

Severe sepsis = sepsis + ≥ 1 variables of organ dysfunction
Organ dysfunction variables

- SBP < 90 mm Hg
- MAP < 70 mm Hg
- SBP decrease > 40 mm Hg from known baseline
- SCr > 2.0 mg/dL
- Urinary output < 0.5 mL/kg/hr for > 2 hr
- Bilirubin > 2.0 mg/dL
- Plt < 100,000/mm^3
- INR > 1.5 or PTT > 60 s
- Altered mental status
- Lactate > 2 mmol/L

Septic shock = severe sepsis + hypoperfusion despite adequate fluid resuscitation or lactate > 4 mmol/L

Sepsis-3 Definitions

Sepsis = suspected/documented infection + increase in SOFA score of at least 2 from baseline

Septic shock = sepsis + need for vasopressors and lactate > 2 mmol/L despite adequate fluid resuscitation

CMS SEP-1 Requirements

Severe sepsis

  Within 3 hr of presentation
- Measure serum lactate
- Obtain blood cultures before antibiotic administration
- Administer antibiotics

  Within 6 hr of presentation
- Repeat serum lactate if initial lactate is > 2 mmol/L

Septic shock

  Within 3 hr of presentation
- Measure serum lactate
- Obtain blood cultures before antibiotic administration
- Administer antibiotics
- Resuscitation with 30 mL/kg of crystalloid fluids

  Within 6 hr of presentation
- Repeat volume status and tissue perfusion assessment
  - Physical examination findings – vital signs, cardiopulmonary examination, capillary refill evaluation, peripheral pulse evaluation, skin examination
  - Document two of the following:
    - CVP
    - Scvo$_2$
    - Bedside cardiovascular ultrasonography
    - PLR or fluid challenge
- Vasopressor administration (if hypotension persists after fluid)

SSC 1-Hr Bundle Requirements

Measure lactate concentration. Re-measure if initial lactate is > 2 mmol/L

Obtain blood cultures before administering antibiotics

Administer broad-spectrum antibiotics

Rapidly administer 30 mL/kg of crystalloid for hypotension or lactate ≥ 4 mmol/L

Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥ 65 mm Hg

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CVP = central venous pressure; HR = heart rate; PLR = passive leg raise; Scvo2 = central venous oxygen saturation; SIRS = systemic inflammatory response syndrome.

HEMODYNAMIC STABILIZATION

Early Goal-Directed Therapy

Early goal-directed therapy (EGDT) was introduced in 2001 (Rivers 2001). This study showed that a 6-hour protocol significantly improved outcomes in patients with severe sepsis and septic shock compared with usual care. In this study, usual care consisted of a protocol for hemodynamic support that did not include parameters such as central venous oxygen saturation ($Scvo_2$), and achieving treatment goals was left to physician discretion. Since that time, 3 large randomized, multicentered studies (ARISE, PROCESS and PROMISE) have reported no mortality benefit with EGDT compared to usual care, making its value somewhat controversial (see Table 1).

A recent meta-analysis examined trials in which the study population included adults with severe sepsis or septic shock, the intervention group received EGDT, and the comparator group consisted of usual care or lactate-guided therapy (Lu 2016). On examination of 13 trials, the data analyses suggested that EGDT was significantly associated with decreased mortality compared with usual care (RR 0.87; 95% CI, 0.77–0.98) but was also significantly associated with increased mortality compared with lactate-guided therapy (RR 1.60; 95% CI, 1.24–2.06).

A second meta-analysis evaluating 17 trials comparing EGDT with usual care found that overall mortality to be reduced with EGDT only if the mortality rate of the usual care group exceeded 30% (Park 2017).

On further examination, it appears the mortality benefit occurred in the subgroup of trials published between the 2004 and the 2012 SSC guidelines. The underlying implication from these data is that over time, usual care has improved, resulting in a less pronounced difference in mortality rates between EGDT and usual care. It is still reasonable to follow the care bundles set forth by SSC guidelines and to use dynamic hemodynamic parameters to inform clinical decisions during fluid resuscitation in sepsis.

Assessment of Hemodynamic Stability

The current SSC guidelines recommend normalizing lactate as a resuscitation goal and no longer recommend that parameters such as central venous pressure (CVP) and $Scvo_2$ guide therapy (Rhodes 2017). This change was partly because of literature suggesting poor correlation between parameters such as CVP and volume status obtained by more reliable methods such as pulse pressure variation or stroke volume variation. Measuring these parameters also failed to show mortality benefit in several trials. Because no harm has been associated with CVP- and $Scvo_2$-guided therapy, it may be reasonable to consider these parameters when evaluating the efficacy of resuscitation efforts. However, dynamic measures such as passive leg raise (PLR) and fluid challenges should be used as well.

A systematic review and meta-analysis of 21 studies assessed the accuracy of PLR in predicting the response of cardiac output to volume expansion (Monnet 2016). The pooled sensitivity of PLR-induced changes in cardiac output (or surrogate) was 0.85 (0.81–0.88), and the pooled specificity was 0.91 (0.88–0.93). For PLR-induced changes in pulse pressure, the pooled sensitivity was 0.56 (0.49–0.53) and pooled specificity, 0.83 (0.77–0.88). The best threshold was a PLR-induced increase in cardiac output of 10% plus or minus 2% or greater. The study concluded that PLR-induced changes in cardiac output reliably indicated cardiac output response to volume expansion in adults with circulatory failure. When using pulse pressure to assess PLR-induced changes, pooled specificity remains intact, but pooled sensitivity is poor. Another systematic review and meta-analysis pooled 23 trials to assess how well PLR performed in various settings (Cherpanath 2016). Pooled sensitivity was 86% (95% CI, 79–92), with pooled specificity 92% (95% CI, 88–96). Passive leg raise–induced changes in flow variables such as cardiac output yielded a sensitivity of 85% and specificity of 92%, whereas changes in pulse pressure on PLR yielded a sensitivity of 58% and specificity of 83% (p<0.001). The authors of this analysis concluded that PLR performed well diagnostically in various settings and that PLR-induced changes in flow variables had a higher predictive value than change in pulse pressure on PLR.

Although PLR seems like a promising dynamic measure of volume status and predictor of fluid responsiveness, it has limitations. In patients with conditions such as limb amputation, head trauma, spinal trauma, and pelvic fractures, use of this technique is precluded for practical reasons. Conditions such as increased intra-abdominal pressure may affect the accuracy of PLR in predicting fluid responsiveness. Most studies using PLR are done on patients on positive pressure ventilation, which can affect certain the interpretation of certain indicies (Pickett 2017).

Cardiac ultrasonography can also help determine volume status and cardiac output in patients with sepsis. A recent prospective, randomized controlled trial compared use of a fairly new monitor, the ultrasonic cardiac output monitor (USCOM), with conventional echocardiography in determining cardiac output (Elgendy 2017). The study found that stroke volume as measured by USCOM correlated with cardiac output measured by conventional echocardiography, showing the usefulness of USCOM in examining the hemodynamic status of critically ill patients.

These data, together with previous data citing issues with CVP-based hemodynamic monitoring, suggest that dynamic measures such as PLR are more likely than static measures to yield accurate predictions of volume responsiveness in adult patients with shock (Box 2).

Fluid Resuscitation

On recognition of sepsis-induced hypotension and/or elevated lactate concentrations, fluid resuscitation is recommended to be initiated immediately and completed within the first

3 hours (Levy 2018). Guidelines recommend at least a 30-mL/kg bolus of crystalloid fluid as the initial resuscitation (Rhodes 2017). After the initial fluid resuscitation, additional fluids should be guided by frequent reassessment of intravascular volume and hemodynamic status. Crystalloid is the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock. Albumin in addition to crystalloids is suggested when patients require a substantial amount of crystalloids. However, neither literature nor guidelines provide a clear definition of what constitutes a substantial amount of crystalloid fluid. Rather, clinical judgment should be used to determine whether albumin might benefit resuscitation after large volumes of crystalloids. Although the guidelines make no recommendation regarding which concentration of albumin should be used, 5% albumin is most commonly used in patients with hypovolemia to administer as much volume as possible. Hydroxyethyl starches are not recommended for fluid resuscitation in patients with sepsis or septic shock because of the increased risk of death and acute kidney injury (AKI)/renal replacement therapy (RRT) in several studies (Rochwerg 2014; Haase 2013).

The current guideline recommendation of using at least 30 mL/kg of intravenous crystalloid fluid as an initial resuscitation measure is not supported by data from randomized controlled trials. However, this practice is supported by observational data as well as the fact that it matches the average fluid administered in the PROCESS and ARISE trials (Rhodes 2017). Although the optimal amount of fluid to be given in sepsis is not known, this is an excellent area for future trials to examine. Literature suggests that a sustained positive fluid balance and volume overload are associated with increased mortality, new organ system dysfunction at discharge, impaired mobility, and discharge to a health care facility. Literature also indicates that sustained positive fluid balance is not protective against AKI. Therefore, fluid administration after initial resuscitation should be done cautiously and only if the patient is likely to benefit (Johnson 2018; Levy 2018; Brotfain 2016; Mitchell 2015). Some patient populations may be especially sensitive to volume overload, such as those with heart failure. In these populations, clinical judgment is often used to determine whether the amount of fluid administered should be reduced. It is reasonable to administer smaller boluses in these patient populations and to reevaluate volume status before administering further boluses. However, the rigidity of the CMS guidelines hinders clinicians' ability to exercise this judgment while following this core measure.

Guideline recommendations do not currently advocate either balanced crystalloids or saline as the resuscitation fluid of choice in sepsis, but state that either is an appropriate first-line therapy (Rhodes 2017). Although normal saline may be the most common choice of fluid resuscitation, there are concerns about its association with hyperchloremic metabolic acidosis, AKI, and even increased mortality (Semler 2018).

An unblinded, cluster-randomized, multiple-crossover trial of 15,802 patients, the SMART trial, compared the use of balanced crystalloids with isotonic saline in critically ill adults in medical and non-medical ICUs (Semler 2018). A total of 1139 patients (14.3%) in the balanced crystalloid group and 1211 patients (15.4%) in the saline group developed a major adverse kidney event within 30 days (p=0.04). There were no significant differences in the components of the primary outcome or secondary end points such as in-hospital death, ICU-free days, or ventilator-free days. The subgroup analysis of patients with sepsis had a significantly lower rate of the composite primary outcome in the balanced crystalloid group. Although this study suggests that balanced crystalloids are favorable in critically ill patients with sepsis, several limitations such as potential treatment bias limit the generalizability of results. These results were echoed by the SALT-ED trial, which compared normal saline with balanced crystalloids in noncritically ill patients and found a lower incidence of major adverse kidney events within 30 days in the group receiving balanced crystalloids (Self 2018). As in the SMART trial, other outcomes such as in-hospital death did not significantly differ between groups. According to these studies, balanced crystalloids are reasonable to reduce the risk of adverse kidney events in patients without relative

contraindications such as traumatic brain injury or hyperkalemia. Balanced crystalloids may be preferred in patients with hypernatremia or hyperchloremia.

Future studies to more definitively determine whether balanced crystalloids offer more benefit than normal saline as initial fluid resuscitation may help settle this debate. One such study is PLUS, which will compare 90-day mortality between Plasma-Lyte A and normal saline in critically ill patients. This study is currently recruiting participants and estimated to be completed in 2021.

Vasopressor Therapy

In patients with septic shock requiring vasopressors, a targeted MAP of 65 mm Hg within the first hour is recommended (Levy 2018). Norepinephrine is the recommended first-line vasopressor in septic shock. If MAP is not maintained at 65 mm Hg or greater with norepinephrine alone or if the norepinephrine dose needs to be decreased, either vasopressin (up to 0.03 unit/minute) or epinephrine can be added to norepinephrine (Rhodes 2017). High-dose (greater than 0.03 unit/minute) vasopressin is not recommended in patients with septic shock because it may cause significant ischemia, especially in myocardium and bowel through significant vasoconstriction (Holmes 2008). Dopamine is recommended as an alternative vasopressor to norepinephrine only in patients with a low risk of tachyarrhythmias and absolute or relative bradycardia. Low-dose dopamine drip is not recommended for renal protection. After adequate fluid resuscitation and vasopressor agents, dobutamine can be considered in patients with persistent hypoperfusion (Rhodes 2017). Angiotensin II is a novel agent that was not addressed in the guidelines. However, the literature surrounding this agent is discussed in the text that follows.

Although only briefly discussed in the current SSC guidelines, phenylephrine is another potential vasopressor option. The guidelines show that data analyses surrounding phenylephrine use are extremely limited. A systematic review and meta-analysis examining differences in outcomes between vasopressors in septic shock showed no mortality benefit of norepinephrine over other vasopressors such as phenylephrine (Avni 2015). Phenylephrine, though not considered first line, can be a useful vasopressor in patients with tachyarrhythmias because it does not increase heart rate.

If a clear diagnosis is unavailable by clinical assessment, further hemodynamic assessments of cardiac function (e.g., echocardiography) are recommended to optimize the patient's hemodynamics. Lactate concentrations are used as a surrogate marker of tissue perfusion. Lactate concentrations should therefore be measured and, if elevated by more than 2 mmol/L, remeasured in 2–4 hours to guide resuscitation until this value normalizes (Levy 2018).

Choice of Vasoactive Medications

Although norepinephrine is widely regarded as the first-line vasoactive medication in sepsis, literature continues to debate whether the early addition of vasopressin should be common practice. Past studies have shown varying degrees of benefits with this practice. However, no clear answer has been attained. Other potential agents such as angiotensin II will be discussed later in the chapter.

The VANISH trial (Gordon 2016) was a factorial, multicenter, double-blind, randomized study examining whether early administration of vasopressin in patients with septic shock would better improve kidney outcomes than norepinephrine. Among the four study groups (vasopressin plus hydrocortisone, vasopressin plus placebo, norepinephrine plus hydrocortisone, and norepinephrine plus placebo), there was no difference in the primary outcome of kidney failure-free days or 28-day mortality. However, the rate of RRT was significantly lower in the vasopressin groups (25.4% vs. 35.3%; OR 0.4 [95% CI, 0.2–0.73]). The authors concluded that the study findings did not support the use of vasopressin over norepinephrine but that results may point toward a clinically useful benefit of vasopressin.

A recent retrospective trial investigated patient characteristics that might predict responsiveness to adding vasopressin in septic shock (Allen 2018). Considering the adjusted logistic regression model results, vasopressin used as an adjunct vasopressor, rather than as the first-line agent, was the only variable significantly associated with responsiveness (OR 1.71 [95% CI, 1.10–2.65]). In the post hoc analysis, female patients had an increased odds of responding to vasopressin compared with male patients. Despite evidence from previous studies that vasopressin may play a role as initial vasoactive therapy, this study shows that vasopressin may be best as an adjunctive agent.

Another retrospective study examined vasopressor agents added to norepinephrine in patients with septic shock (Nguyen 2017). This study reported that mortality was significantly decreased with dobutamine as a second vasoactive medication compared with vasopressin after adjusting for confounding variables (OR 0.34 [95% CI, 0.14–0.84]). The relative risk of dying was 55.8% lower in patients receiving dobutamine than in those receiving vasopressin (p<0.001). Although the study's findings contradict the common clinical practice of using vasopressin as the second-line vasoactive agent when norepinephrine is insufficient to control shock, a randomized, prospective trial should corroborate these findings before implementing this into practice.

A single-center, retrospective cohort study looked at patients receiving fixed-dose vasopressin for septic shock with other catecholamines (Sacha 2018a). Patients were classified as responders or nonresponders to vasopressin on the basis of decreased catecholamine dose requirements and achievement of MAP goal 6 hours after vasopressin initiation. Responders had lower rates of in-hospital mortality (57% vs. 72%, p<0.001) and ICU mortality (50% vs. 68%, p<0.001) and increased ICU-free days at day 14 (2.3 vs. 1.6, p<0.001). Following multivariable analysis, nonmedical ICU location

was associated with increased response (OR 1.7; p=0.0049), and elevated lactate concentrations at vasopressin initiation was associated with decreased response (OR 0.93; p<0.001).

Angiotensin II

As knowledge about vasodilatory shock increases, the search for optimal medication therapies continues. Angiotensin II has sparked interest as a vasoactive medication for distributive or septic shock. The ATHOS-3 trial evaluated the effects of angiotensin II on MAP in patients with vasodilatory shock receiving high doses of catecholamines compared with placebo. Although lacking in clinically meaningful end points such as mortality, this trial showed that angiotensin II increases mean arterial blood pressure in this population. The primary end point of MAP response at hour 3, defined as a MAP of 75 mm Hg or higher or an increase in MAP from baseline of at least 10 mm Hg, was significantly higher in the angiotensin II group than in placebo (69.9% vs. 23.4%, p<0.001). However, only around 30% of patients in the trial had a MAP less than 65 mm Hg at baseline. Therefore, these results may be limited in their clinical usefulness. Adverse effects were largely similar between the two groups, according to the study results. There is a warning for an increased risk of thrombotic events with this medication, with the FDA reporting an incidence rate of 12.9% compared with 5.1% in placebo group. Because of this finding, the FDA recommends prophylactic treatment for blood clots if angiotensin II is used. The expanded supplementary adverse event report from the ATHOS-3 trial also showed a higher incidence of infections and infestations (30.1% vs. 19%) (Khanna 2017).

In a post hoc analysis of the ATHOS-3 trial examining patients with AKI treated with RRT at the time of angiotensin II initiation, survival rates through day 28 were higher in the angiotensin II group than in placebo (53% vs. 30%, p=0.012). Discontinuation rate of RRT by day 7 was higher in the angiotensin II group (38% vs. 15%, p=0.007), and MAP response was achieved in 53% of the angiotensin II group compared with 22% in the placebo group (p=0.001). The authors concluded that these data suggest that patients who develop AKI requiring RRT in the setting of vasodilatory shock will benefit from angiotensin II.

More data are needed to explore exactly where angiotensin II fits into the treatment algorithm for septic shock. However, currently, data analyses show that angiotensin II can be considered for patients with refractory shock who are not responding to other vasoactive medications. The dosing recommended is 20 ng/kg/minute initially, titrated by 15 ng/kg/minute every 5 minutes to a maximum dose of 80 ng/kg/minute during the first 3 hours of treatment and a maximum maintenance dose of 40 ng/kg/minute (Lexi-Comp Online™). Optimal angiotensin II dosing, effects on microcirculation, clinical outcomes, and efficacy compared with other vasoactive medications are among the topics that should be explored in the near future (Antonucci 2017). Pricing may preclude or limit the use of angiotensin II in the near future until data on improved clinical outcomes are available or a generic version is introduced.

Weight-Based Dosing and Extremes in Body Weight

Literature has provided no clear answer regarding whether vasopressors should be dosed by weight. The controversy surrounding this clinical question is compounded by patients with extremes in body weight. Because the BMI of a significant portion of patients falls outside what is considered normal, investigating the optimal strategy to dose vasoactive medications in this population could significantly affect patient care.

A retrospective cohort study that took place in all ICUs at the Mayo Clinic in Rochester investigated the effect of weight-based norepinephrine dosing on patients with septic shock with extremes in body weight (Kotecha 2018). A challenge in interpreting this study were the significant differences in baseline characteristics across the underweight, normal weight, and morbidly obese groups. However, the Charlson Comorbidity Index and SOFA score were similar across groups. The baseline differences were largely to be expected (e.g., a higher prevalence of diabetes mellitus in the morbidly obese population). Not surprisingly, the group with obesity had significantly greater total drug exposure. In-hospital mortality was inversely related to BMI, giving the underweight population the highest mortality rate, but this did not hold true for 1-year mortality. Adjusted univariate and multivariable predictors showed that norepinephrine exposure was an independent predictor of in-hospital and 1-year mortality. This finding remained after a propensity-matched analysis. Overall, increased exposure to norepinephrine was associated with increased mortality, length of stay, incidence of AKI, and cardiac arrhythmias. The authors concluded that weight-based dosing resulted in higher cumulative norepinephrine exposure in patients with morbid obesity. Because higher norepinephrine doses predicted mortality, prospective trials comparing weight-based with non–weight-based dosing strategies, particularly in the population with obesity, are needed to further elucidate this subject.

Another retrospective study compared a weight-based norepinephrine dosing strategy with a historical control of non–weight-based dosing in patients with morbid obesity and septic shock (Vadiei 2017). The primary end point of time to achieving the goal MAP did not significantly differ between the two groups. Logistic regression analysis identified only severity of illness as a predictor for reaching the goal MAP within 6 hours. Median cumulative norepinephrine doses were higher in the weight-based dosing group (12.6 mg vs. 10.5 mg, p=0.04), and time to norepinephrine discontinuation was longer in this group (33 hours vs. 27 hours, p=0.03). Although the difference in dose and time to norepinephrine discontinuation reached statistical significance, the

clinical relevance of these differences is less certain. Adverse effects, hospital length of stay, and mortality were similar between groups. Given these findings, the authors suggest not pursuing the transition from non–weight-based dosing to weight-based dosing because outcomes did not significantly differ and weight-based dosing could increase the cumulative exposure and duration of norepinephrine.

A recent retrospective trial examined the change in MAP 1 hour after initiating vasopressin in relation to patient weight (Hodge 2016). For the primary outcome, no correlation was found for change in MAP at 1 hour after vasopressin initiation compared with vasopressin dose in relation to patient weight. In the subgroup of patients with a BMI greater than 30 kg/m^2, a significantly negative correlation was found between BMI and change in MAP at 6 hours (correlation coefficient r = −0.951, p=0.0009). Linear regression analysis was used to account for change in norepinephrine dosing. This analysis showed that the vasopressin dose in relation to body weight significantly increased MAP at 1, 6, and 12 hours. The authors concluded that vasopressin dose in relation to body weight did not significantly affect change in MAP at 1 hour before regression analysis. However, the study raises the question of whether fixed-dose vasopressin is adequate for the patient subset with a BMI greater than 30 kg/m^2.

These studies raise the concern of risks associated with increased cumulative vasopressor exposure. According to the most recent literature, it seems reasonable to use non–weight-based dosing strategies for norepinephrine and to be cognizant of cumulative exposure if weight-based dosing is used. More information is needed regarding weight-based dosing of other catecholamines and the effect of BMI in relation to fixed-dose vasopressor.

Discontinuation Strategies

The decision of which vasopressor should be discontinued first in the recovery phase of septic shock is fairly clinician-specific. Guidelines offer no insight into this clinical question, and data are limited.

A retrospective study compared discontinuation strategies in critically ill medical patients in the recovery phase of septic shock requiring both vasopressin and norepinephrine (Hammond 2017). In both the unadjusted and adjusted analyses, clinically significant hypotension was more likely if vasopressin was discontinued first. Hospital length of stay and 28-day mortality did not differ between the groups.

A single-center, retrospective chart review examined patients with septic shock receiving both norepinephrine and vasopressin for at least 4 hours (Musallam 2018). Comparisons were made regarding which vasopressor was discontinued first. For the group in which vasopressin was discontinued first, significantly higher norepinephrine doses were received. The primary outcome of hypotension rate was significantly higher in the group for whom vasopressin was discontinued first. In univariate and multivariate analysis, vasopressin

discontinuation first remained an independent predictor of hypotension. Secondary outcomes of time to hypotension, hospital length of stay, and ICU mortality did not differ between groups. However, the group in whom norepinephrine was discontinued first had a longer ICU length of stay. The authors concluded that their study contributed to the growing literature stating that discontinuing vasopressin first may result in a higher hypotension rate.

Another retrospective trial examined 61 patients admitted to the medical ICU with septic shock who received both norepinephrine and vasopressin for hemodynamic support (Bissell 2017). The primary outcome, hemodynamic instability, was defined as hypotension after vasopressor discontinuation (two consecutive MAPs less than 60 mm Hg), fluid bolus administration, greater than a 0.05-mcg/kg/minute increase in norepinephrine requirements, or addition of an alternative vasopressor. Vasopressin was discontinued first in 19 patients, and norepinephrine was discontinued first in 42 patients. Vasopressin discontinuation first resulted in a significantly higher incidence of hypotension (74% vs. 16.7%, p<0.01). This study also suggests that discontinuing vasopressin first is associated with a higher incidence of hemodynamic instability.

A retrospective cohort study of patients with septic shock in medical, surgical, and neuroscience ICUs examined the incidence of hypotension after discontinuing either vasopressin or norepinephrine first (Sacha 2018b). The patients in this study received vasopressin for at least 6 hours in addition to norepinephrine. Vasopressin was discontinued first in 155 patients, and norepinephrine was discontinued first in 430 patients. Hypotension in the 24 hours after discontinuing the first vasopressor occurred at a similar rate between these groups (55% vs. 50%, p=0.28). After multivariable Cox proportional hazards regression was used to adjust for baseline factors, discontinuing vasopressin first was independently associated with an increased risk of hypotension, which decreased over time. No differences in outcomes such as mortality or days alive outside the ICU or hospital were found between the groups. The results of this study are less clear than in previously discussed studies and raise the question of whether incidence of hypotension translates to differences in clinical outcomes.

A prospective, randomized controlled trial evaluated hypotension within 1 hour of discontinuing either vasopressin or norepinephrine in patients with septic shock receiving both of these vasopressors (Jeon 2018). Thirty-eight patients were assigned to have norepinephrine tapered off first, and 40 patients were assigned to have vasopressin tapered off first. This study was terminated early because of a significantly higher incidence of hypotension in the group in whom norepinephrine was tapered off first (68.4% vs. 22.5%, p<0.001). Although the authors concluded that tapering norepinephrine off first may be associated with an increased risk of hypotension, they acknowledged that studies with larger sample sizes should confirm these findings.

These studies raise an interesting question that could significantly affect patients recovering from septic shock. According to this most recent literature, it may be reasonable to discontinue norepinephrine before vasopressin during the recovery phase of septic shock. Randomized controlled trials should more definitively answer this question in the future and evaluate the effect of discontinuing vasopressors on clinical outcomes of hypotension. This type of evaluation will provide more guidance on optimal vasopressor discontinuation strategies.

Peripheral Administration

Historically, vasoactive medications have been administered largely through central venous catheters. The reasoning behind this is to minimize adverse effects such as extravasation and subsequent tissue injury. A recent single-center retrospective chart review documented peripheral administration of vasoactive medications and the associated extravasation events (Lewis 2017). The most common vasopressor to be administered peripherally was norepinephrine, followed by phenylephrine. Vasopressin, epinephrine, and dopamine were included as well, though they were only a very small percentage of the vasopressor agents administered. The most common administration sites were the forearm and antecubital fossa. Extravasation occurred in 4% of patients, equally distributed between norepinephrine and phenylephrine. None of these events required administration of antidote or surgical intervention. The median dose of vasopressor in norepinephrine equivalents at the time of extravasation was 0.11 mcg/kg/minute. The findings of this study suggest that extravasation rates are relatively low, even with peripheral administration of vasoactive agents. However, if this route is to be used, protocols should be instituted to ensure safe, standardized use.

A case report showed the potential for peripheral administration of low-dose vasopressin to cause skin necrosis (Kahn 2002). In this patient, vasopressin was administered by a peripheral venous catheter in the patient's left wrist at a dose of 0.04 unit/minute for septic shock. After 23 hours of this infusion, the patient developed an area of erythematous skin with central necrosis just proximal to the intravenous site. Vasopressin was discontinued, the catheter was removed, and the necrosis was treated with elevation and warm compresses. Twelve hours later, the areas of necrosis expanded, and bulla formation was noted. The wound was eventually left to heal without requiring skin grafting. However, this case highlights the potential risks associated with peripheral administration of vasopressin.

Although some data analyses suggest that vasoactive medications can safely be administered through peripheral intravenous access, there is still a significant risk with this practice and lack of data for certain agents such as angiotensin II. Peripheral administration should be reserved for when central venous access is not possible, and the lowest effective dose should be used until central line access can be obtained.

Steroids

If hemodynamic stability is achieved with fluid resuscitation (with or without vasopressors), intravenous corticosteroids are not recommended as a treatment for septic shock. Intravenous hydrocortisone (200 mg/day) can be considered in patients who have not achieved hemodynamic stability with fluid resuscitation plus vasopressors.

A weak recommendation exists to use hydrocortisone for septic shock that is unresponsive to adequate fluid resuscitation and vasoactive medications. Evidence of the benefit associated with steroid use in the population with septic shock is conflicting, and several adverse effects of concern are associated with steroids, such as hyperglycemia and hypernatremia (Rhodes 2017).

A recent meta-analysis aimed to categorize steroid use and outcomes in both adults and children with septic shock (Gibbison 2017). Although outcomes among the various types of steroids differed slightly, the authors concluded that no one glucocorticoid is more likely to reduce mortality or GI bleeding than another. Findings suggest that hydrocortisone increases the likelihood of shock reversal compared with placebo or methylprednisolone, which supports the guideline recommendation to use hydrocortisone. Among the limitations of this analysis is the exclusion of certain outcome measures because of variability in study definitions. One such outcome is hyperglycemia, a common and worrisome adverse effect associated with glucocorticoid use.

An international, double-blind, randomized, placebo-controlled trial investigated the effects of intravenous hydrocortisone (200 mg/day) compared with placebo in mechanically ventilated patients with septic shock who had received vasopressor therapy for at least 4 hours (Venkatesh 2018). The primary end point of all-cause mortality at 90 days did not differ between the two groups, nor did 28-day mortality. Secondary end points of time to resolution of shock, time to ICU discharge, incidence of blood transfusions, and duration of initial mechanical ventilation were significantly lower in the hydrocortisone group. However, total days free of mechanical ventilation, recurrence of shock, time to hospital discharge, rate of recurrent mechanical ventilation, duration and rate of RRT, and development of new-onset bacteremia or fungemia did not differ between hydrocortisone and placebo. Adverse effects occurred at a higher rate in the hydrocortisone group, including hyperglycemia, hypernatremia, hypertension, encephalopathy, and myopathy, though the occurrence rate was relatively low with all of these. This study does not show decreased mortality from hydrocortisone use as a single agent in this setting. However, hydrocortisone had a favorable profile in several of the study's secondary end points. According to this trial, hydrocortisone may result in some benefit when used in the subset of patients with septic shock who require mechanical ventilation.

The APROCCHSS study, a prospective, multicenter, double-blind, placebo-controlled, trial, examined the effects of

hydrocortisone (50 mg intravenously every 6 hours) plus fludrocortisone (50 mcg orally daily) on mortality rates, among other end points, in adults with septic shock who had received vasopressor therapy for at least 6 hours (Annane 2018). Significantly improved outcomes in the steroid group included the primary end point of all-cause mortality at 90 days (43% vs. 49%, p=0.03) and the secondary end points of death at ICU discharge, death at hospital discharge, death at 180 days, vasopressor-free days, and organ failure–free days. Outcomes that did not differ between groups included death at 28 days, decision to withhold or withdraw active treatment by day 90, and ventilator-free days. The total number of adverse events did not significantly differ, nor did the incidence of GI bleeding or superinfection. However, the hyperglycemia risk was significantly higher in the steroid group (RR 1.07; 95% CI, 1.03–1.12; p=0.002). The findings of this study suggest that the combination of hydrocortisone and fludrocortisone in adults with septic shock who do not respond to initial resuscitation measures improves mortality and patient outcomes. Adding fludrocortisone to the commonly used hydrocortisone regimen may account for the positive results, but more data analyses are needed to confirm this. The patient population examined in this trial matches the population the guidelines describe as potentially benefiting from the addition of glucocorticoid therapy, reinforcing the current recommendation.

Interest has been expressed in using glucocorticoids to prevent septic shock. The HYPRESS trial was a multicenter, placebo-controlled, double-blind, randomized study in Germany that examined patients with evidence of sepsis and organ dysfunction (Keh 2016). Patients were randomized to either receive placebo or a hydrocortisone bolus and an 11-day tapered continuous infusion regimen. The primary end point, development of septic shock within 14 days, did not significantly differ between the two groups. Secondary end points of 28-day, 90-day, 180-day, ICU, or hospital all-cause mortality, ICU or hospital length of stay, and ventilation- or renal replacement-free days did not differ between the two treatment arms. However, the incidence of hyperglycemia was significantly increased in the hydrocortisone group. Total insulin administration, secondary infections, and hypernatremia did not differ between the groups. The findings of this study do not support using hydrocortisone to prevent septic shock.

Although the topic of steroid use in sepsis and septic shock is still controversial, no clear mortality benefit has consistently been shown in the literature, and data analyses for improving other outcomes are mixed. Therefore, it is reasonable to continue following guideline recommendations to use hydrocortisone in the face of septic shock that is unresponsive to adequate fluid resuscitation and vasopressor therapy, but its use should not be prioritized.

Vitamin C, Hydrocortisone, and Thiamine

Vitamin C modulates inflammation caused by sepsis in animal models. Because of this, interest has developed in using this therapy in human patients with sepsis. A randomized, double-blind, placebo-controlled phase I trial examined the effect of intravenous ascorbic acid on SOFA scores and CRP, procalcitonin, and thrombomodulin concentrations in patients with sepsis (Fowler 2014). The study deemed the treatment safe, as evidenced by a lack of adverse events in patients who received ascorbic acid. Reductions occurred in SOFA scores, CRP, and procalcitonin, as did lack of a rise in thrombomodulin compared with the placebo group. The authors concluded that vitamin C therapy may attenuate inflammation in patients with sepsis. This study was small, including only 24 patients, and did not examine clinical outcomes. However, the study generated more interest in ascorbic acid as an adjuvant treatment option in sepsis.

Another randomized, double-blind trial compared the effect of intravenous ascorbic acid with placebo on vasopressor dose in patients with septic shock (Zabet 2016). The mean dose of norepinephrine was 7.44 mcg/kg/minute in the ascorbic acid group compared with 13.79 mcg/kg/minute in the placebo group (p=0.004), and the norepinephrine infusion duration was lower in the ascorbic acid group (49.64 hours vs. 71.57 hours, p=0.007). The study also showed a significantly lower incidence in 28-day mortality in the ascorbic acid group compared with placebo (14.28% vs. 64.28%, p=0.009). This study was also small, including only 28 patients, and had a short intervention period. Although the results seem promising, they must be interpreted with caution, given the study's limitations.

One sepsis trial that gained the most attention in recent years was the retrospective before-and-after study examining the use of vitamin C, hydrocortisone, and thiamine in sepsis and septic shock (Marik 2017). The regimen used consisted of hydrocortisone 50 mg intravenously every 6 hours for 7 days or until ICU discharge, followed by a 3-day taper, vitamin C 1.6 g intravenously every 6 hours for 4 days or until ICU discharge, and thiamine 200 mg intravenously every 12 hours for 4 days or until ICU discharge. Although this was a small (n=94) retrospective study, the results were seemingly impressive, with a significant difference in hospital mortality (8.5% in intervention arm vs. 40.4% in control group, p<0.001). Duration of vasopressor therapy, need for RRT for AKI, change in SOFA score, and procalcitonin clearance were all statistically improved in the intervention group, whereas ICU length of stay did not differ. The authors concluded that the cocktail of vitamin C, thiamine, and hydrocortisone is safe and may prevent organ dysfunction and reduce mortality in patients with sepsis and septic shock.

A major limitation of this study is the before-and-after design, which prohibits the study from proving causality. The single-center nature of the study as well as the smaller population size also limit the ability to generalize these results.

Several confounding factors existed, such as the control and treatment periods being in different seasons, which may have influenced the results. Similarly, several potential confounders were not discussed. Despite the authors' conclusion that the combination of vitamin C, thiamine, and hydrocortisone is safe in this setting, more data are needed to determine whether this treatment is truly without risk. Although this study certainly generates hypotheses and questions about using vitamin C, thiamine, and hydrocortisone in sepsis, well-designed, randomized, controlled trials should confirm these findings before the practice is routinely used. Several studies examining the role of vitamin C, thiamine, and hydrocortisone in sepsis may shed light on this relatively new area of interest.

β-Blocker Use in Sepsis

A novel potential treatment option in sepsis, β-blockers, has sparked a lot of interest in recent years. The foundation for using β-blockers in sepsis and septic shock is the thought that there may be inappropriate activation of the sympathetic nervous system in sepsis, causing harmful effects. An association between high sympathetic stress and sepsis-induced myocardial depression has been a growing area of interest in the literature, suggesting that heart rate control and modulation of these effects by β-blockers are beneficial. The concern is that an excess of β-blockers may cause low cardiac output because of negative inotropic and chronotropic properties. Recent literature has investigated this therapy not only in sepsis, but also in other high-stress disease states such as trauma, burns, and traumatic brain injury. Although this chapter focuses on outlining the most recent literature, Table 2 provides an overview of studies examining β-blockade therapy in sepsis.

A prospective trial in China investigated the effects of esmolol, a bolus dose and then an intravenous infusion titrated to a goal heart rate of 10%–15% less than baseline, on various hemodynamic parameters in patients with septic shock (Du 2016). Significant findings after esmolol initiation included decreased lactate concentrations, increased stroke volume, decreased heart rate, decreased cardiac output, increased left ventricular end diastolic volume, and increased CVP. Although this study did not examine clinical outcomes, the evidence suggests that adding a β-blocker in patients with sepsis can increase stroke volume and, despite decreasing cardiac output, avoid decreasing tissue perfusion.

The guidelines have not yet made any recommendations regarding β-blocker use in septic shock. Although preliminary studies show a potential benefit of β-blocker therapy on hemodynamic parameters, large, well-designed randomized controlled trials are needed to fully show the role of β-blockers in septic shock. Practitioners may consider using β-blockers in patients with septic shock with tachycardia and high cardiac output. However, data are insufficient to routinely recommend β-blocker therapy.

INFECTION MANAGEMENT

Timing of Therapy

Empiric, broad-spectrum intravenous antimicrobials should be initiated as soon as possible after recognition, ideally after collection of blood cultures and other cultures, and within 1 hour for both sepsis and septic shock according to the current guidelines with moderate evidence (Levy 2018). Initially, one study showed an average 7.6% decrease in survival rate per every 1-hour delay in antibiotic administration (Kumar 2006). Another study later confirmed a similar mortality benefit from early administration of antibiotics in a larger population (Ferrer 2014). Even though a meta-analysis showed no mortality benefit, because of the methodological limitation of the analysis (including low quality studies), a 1-hour antibiotic administration time is considered as a reasonable target.

The SSC guidelines advocate broad-spectrum intravenous antibiotics within the first hour of identifying sepsis and septic shock. Although the literature has shown the benefits of administering appropriate antimicrobial therapy as quickly as possible in sepsis, this still represents a logistical obstacle in most institutions (Rhodes 2017).

A recent retrospective analysis with a historic control investigated compliance with SSC recommendations for the timing of antimicrobial therapy after implementing a combination antibiotic bag (Lorenzo 2018). The primary end point of proportion of patients receiving at least two antibiotics and 30 mL/kg of crystalloid fluid challenge within 3 hours after ED admission was 2.32 (95% CI, 1.67–3.23) times more likely in the intervention group than in the historical control group. These results remained significant when the end point was broken into individual components. The combination bag in this study contained both cefepime and vancomycin. According to these findings, it may be reasonable to consider using the combination bag to decrease the time to antibiotic administration in patients with sepsis. However, prospective trials are needed to confirm the benefit.

The importance of prompt antibiotic administration was highlighted in a retrospective analysis of data collected prospectively for the SSC (Ferrer 2014). The study examined 17,990 patients who received antibiotics after sepsis identification. A statistically significant increase in probability of death occurred for each hour that antibiotic administration was delayed. These results reinforce that delaying antibiotics in patients with sepsis is associated with an increased risk of mortality.

Antimicrobial Therapy

In patients with a severe inflammatory state of noninfectious origin, prophylactic systemic antimicrobials are not recommended. Historically, prophylactic antibiotic therapy was administered in some situations (e.g., severe necrotizing pancreatitis, severe burns). However, meta-analyses show

Table 2. Studies of β-Blocker Use in Sepsis

Study	Design and Population	Intervention	Results	Conclusion
Wang 2015	Prospective, randomized study of patients with severe sepsis (n=90)	Control (C) Milronone (M) Milrinone + esmolol (ME)	HR lower in ME group at 12 hr Higher survival rate at 28 days in ME group (ME vs. M, p=0.02, ME vs. C, p=0.001)	ME may improve cardiac function and 28-day survival in severe sepsis
Yang 2014 [abstract]	Prospective, randomized study of patients with septic shock (n=41)	Control Esmolol (to ↓ HR < 100 beats/min within 2 hr)	Decreased HR (93 vs. 118 beats/min; p<0.05 and cardiac index (3.3 vs. 4.5 L/in/m², p<0.05) in treatment group Increased SVR index (159.2 vs. 130.5, p<0.05) and global end diastolic volume index (668 vs. 588 mL/m², p<0.01) in treatment group	β-Blockade may improve cardiac function without decreasing circulation and tissue perfusion
Morelli 2013	Open-label, randomized, phase II study of patients with septic shock (n=154)	Control Esmolol infusion (titrated to HR 80–94 beats/min)	Lower HR in esmolol group (p<0.001) Lower NE requirements in esmolol group (p<0.01) Increased SV (p=0.03), SVR (p<0.001), and LV stroke work (p=0.03) in esmolol group Decreased fluid requirements in esmolol group (p<0.001) Decreased arterial lactate concentrations in esmolol group (p=0.006) Decrease 28-day, ICU, and hospital mortality in esmolol group (p<0.001)	Esmolol decreased HR without adverse effects in patients with septic shock Observed decreases in mortality warrant further investigation
Balik 2012 [abstract]	Prospective, open-label study of patients with septic shock with tachycardia (n=10)	Esmolol bolus; then continuous infusion	Decrease in HR (142 vs. 112 beats/min, p<0.001) and cardiac index (4.94 vs. 4.35 L/min/m², p=NS) Increase in SV (67.1 vs. 72.9, p=NS) No change in lactate or NE requirements	Lowering HR with esmolol did not result in adverse events Use of a β-blocker may be safe and cardioprotective in patients with septic shock with high cardiac output

HR = heart rate; LV = left ventricular; NE = norepinephrine; SV = stroke volume; SVR = systemic vascular resistance.

Information from: Wang Z, Wu Q, Nie X, et al. Combination therapy with milrinone and esmolol for heart protection in patients with severe sepsis: a prospective, randomized trial. Clin Drug Investig 2015;35:707-16; Yang S, Liu Z, Yang W, et al. Effects of the β-blockers on cardiac protection and hemodynamics in patients with septic shock: a prospective study. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2014;26:714-7; Morelli A, Ertmer C, Westphal M, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. JAMA 2013;310:1683-91; and Balik M, Rulisek J, Leden P, et al. Concomitant use of beta-1 adrenoreceptor blocker and norepinephrine in patients with septic shock. Wien Klin Wochenschr 2012;124:552-6.

no benefit from prophylactic antibiotics (Barajas-Nava 2013; Working Group IAP/APA 2013; Wittau 2011; Avni 2010).

For optimal antimicrobial dosing strategies, pharmacokinetic and pharmacodynamic principles and specific drug properties should be considered (Rhodes 2017). β-Lactams will have a benefit with more frequent dosing or prolonged infusion because they target an fT>MIC of at least 50 for penicillins, 50–70 for cephalosporins, and 30–40 for carbapenems (Connors 2013). Aminoglycosides are representative concentration-dependent antibiotics and target an fCpeak/MIC of at least 10–12. Fluoroquinolones are also concentration-dependent antibiotics, but they target an fAUC/MIC of greater than 125 for gram-negatives and greater than 30–50 for gram-positives (Connors 2013). Vancomycin therapy requires monitoring of trough concentrations that target 15–20 mg/L. With increasing methicillin-resistant *Staphylococcus aureus* MICs to vancomycin, fAUC/MIC greater than 400 is the target pharmacodynamic goal for better clinical outcomes (Connors 2013).

Empiric broad-spectrum therapy with one or more antimicrobials is recommended to cover all likely pathogens (Box 3). Especially in patients with septic shock, empiric combination antibiotic therapy is recommended to target the most likely pathogen(s). However, combination therapy should not be routinely used if multidrug-resistant pathogens are not suspected. Empiric antimicrobial therapy should be narrowed once pathogen identification and sensitivities are available and/or adequate clinical improvement is noted. An antimicrobial treatment of 7–10 days is adequate for most infections associated with sepsis and septic shock (Box 3).

Daily assessment for de-escalation of antimicrobial therapy is recommended in patients with sepsis and septic shock.

Procalcitonin

The benefits of using procalcitonin to guide antimicrobial therapy in sepsis are still uncertain. A Cochrane review examined outcomes when procalcitonin was used to guide therapy compared with other methods such as clinical judgment and other infection markers (Andriolo 2017). No differences in mortality, mechanical ventilation, reinfection, or antimicrobial therapy duration occurred between the procalcitonin and non-procalcitonin groups.

The SISPCT trial, a multicenter, randomized, placebo-controlled trial examining the effect of sodium selenite on outcomes in patients with sepsis as well as the effect of procalcitonin-guided therapy compared with therapy without procalcitonin guidance, found no difference in 28-day mortality or frequency or diagnostic or therapeutic procedures. However, the study found a statistically significant 4.5% reduction in antimicrobial exposure in the procalcitonin-guided group (Bloos 2016).

A multicenter, prospective, randomized, controlled, open-label trial in the Netherlands, the SAPS trial, compared antibiotic discontinuation on the basis of standard of care with that of procalcitonin guidance (de Jong 2016). The procalcitonin group (n=761) had significantly fewer antibiotics, as defined by daily doses, as well as significantly lower durations of antibiotic therapy than the standard-of-care group (n=785). This reduction in antibiotic use occurred without an increase in 28-day mortality (19.6% in the procalcitonin group vs. 25% in the standard-of-care group) or mortality at 1 year after randomization (34.8% in the procalcitonin group vs. 40.9% in the standard-of-care group). The authors concluded that adding procalcitonin-guided therapy to clinical judgment may decrease antibiotic consumption without increasing mortality.

Another multicenter, randomized controlled trial, the ProACT study, examined the effect of using procalcitonin to guide antibiotic therapy compared with usual care (Huang 2018). This study included 1656 patients with lower respiratory tract infections across 14 U.S. hospitals. No difference was shown in antibiotic-days (4.2 days in procalcitonin group vs. 4.3 days in usual care, p=0.87). The authors concluded that using procalcitonin to guide antibiotic therapy did not decrease antibiotic exposure in this population.

Although some data analyses suggest that procalcitonin-guided antibiotic therapy can decrease antibiotic exposure, large, randomized controlled trials are needed to better understand its usefulness in sepsis and septic shock. There are also limitations to using procalcitonin as a marker for sepsis. One such limitation is that procalcitonin may be elevated in conditions outside bacterial infections, such as severe trauma or surgery (Lee 2013).

Procalcitonin concentrations can be measured to support shortening the antimicrobial therapy duration in patients with sepsis (Rhodes 2017). However, this is a weak guideline recommendation, and procalcitonin concentrations should be used in conjunction with the patient's clinical assessment.

Box 3. Patient Characteristics to Differentiate Antimicrobial Therapy Duration

Longer therapy duration (> 10 days)
- Slow clinical response
- Immunologic deficiencies
- *S. aureus* bacteremia
- Fungal and viral infections (e.g., *Candida*, *Aspergillus*, influenza virus)
- Undrainable foci of infection

Shorter therapy duration (≤ 10 days)
- Rapid clinical resolution after effective source control (i.e., intra-abdominal infection or UTI)
- Uncomplicated pyelonephritis

Patient Care Scenario

A 68-year-old woman has a medical history of heart failure with reduced ejection fraction and type 2 diabetes. She was admitted to the medical floor 2 days ago after a hip replacement surgery. She refuses to participate in the recommended physical therapy while in the hospital and has declined incentive spirometry several times. The patient was seen in a clinic for a routine checkup 1 week before hospital admission. At that time, she had normal mental status, and her baseline vital signs and laboratory values were as follows:

Vital Signs	Laboratory Values
• Temperature 98.6°F • Blood pressure (BP) 106/64 mm Hg (MAP 78 mm Hg) • HR 86 beats/min • Respiratory rate 14 breaths/min • Sao_2 98% on room air	• WBC 8.2 x 10^3 cells/mm^3 • Plt 172,000/mm^3 • SCr 1.0 mg/dL • Total bilirubin 0.6 mg/dL • Weight 50 kg

On hospital day 3, the patient has shortness of breath, and chest radiography reveals diffuse patchy infiltrates in the left lower lobe. The nurse states the patient has seemed confused at times. During rounds, the team evaluates the patient through a clinical examination and objective laboratory data. The resident finds that the patient's GCS score is 14.

Vital Signs	Laboratory Values
• Temperature 100.9°F • BP 94/52 mm Hg (MAP 66 mm Hg) • HR 108 beats/min • Respiratory rate 18 breaths/min • Sao_2 96% on room air	• WBC 14.2 x 10^3 cells/mm^3 • Plt 160,000/mm^3 • SCr 1.3 mg/dL • Total bilirubin 0.8 mg/dL • Weight 50 kg

How would you classify this patient at this time? What factors did you consider to arrive at this classification? What is the best treatment course for the patient at this time?

Broad-spectrum empiric antibiotic therapy is administered for suspected pneumonia, and the patient is given a 1500-mL bolus of normal saline. However, 8 hours later, the patient's respiratory and hemodynamic status worsens, and repeat laboratory values are obtained. The patient is intubated because of hypoxic respiratory failure.

Vital Signs	Laboratory Values
• Temperature 101.1°F • BP 86/48 mm Hg (MAP 61 mm Hg) • HR 112 beats/min • Respiratory rate 20 breaths/min • Fio_2 70%	• WBC 15.4 x 10^3 cells/mm^3 • Plt 142,000/mm^3 • SCr 1.6 mg/dL • Total bilirubin 1.2 mg/dL • Lactate 4.2 mmol/L

What is best to recommend for the patient, given the changes in her status?

ANSWER

At first, the patient would be classified as having sepsis. Patients with suspected infection should be monitored with the qSOFA score for the possibility of developing sepsis. In this case, the patient has two criteria from the qSOFA score (altered mental status and hypotension on the basis of systolic blood pressure) and should therefore be evaluated using the SOFA score. Her baseline SOFA score at the clinic visit was zero. The patient's SOFA score on hospital day 3 is 3 (MAP less than 70 mm Hg = 1 point, GCS score of 14 = 1 point, SCr of 1.3 mg/dL = 1 point), which indicates sepsis. The 1-hour bundle would currently be appropriate for the patient. This would include administering fluid with a crystalloid, obtaining cultures, measuring lactate concentrations, administering broad-spectrum antibiotics, and providing vasopressor therapy if fluid administration does not maintain the MAP goal. Because of the patient's history of heart failure, a decreased amount of fluid could be administered for the initial bolus to avoid volume overload.

After the patient's status worsened, she would be classified as having septic shock because of her lactate concentration and persistently low MAP. At this time, using a dynamic measure of volume status (e.g., PLR) would best determine whether she is fluid responsive and could help avoid volume overload. Vasopressor therapy should be initiated on the basis of the decreased MAP. Norepinephrine would be first line for this patient. If the patient's MAP did not improve after adding norepinephrine, second-line options such as vasopressin could be considered as well as hydrocortisone with fludrocortisone.

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OTHER THERAPIES

Transfusions

Red blood cell transfusion is recommended only in patients with an Hgb of less than 7 g/dL in the absence of severe hypoxemia, myocardial ischemia, or acute hemorrhage. Erythropoietin is not recommended for the treatment of anemia caused by sepsis. In the absence of bleeding or a planned invasive procedure, fresh frozen plasma is not recommended to correct clotting abnormalities in patients with sepsis or septic shock.

Bicarbonate

In patients with hypoperfusion-induced lactic acidemia with a pH of 7.15 or greater, sodium bicarbonate therapy is not recommended for improving hemodynamic status or reducing vasopressor needs.

Acetylcysteine

Acetylcysteine has anti-inflammatory and antioxidant properties that could theoretically benefit patients with sepsis. Acetylcysteine also has data analyses supporting that it has vasodilatory properties that may improve microcirculation. A recent review of pooled data on acetylcysteine in sepsis showed that although acetylcysteine has been investigated as an adjunctive therapy for sepsis, the results suggesting benefit are inconsistent (Chertoff 2018). Benefits throughout the review included improvements in regional blood flow, reductions in lactic acidosis, and reductions in mortality. However, larger randomized controlled trials need to investigate and prove benefit before acetylcysteine therapy can gain popularity.

SUPPORTIVE MANAGEMENT

Pain Management and Sedation

Pain Management

The 2018 guidelines for preventing and managing pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU, or PADIS guidelines, do not specifically address patients with sepsis. However, they recommend regular pain assessment in critically ill adults and use of clinical judgment to balance the risk of negative outcomes associated with pain and potential negative effects of opioid exposure (Devlin 2018).

A retrospective cohort study at two academic medical centers examined whether acetaminophen use in sepsis might attenuate the risk of developing AKI (Patanwala 2018). Interest in this topic developed because of data analyses showing that acetaminophen inhibits lipid peroxidation (Boutaud 2010). Acute kidney injury developed in 16.4% of patients in the acetaminophen group and 19.8% of the patients in the non-acetaminophen group, a nonstatistically significant difference (Patanwala 2018).

Sedation

According to the 2018 PADIS guidelines, non-benzodiazepine agents are first line for sedation in mechanically ventilated adults. However, patient-specific characteristics, including disease states such as septic shock, should also be considered (Devlin 2018). The SSC guidelines make no detailed recommendations regarding which sedative agents to use but state that non-benzodiazepine agents may result in better outcomes than benzodiazepines (Rhodes 2017). Recent literature has tried to elucidate which sedative agents may offer the most benefit in patients with sepsis, focusing mainly on dexmedetomidine.

The DESIRE study was a multicenter, open-label, randomized clinical trial conducted in Japan assessing the effects of dexmedetomidine sedation on patients with sepsis requiring mechanical ventilation for more than 24 hours (Kawazoe 2017). The intervention arm consisted of patients receiving sedation with dexmedetomidine (n=100) and other sedatives, as necessary, and the control arm consisted of patients receiving treatment with sedatives other than dexmedetomidine (n=101). For the co-primary end points of 28-day mortality and ventilator-free days, the intervention and control arms did not differ. Median length of ICU stay, delirium-free days, and frequency and doses of fentanyl did not significantly differ between groups. Rate of well-controlled sedation during ICU stay, as defined by a Richmond Agitation-Sedation Scale (RASS) score of -3 to +1, was significantly higher in the dexmedetomidine group, and the frequency and doses of propofol and midazolam were significantly lower in the dexmedetomidine group. Within the subgroup that had APACHE II (Acute Physiology and Chronic Health Evaluation II) scores of 23 or higher, mortality was significantly lower in the dexmedetomidine group. Bradycardia was more common in the dexmedetomidine group. No data were provided on the type or amount of other sedatives used in the dexmedetomidine group. The authors concluded that dexmedetomidine in this patient population did not significantly reduce mortality or ventilator-free days, but may have better controlled sedation. The authors also noted that the study may have been underpowered to detect differences in mortality; therefore, further research should evaluate these clinical outcomes.

A prospective, open-label, crossover study evaluated 38 patients with septic shock requiring norepinephrine to maintain adequate MAP and requiring deep sedation (RASS score between -3 and -4) with propofol and remifentanil (Morelli 2019). Hemodynamic measurements, norepinephrine doses, and depth of sedation were all measured while patients were receiving propofol. These parameters were measured again 4 hours after changing to dexmedetomidine instead of propofol and then a third time 8 hours after changing back to propofol. The norepinephrine dose decreased from 0.69 plus or minus 0.72 mcg/kg/minute to 0.30 plus or minus 0.25 mcg/minute when propofol was changed to dexmedetomidine and then increased to 0.42 plus or minus 0.36 mcg/minute when

sedation was changed back to propofol (p<0.005). The propofol and remifentanil doses remained unchanged before and after dexmedetomidine infusion. The authors concluded that changing from propofol to dexmedetomidine reduced norepinephrine requirements. A limitation of this trial is that a light level of sedation (RASS score of -2 to 0) is typically desired in most patients. Therefore, the propofol dose, and thus the catecholamine requirements, may have been increased in this study.

Although non-benzodiazepine agents are reasonable for sedation whenever possible, further studies investigating sedative agents specifically in sepsis may provide better information regarding optimal treatment regimens. Trials comparing propofol alone with dexmedetomidine alone or with midazolam alone would add to the literature.

Nutrition

Enteral nutrition (EN) is recommended as soon as feasible in critically ill patients with sepsis or septic shock. Early parenteral nutrition alone or parenteral nutrition in combination with enteral feedings is not recommended in patients who can be fed enterally. In patients who cannot be fed enterally, parenteral nutrition alone or in combination with enteral feedings is not recommended over the first 7 days. Monitoring of gastric residual volumes is not routinely recommended in critically ill patients with sepsis or septic shock. Only in patients with feeding intolerance or at high risk of aspiration should gastric residuals be measured and prokinetic agents considered (Rhodes 2017; McClave 2016).

The ASPEN guidelines currently recommend that EN be initiated within 24–48 hours after the diagnosis of severe sepsis or septic shock, provided resuscitation has been completed and the patient is hemodynamically stable. Data are lacking to compare early EN with delayed EN in patients with sepsis. However, benefit is expected with this practice, given the GI dysfunction rates and hypermetabolism in sepsis (McClave 2016).

A single-center retrospective review of adult patients with septic shock investigated the tolerance of EN in the setting of vasopressor use (Merchan 2017). In this study, 62% of patients tolerated EN, and the most common reason for intolerance was gastric residual volumes greater than 250 mL. Those who received EN within 48 hours and had norepinephrine-equivalent doses of 0.14 mcg/kg/minute or less were more likely to tolerate EN, by multivariate analysis. The authors concluded that EN may be safe and well tolerated in patients with septic shock after adequate fluid resuscitation and for those with lower vasopressor requirements.

A small observational study used indirect calorimetry to measure the energy expenditure of patients during and after mechanical ventilation (Lee 2017). The principal finding of this study was that energy expenditure was higher during mechanical ventilation than afterward. This study poses several interesting questions that necessitate further study,

including whether nutritional intake should be more closely matched to expenditure.

Many questions remain regarding best nutritional practices in patients with sepsis and septic shock, but the current literature suggests that initiating early EN in this population, assuming adequate fluid resuscitation and relative hemodynamic stability, is safe and may be beneficial.

VTE Prophylaxis

Critically ill patients with sepsis are at an increased risk of venous thromboembolism (VTE). Chemoprophylaxis should be considered for patients without a contraindication to therapy. However, patient subsets with sepsis may still be at risk of VTE, despite appropriate chemoprophylaxis. The guidelines recommend both chemoprophylaxis and mechanical VTE prophylaxis, when possible. However, this is a weak recommendation with low-quality evidence (Rhodes 2017).

A retrospective study to identify the rate of VTE chemoprophylaxis failure in critically ill patients with sepsis (Hanify 2017) showed that the rate of VTE development despite heparin or enoxaparin therapy for prophylaxis was 12.5%. Acute respiratory distress syndrome and higher positive end-expiratory pressure (10 vs. 8 cm H_2O) were both associated with an increased risk of VTE prophylaxis failure. This study also showed that VTE development was associated with increased ICU and hospital length of stay. This study highlights the need to identify patients who may be at an increased risk of VTE prophylaxis failure and consider additional measures such as sequential compression devices.

Stress Ulcer Prophylaxis

The current guidelines recommend that critically ill patients with sepsis with bleed risks should receive stress ulcer prophylaxis (SUP). However, literature is limited evaluating the risk-benefit of this practice. Given the recent concerns with SUP therapy such as increased risk of hospital-acquired pneumonia and *Clostridium difficile* infection, this issue should be explored in the setting of sepsis.

A prospective, double-blind, placebo-controlled, randomized trial compared intravenous pantoprazole with early EN as SUP in mechanically ventilated patients (El-Kersh 2018). This study included 102 patients in the final analysis. One patient from each group had overt GI bleeding, yielding an overall incidence of 1.96% and no statistically significant difference in this end point between groups (p=0.99). The authors concluded that pantoprazole offers no benefit for preventing GI bleeding when added to early EN in mechanically ventilated patients.

Another randomized clinical trial compared intravenous pantoprazole with placebo in mechanically ventilated patients (Alhazzani 2017). Upper GI bleeding developed in 6.1% of patients in the pantoprazole group and 4.8% of patients in the placebo group (p=1.0). The incidence of ventilator-associated pneumonia was insignificantly lower in the

placebo group (20.4% vs. 14.3%, p=0.58), as was the incidence of *C. difficile* infection (4.1% vs. 2.4%, p=1.0). The authors concluded that larger studies should examine the feasibility of withholding SUP in this population.

A retrospective study in Japan compared patients with severe sepsis who received SUP within 2 days of admission with patients who did not receive SUP using propensity matching (Sasabuchi 2016). Gastrointestinal bleeding requiring endoscopic hemostasis, 30-day mortality, and incidence of *C. difficile* infection did not significantly differ between the two groups. However, the proportion of patients with hospital-acquired pneumonia was significantly higher in the group that received SUP. The authors concluded that SUP may be unnecessary in this patient population, given these findings.

A multicenter, parallel-group, blinded trial examined the effect of daily intravenous pantoprazole at a dose of 40 mg on various outcomes compared with placebo (Krag 2018). The primary outcome was 90-day mortality. Secondary end points included clinically important ICU events, defined as clinically important GI bleeding, new-onset pneumonia, *C. difficile* infection, or acute myocardial ischemia. Around 20% of patients in each group had a coagulopathy, and around 80% of patients in each group required mechanical ventilation. The primary end points of 90-day mortality occurred in 31.1% of the pantoprazole group and 30.4% of the placebo group (p=0.76). These results did not significantly differ after adjustment for baseline characteristics. In the treatment group, 21.9% of patients had one or more clinically important event compared with 22.6% in the placebo group (RR 0.96; 95% CI, 0.83–1.11). Episodes of clinically important GI bleeding did not significantly differ between groups, nor did the incidence of serious adverse events. The authors concluded that pantoprazole did not significantly change patient outcomes.

Although data for SUP in this population are limited, risk-benefit should be weighed before routinely using medications for this purpose. The findings of the studies mentioned earlier suggest that routine use of SUP is unnecessary in patients with sepsis. Careful consideration should be used when deciding whether to use SUP in patients with sepsis rather than simply using it in every patient.

ROLE OF THE PHARMACIST

Pharmacists can positively influence patient care in patients with sepsis because of their extensive knowledge of the medications used in this disease state. This been supported by several studies and reviews that show the benefit of pharmacist involvement in patient care.

In 2013, authors identified the role of an ED clinical pharmacist in sepsis management (Weant 2013). Of the 585 consultations performed for 130 patients, the most common consultations provided were dosing recommendations (53%) and optimizing the empiric antibiotic management (22%).

One study showed the impact of a clinical pharmacist in the ED on shortening the time to administration and on more appropriate intravenous antibiotics in sepsis (Moussavi 2016). Time to antibiotic administration was significantly shorter when a pharmacist was present than when a pharmacist was not present (0.61 vs. 0.88 hours, p=0.001). However, ED clinical pharmacists did not significantly change ICU length of stay, hospital length of stay, ventilator-days, or in-hospital mortality.

A small retrospective study observed the successful selection of antimicrobial therapy before and after pharmacist intervention, time to administration of antimicrobial therapy, and time to appropriate antimicrobial administration in a cohort of patients with septic shock (Laine 2018). Results showed that the percentage of patients with successful selection of antimicrobial therapy significantly increased with pharmacist intervention from 66% to 80% (p=0.04). The study also showed significantly decreased time to appropriate antimicrobial therapy with pharmacist intervention in patients without initial successful selection of antimicrobial therapy. The authors concluded that pharmacist involvement can improve successful selection of antimicrobial therapy, facilitate rapid administration, and improve surrogate outcomes for mortality in septic shock.

A review of pharmacist impact on various aspects of sepsis management when pharmacists were part of a multidisciplinary team ultimately showed decreased time to antibiotic administration, decreased mortality (by 4.8%), significantly decreased overall health care costs (around $225,000,000 billing costs, $3,345,000 in drug charges, and $23,295,000 in laboratory charges), and increased appropriate medication selection (Cavanaugh 2017). Identified pharmacists' roles included ordering new antibiotics, verifying orders, expediting preparation or delivery processes, ordering antibiotics on the basis of the order set, assessing antibiotic appropriateness, facilitating vasopressor preparation, recommending doses or appropriate antibiotics, providing daily ICU patient care rounds, and being a medical response team and bedside response.

Although not specific to pharmacy, a time-series analysis found bundle compliance before and after various interventions (Grek 2017). One such intervention was the implementation of a multidisciplinary sepsis and shock response team, which included a pharmacist. This team was called once patients were determined to have severe sepsis or septic shock and aimed to evaluate them within 15 minutes to ensure bundle compliance. Among the ED admissions, in particular, mortality caused by sepsis or septic was reduced by implementing this team.

The literature advocates developing and implementing multidisciplinary teams to manage complex disease states such as sepsis and septic shock. Each discipline can offer unique perspectives and benefits to patient care and outcomes. Pharmacists are a great resource in sepsis management with development of guidelines/protocols, appropriate identification/dosing, improved time to antibiotics/vasopressors, and antibiotic de-escalation.

Practice Points

The SSC released Sepsis-3 for the new sepsis definition, with sepsis as "life-threatening organ dysfunction caused by dysregulated host response to infection" and septic shock as "subset of sepsis with circulatory and cellular/metabolic dysfunction associated with higher risk of mortality."

- qSOFA can be used to identify patients at risk of developing sepsis.
- Unlike with SIRS, patients with sepsis should have acute increase of at least 2 SOFA points as well as documented or suspected infection.
- Septic shock requires vasopressor therapy to meet a MAP of 65 mm Hg and when the lactate concentration is greater than 2 mmol/L (18 mg/dL) despite adequate fluid resuscitation.
- For the fluid resuscitation, at least 30 mL/kg of intravenous crystalloid fluid is recommended within the first 3 hours, ideally within the first hour.
- Broad-spectrum intravenous empiric antibiotic therapy should be administered within 1 hour of sepsis recognition.
- Norepinephrine is the first-line recommended vasopressor to maintain a MAP of 65 mm Hg.

Updates in the literature surrounding sepsis largely support the SSC guideline recommendations. In addition to these recommendations, recent data analyses suggest the following:

- Balanced crystalloids are a reasonable choice over normal saline for fluid resuscitation to prevent AKI in patients without contraindications.
- Angiotensin II may be reasonable in patients with shock that does not respond to other vasoactive medications. However, serious adverse effects such as thromboembolism may occur with its use; therefore, angiotensin II should be reserved until further studies investigate its use.
- Weight-based dosing of norepinephrine may increase cumulative drug exposure; however, the most recent data analyses suggest no benefit to this strategy, and it may increase costs.
- It may be reasonable to discontinue norepinephrine before vasopressin to avoid hypotension.
- β-Blocker therapy in sepsis may improve cardiac function without compromising tissue perfusion.
- Pharmacists can significantly and positively affect sepsis management through multidisciplinary teams.

CONCLUSION

Sepsis management is constantly changing as new research continues to investigate lingering clinical questions. Because sepsis remains a major cause of morbidity and mortality and the incidence of sepsis is increasing, new literature is needed to more definitely outline best practices in this disease state. When the most recent literature is considered, the latest SSC guideline recommendations remain appropriate. However, the new literature answers some of the clinical questions not directly addressed in the guidelines. Pharmacists continue to play a pivotal role in managing sepsis, not only by staying up to date on the literature but also by being involved in multidisciplinary teams.

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Self-Assessment Questions

Questions 1–3 pertain to the following case.

M.R., a 43-year-old woman (weight 65 kg), is admitted to the ICU with respiratory failure. Her chief concerns are shortness of breath and fever. In the ED, chest radiography reveals left lower lobe infiltration, and piperacillin/tazobactam and vancomycin are initiated. On ICU admission, M.R.'s blood pressure drops to 80/40 mm Hg (MAP 53 mm Hg).

1. Which one of the following is best to recommend for M.R.'s initial fluid resuscitation?

    A. 1000 mL of hydroxyethyl starches
    B. 1500 mL of 5% dextrose in ½ normal saline
    C. 1500 mL of 5% albumin
    D. 2000 mL of normal saline

2. After M.R.'s fluid resuscitation, norepinephrine continuous infusion is administered to maintain a MAP of at least 65 mm Hg. She is receiving norepinephrine at 25 mcg/minute, which was initiated 2 hours ago. Her heart rate is 130 beats/minute and MAP is 60 mm Hg. Her physician examination reveals 2+ pitting edema, and a passive leg raise (PLR) maneuver results in a stroke volume increase of 8%. Which one of the following is the best next step to recommend for M.R.?

    A. Increase the norepinephrine rate.
    B. Add vasopressin (at 0.03 unit/minute).
    C. Add methylprednisolone.
    D. Administer a 1-L bolus of normal saline.

3. M.R. continues to receive the norepinephrine continuous infusion, and her lactate concentration has been measured. Initial lactate was 5.7 mmol/L in the ED and, 3 hours later, is 3.2 mmol/L. Which one of the following best interprets M.R.'s lactate concentrations?

    A. Another vasopressor should be added because lactate is still greater than 2 mmol/L.
    B. Hypoperfusion has not been resolved and the patient's hospital mortality is greater than 40%.
    C. Norepinephrine continuous infusion can be tapered because lactate is trending downward
    D. The most recent lactate is less than 4 mmol/L; intravenous fluid should be changed to 5% albumin.

4. A patient was admitted to the medical floor for a deep venous thrombosis 2 days ago. No complications or abnormal laboratory values were associated with this condition when she was admitted. However, imaging now reveals new lung infiltrates. Her abnormal laboratory values and vital signs are SCr 2.0 mg/dL, MAP 60 mm Hg, and GCS score 13. Which one of the following best classifies this patient's disease, according to the Sepsis-3 definitions?

    A. Severe sepsis on the basis of the SOFA score
    B. Sepsis on the basis of an increase of 4 in the SOFA score

    C. Septic shock on the basis of signs of organ dysfunction
    D. Sepsis on the basis of the qSOFA score of 2

Questions 5 and 6 pertain to the following case.

Z.T., a 72-year-old woman, is admitted to the ICU with pneumonia. At presentation, she has temperature 101.2°F, blood pressure 82/44 mm Hg, heart rate 102 beats/minute, respiratory rate 20 breaths/minute, and GCS score 12. The patient's CBC shows WBC 16.2 x 10^3 cells/mm³, Hgb 6.2 mg/dL, and Plt 100,000/mm³. Her SCr is 2.1 mg/dL, Na is 145 mEq/L, K is 3.5 mEq/L, Cl is 115 mEq/L, INR is 1.9, and lactate is 1.5 mmol/L; arterial blood gas shows pH 7.2.

5. According to the Sepsis-3 guidelines, which one of the following best classifies Z.T.'s disease?

    A. Sepsis
    B. Severe sepsis
    C. Septic shock
    D. At risk of sepsis

6. The attending physician asks for a recommendation on balanced versus unbalanced crystalloids for Z.T. According to the SMART and SALT-ED trials, which one of the following is best to recommend for Z.T.'s initial fluid management in sepsis or septic shock?

    A. Lactated Ringer solution is preferred to normal saline because of decreased ventilator-free days.
    B. No preference between balanced and unbalanced fluid because of no difference in clinical outcomes.
    C. Normal saline is preferred to lactated Ringer solution because of decreased hospital mortality.
    D. Balanced crystalloids are preferred to reduce the risk of adverse kidney events.

Questions 7 and 8 pertain to the following case.

M.P. is a 49-year-old woman (height 64 in, weight 110 kg) admitted to the ICU 30 minutes ago for septic shock secondary to an intra-abdominal infection. The patient has received adequate volume resuscitation but now requires norepinephrine to maintain her MAP. M.P.'s vital signs are temperature 100.8°F, blood pressure 96/44 mm Hg, heart rate 110 beats/minute, and respiratory rate 20 breaths/minute, and her laboratory values are WBC 18.4 x 10^3 cells/mm³, SCr 1.4 mg/dL, lactate 2.4 mmol/L, and glucose 212 mg/dL.

7. Which one of the following is best to recommend for M.P.'s vasopressor therapy?

    A. Weight-based dosing should be used to achieve faster goal MAP.
    B. Non−weight-based dosing should be used to avoid increased cumulative norepinephrine exposure.

C. Norepinephrine should be initiated with vasopressin.
D. Norepinephrine should be administered peripherally to avoid central line placement.

8. Which one of the following, if initiated, would best help decrease M.P.'s risk of mortality?

   A. Piperacillin/tazobactam and vancomycin
   B. Vitamin C, thiamine, and hydrocortisone
   C. Esmolol continuous infusion
   D. Hydrocortisone

Questions 9–12 pertain to the following case.

N.Q., a 63-year-old woman (weight 74 kg), is admitted to the ICU with shortness of breath and altered mental status. Her medical history includes diabetes mellitus and hypertension. N.Q.'s vital signs are temperature 100.6°F, blood pressure 84/46 mm Hg (MAP 59), heart rate 104 beats/minute, and respiratory rate 22 breaths/minute. Chest radiography reveals bilateral lower lobe infiltrates. N.Q.'s laboratory data are as follows: Na 150 mEq/L, K 3.2 mEq/L, Cl 115 mEq/L, SCr 1.6 mg/dL, BUN 37 mg/dL, WBC 16.2 x 10^3 cells/mm^3, and lactate 2.2 mmol/L.

9. Which one of the following is best to recommend for N.Q.'s initial fluid resuscitation?

   A. 2000 mL of normal saline
   B. 100 mL of 5% albumin
   C. 2000 mL of lactated Ringer solution
   D. 1500 mL of 5% dextrose in ½ normal saline

10. After the initial fluid resuscitation, N.Q.'s MAP remains below goal. Which one of the following is best to recommend for N.Q.?

    A. Repeat the 30-mL/kg fluid bolus.
    B. Monitor change in cardiac output after PLR.
    C. Initiate hydrocortisone and fludrocortisone.
    D. Obtain central venous pressure (CVP) to determine the need for further fluid.

11. One hour later, N.Q.'s care team determines that vasopressor therapy is needed to maintain her MAP. Which one of the following vasopressors is best to recommend initiating first for N.Q.?

    A. Angiotensin II
    B. Vasopressin
    C. Dopamine
    D. Norepinephrine

12. N.Q. is now in the recovery phase of septic shock, and her vasopressor requirements are decreasing. Her MAP has been 70 mm Hg for the past hour. However, the physician is concerned about inducing hypotension. Currently, her vasoactive medications include norepinephrine 5 mcg/minute and vasopressin 0.03 unit/minute. According to the recent literature, which one of the following is best to recommend for N.Q.?

    A. Discontinue norepinephrine.
    B. Initiate hydrocortisone.
    C. Discontinue vasopressin.
    D. Administer a fluid bolus.

13. A 51-year-old man is admitted to the ICU with sepsis secondary to a UTI. His vital signs are temperature 100.2°F, blood pressure 104/48 mm Hg (MAP 67) while receiving high-dose norepinephrine, heart rate 117 beats/minute, and respiratory rate 18 breaths/minute. Laboratory values are as follows: WBC 14.8 x 10^3 cells/mm^3, K 4.1 mEq/L, SCr 1.1 mg/dL, and BUN 18 mg/dL. Appropriate antimicrobial therapy is administered. The patient's self-reported pain scale is currently 0, and he is in no apparent distress. His PLR does not show that he would benefit from additional fluid. Which one of the following is best to recommend for this patient to improve heart rate and stroke volume without compromising tissue perfusion?

    A. Add dopamine.
    B. Add dobutamine.
    C. Add esmolol.
    D. Increase norepinephrine dose.

Questions 14 and 15 pertain to the following case.

J.T. is a 69-year-old man presenting to the ED with altered mental status, according to his wife. She states that J.T. has had headaches and a sore throat recently. His vital signs on admission are temperature 101.2°F, blood pressure 92/40 mm Hg, heart rate 112 beats/minute, and respiratory rate 18 breaths/minute. Laboratory values are as follows: WBC 23.2 x 10^3 cells/mm^3, BUN 22 mg/dL, SCr 1.8 mg/dL, and glucose 106 mg/dL. Despite adequate fluid resuscitation, high-dose norepinephrine and fixed-dose vasopressin are not maintaining J.T.'s MAP above 65 mm Hg.

14. According to the recent literature, which one of the following is most likely to reduce J.T.'s risk of mortality?

    A. Hydrocortisone plus fludrocortisone
    B. Methylprednisolone
    C. Hydrocortisone
    D. Dexamethasone

15. J.T.'s nurse wonders whether she can titrate his vasopressin dose to maintain a MAP of 65 mm Hg or greater. Which one of the following is best to relate to J.T.'s nurse regarding high-dose vasopressin?

    A. May cause myocardial and bowel ischemia.
    B. May increase the heart rate in patients with septic shock.
    C. May cause hypernatremia.
    D. May not increase blood pressure.