REVIEW Siddharth Dugar, MD Department of Critical Care, Respiratory Institute, Cleveland Clinic; Clinical Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH Chirag Choudhary, MD, MBA Department of Critical Care, Respiratory Institute, Cleveland Clinic; Clinical Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University,

Cleveland, OH Abhijit Duggal, MD, MPH, MSc, FACP Department of Critical Care, Respiratory Institute, Cleveland Clinic; Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH Sepsis and septic shock: Guideline-based management ABSTRACT Sepsis is a life-threatening organ dysfunction that results from the body's response to infection. It requires prompt recognition,

appropriate antibiotics, careful hemodynamic support, and control of the source of infection. With the trend in management moving away from protocolized care in favor of appropriate usual care, an understanding of sepsis physiology and best practice guidelines is critical. Sepsis and particularly septic shock should be recognized as medical emergen cies in which time matters, as in stroke and acute myocardial infarction. Early recognition

and rapid institution of resuscitative measures are critical. But recognizing sepsis can be a challenge, and best management practices continue to evolve. KEY POINTS Tools such as the Systemic Infl ammatory Response Syndrome criteria and the quick version of the Sequential Organ Failure Assessment can help with early diagnosis and triage. The initial antibiotic should be broad-spectrum, based on local sensitivity patterns, with daily

assessment of appro priate antibiotic de-escalation and cessation. Resuscitation with initial fl uid boluses should be followed by weighing benefi ts and risks of additional fl uid admin istration based on dynamically assessed volume status, and then aggressive fl uid removal during recovery. During resuscitation, a goal mean arterial pressure of 65 mm Hg is preferred, using norepinephrine (with vasopres sin if needed) to achieve it. Glucocorticoids

are not recommended if fl uid resuscita tion and vasopressors are suffi cient to restore hemo dynamic stability. doi:10.3949/ccjm.87a.18143 This article reviews guidance on the di agnosis and management of sepsis and septic shock, with attention to maximizing adher ence to best practice statements, and contro versies in defi nitions, diagnostic criteria, and management. ■ COMMON AND LIFE-THREATENING Sepsis affects 750,000 patients each

year in the United States and is the leading cause of death in critically ill patients, killing more than 210,000 people every year.1 About 15% of patients with sepsis go into septic shock, which accounts for about 10% of admissions to intensive care units (ICUs) and has a death rate of more than 50%. The incidence of sepsis doubled in the United States

between 2000 and 2008,2 pos sibly owing to more chronic diseases in our aging population, along with the rise of anti biotic resistance and the increased use of in vasive procedures, immunosuppressive drugs, and chemotherapy. The cost associated with sepsis-related care in the United States is more than $20.3 billion annually.3 ■ DEFINITIONS HAVE EVOLVED In 1991, sepsis was fi rst defi ned as a systemic infl ammatory response syndrome (SIRS) due CLEVELAND CLINIC JOURNAL OF MEDICINE

VOLUME 87 • NUMBER 1 JANUARY 2020 www.ccjm.org on September 19, 2025. For personal use only. All other uses require permission. 53 Downloaded from SEPSIS AND SEPTIC SHOCK to a suspected or confi rmed infection with 2 or more of the following criteria4: • Temperature below 36°C or above 38°C • Heart rate greater than 90/minute • Respiratory rate above 20/minute, or arte rial partial pressure of carbon dioxide less than 32

mm Hg • White blood cell count less than 4 × 109/L or greater than 12 × 109/L, or more than 10% bands. Severe sepsis was defi ned as the progression of sepsis to organ dysfunction, tissue hypoper fusion, or hypotension. Septic shock was described as hypotension and organ dysfunction that persisted despite volume resuscitation, necessitating vasoactive medication, and with 2 or more of the SIRS criteria listed above.

Appropriate antimicrobials should be started within an hour of recognizing sepsis In 2001, defi nitions were updated with clinical and laboratory variables.5 In 2004, the Surviving Sepsis Campaign guidelines adopted those defi nitions, which led to the development of a protocol-driven model for sepsis care used worldwide.6 The US Centers for Medicare and Medicaid Services (CMS) followed suit, defi ning sepsis as the presence of at least 2 SIRS

criteria plus infec tion; severe sepsis as sepsis with organ dysfunc tion (including serum lactate > 2 mmol/L); and septic shock as fl uid-resistant hypotension requiring vasopressors, or a lactate level of at least 4 mmol/L.7 In 2016, the Sepsis-3 committee8 issued the following new defi nitions: • Sepsis—A life-threatening condition caused by a dysregulated host response to infection, resulting in organ dysfunction • Septic shock

—Circulatory, cellular, and metabolic abnormalities in septic patients, presenting as fl uid-refractory hypotension requiring vasopressor therapy with asso ciated tissue hypoperfusion (lactate > 2 mmol/L). The classifi cation of severe sepsis was elim inated. Multiple defi nitions create confusion Both the CMS and international consen sus defi nitions are currently used in clinical practice, with distinct terminology and dif ferent identifi cation criteria, including blood pressure and lactate cutoff points. The CMS defi

nition continues to recommend SIRS for sepsis identifi cation, while Sepsis-3 uses se quential organ failure assessment (SOFA) or the quick version (qSOFA) to defi ne sepsis (described below). This has led to confusion among clinicians and has been a contentious

factor in the development of care protocols. ■ TOOLS FOR IDENTIFYING HIGH RISK: SOFA AND qSOFA SOFA is cumbersome SOFA is an objective scoring system to de termine major organ dysfunction, based on oxygen levels (partial pressure of oxygen and fraction of inspired oxygen), platelet count, Glasgow Coma Scale score, bilirubin level, creatinine level (or urine output), and mean arterial pressure (or whether vasoactive agents are required). It is routinely used in clinical and research practice to track individual and aggregate organ failure in critically ill pa tients.9 But the information needed is burden some to collect and not usually available at the bedside to help with clinical decision-making. qSOFA is

simpler... Singer et al8 compared SOFA and SIRS and identifi ed 3 independent predictors of organ dysfunction associated with poor outcomes in sepsis to create the simplifi ed qSOFA: • Respiratory rate at least 22 breaths/minute • Systolic blood pressure 100 mm Hg or lower • Altered mental status (Glasgow Coma Scale score < 15). A qSOFA score of 2 or more with a sus pected or confi rmed infection was proposed as a trigger for aggressive

treatment, includ ing frequent monitoring and ICU admission. qSOFA has the advantage of its elements be ing easy to obtain in clinical practice. ...but has limitations Although qSOFA identifi es severe organ dys function and predicts risk of death in sepsis, it needs careful interpretation for defi ning sepsis. One problem is that it relies on the clinician's ability to identify infection as the cause of organ dysfunction, which may not be apparent early on,

making it less sensitive than SIRS for diagnosing early sepsis.10 Also, preexisting chronic diseases may infl uence 54 CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 87 • NUMBER 1 JANUARY 2020 www.ccjm.org on September 19, 2025. For personal use only. All other uses require permission. Downloaded from DUGAR AND COLLEAGUES accurate qSOFA and SOFA measurement.11 In addition, qSOFA has only been validated outside the ICU, with limited utility in pa tients already admitted to an ICU.12 Studies have suggested

that the SIRS cri teria be used to detect sepsis, while qSOFA should be used only as a triaging tool.11,13 ■ ANTIMICROBIAL THERAPY Prompt, broad-spectrum antibiotics Delay in giving appropriate antibiotics is asso ciated with a signifi cant increase in mortality rate.14–16 Appropriate antimicrobials should be initiated within the fi rst hour of recognizing sepsis, after obtaining relevant samples for cul ture—provided that doing so does not signifi cantly delay antibiotic administration.17 The initial antimicrobial drugs should be broad-spectrum, covering all likely pathogens. Multidrug regimens are favored to

ensure suffi cient coverage, especially in septic shock. The empiric choice of antimicrobials should con sider the site of infection, previous antibiotic use, local pathogen susceptibility patterns, im munosuppression, and risk factors for resistant organisms. Double coverage for gram-negative organisms and for methicillin-resistant

Staphy lococcus aureus (MRSA) should be considered for patients with a high likelihood of infection with such pathogens.18 Double gram-negative coverage may be appropriate when a high degree of suspicion exists for infection with multi-drug-resistant organisms such as Pseudo monas or Acinetobacter. If a nosocomial source of infection is suspected to be the cause of sep sis, anti-MRSA agents are recommended. Appropriate dosing is also important, as effi cacy depends on peak blood level of the drug and on how long the blood level remains above the minimum inhibitory concentration for the pathogen. An initial higher loading dose may be the best strategy to achieve the therapeutic blood level, with further dosing based on consultation with an infectious dis ease physician or pharmacist, as well as thera peutic drug monitoring if needed.17 Consider antifungals The last few decades have seen a 200% rise in the incidence of sepsis due to fungal organ isms.19 Antifungals should be considered for patients at risk, such as those who have had total parenteral nutrition, recent broad-spec trum antibiotic exposure, perforated abdomi nal viscus, or immunocompromised status, or when clinical suspicion of fungal infection is high. Risk factors for fungal infection in septic shock should trigger the addition of echino candins or liposomal amphotericin B. Azoles are considered appropriate for hemodynami cally stable patients.20 De-escalation and early cessation Antibiotics are not harmless: prolonged use of broad-spectrum antibiotics is associated with antimicrobial resistance, Clostridium diffi cile infection, and even death.21 A robust de-escalation strategy is needed to balance an initial broad-spectrum approach. A pragmatic strategy may involve starting with broad-spectrum antimicrobials, particu larly in the setting of hypotension, and then rapidly de-escalating to an antimicrobial with the narrowest spectrum based on local sensi tivity patterns. If the clinical course suggests the illness is not actually due to infection, the antibiotics should be stopped immediately. A rapid nasal polymerase chain reaction test for MRSA to guide de-escalation has been shown to be safe and to signifi cantly reduce empiric use of vancomycin and linezolid.22,23 Antibiotic de-escalation should be dis cussed daily and should be an essential com ponent of daily rounds.17 A 7- to 10-day course or even shorter may be appropriate for most infections,24,25 although a longer course may be needed if source control cannot be achieved, in immunocompromised hosts, and in S aureus bacteremia, endocarditis, or fungal infections. ■ FLUID RESUSCITATION Sepsis is associated with vasodilation, capil lary leak, and decreased effective circulating blood volume, reducing venous return. These hemodynamic effects lead to impaired tissue perfusion and organ dysfunction. The goals of resuscitation in sepsis and septic shock are to restore intravascular volume, increase oxygen delivery to tissues, and reverse organ dysfunc tion. A crystalloid bolus of 30 mL/kg

is recom mended within 3 hours of detecting severe sepsis or septic shock.17 However, only limited A robust antimicrobial de-escalation strategy needs to balance an initial broad-spectrum approach CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 87 • NUMBER 1 JANUARY 2020 www.ccjm.org on September 19, 2025. For personal use only. All

other uses require permission. 55 Downloaded from SEPSIS AND SEPTIC SHOCK data support the benefi ts of this recommen dation, and evidence of harm from sustained positive fl uid balance is growing. Some have cautioned against giving too much fl uid, especially in patients who have limited cardiorespiratory reserve.26 Overzeal ous fl uid administration can result in pulmo nary edema, hypoxemic respiratory failure, organ edema, intra-abdominal hypertension, prolonged ICU stay and time on mechani cal

ventilation, and even increased risk of death.26,27 With this in mind, fl uid resuscitation should be managed as follows during consecu tive phases28: • Rescue: During the initial minutes to hours, fl uid boluses (a 1- to 2-L fl uid bolus of crystalloid solution) are required to re verse hypoperfusion and shock • Optimization: During the second phase, the benefi ts of giving additional fl uid to improve cardiac output and tissue perfu sion should be weighed against potential harms27 Antibiotic de-escalation should be discussed daily •

Stabilization: During the third phase, usu ally 24 to 48 hours after the onset of sep tic shock, an attempt should be made to achieve a net-neutral or a slightly negative f l uid balance • De-escalation: The fourth phase, marked by shock resolution and organ recovery, should trigger aggressive fl uid removal strategies.27 Assess volume with dynamic measures Clinicians should move away from using static measures to assess volume status. Central ve nous pressure, the static measure most often used to guide resuscitation, has been found to be accurate in only half of cases, compared with

thermodilution using pulmonary artery catheters to assess change in cardiac output with volume administration.29 A 2017 meta analysis30 showed that the use of dynamic as sessment in goal-directed therapy is associated with lower mortality risk, shorter ICU stay, and shorter duration of mechanical ventilation. Dynamic measures are used to estimate the effects of additional volume on cardiac out put. Two methods are used: either giving a fl u id bolus or passively raising the legs. The latter method returns 200 to 300 mL of blood

from the lower extremities to the central circula tion and is performed by starting the patient in a semirecumbent position, then lowering the trunk while passively raising the legs. With either method, the change in cardiac output is measured either directly (eg, with thermodilution, echocardiography, or pulse contour analysis) or using surrogates (eg, pulse pressure variation). Alternatively, changes in cardiac output can be evaluated by heart-lung

interactions in a patient on a mechanical ventilator. Changes in intrathoracic pressure are assessed during the inspiratory and expiratory cycle to detect changes in cardiac output using pulse pressure variation, stroke volume variation, and varia tion in inferior vena cava size. The dynamic measures mentioned above are more accurate than static measurements in predicting preload responsiveness, so they are recommended to guide fl uid management.31,32 But they do have limitations.33 Although giv ing a fl uid bolus

remains the gold standard for critically ill patients, indiscriminate fl uid administration carries the risk of fl uid over load. Heart-lung interactions are imprecise for patients with arrhythmias, those who are spontaneously breathing with active effort on the ventilator, and those with an open chest or abdomen. Thus, their use is limited in most critically ill patients.34 Unlike other dynamic tests, the passive leg-raise test is accurate in spontaneously breathing patients, for patients with cardiac arrhythmias, and for those on

low tidal vol ume ventilation.35 Due to its excellent sensi tivity and specifi city, the passive leg-raise test is recommended to determine fl uid respon siveness.17,32 Lactate level as a resuscitation guide Lactate-guided resuscitation can signifi cantly lessen the high mortality rate associated with elevated lactate levels (> 4 mmol/L).36,37 A rise in lactate during sepsis can be due to tissue hypoxia, accelerated glycolysis from a hyper adrenergic state, medications (epinephrine, beta-2 agonists), or liver failure. Measuring the lactate level is an

objective way to assess response to resuscitation, better than other clinical markers, and it continues to be an in tegral part of sepsis defi nitions and the Sur 56 CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 87 • NUMBER 1 JANUARY 2020 www.ccjm.org on September 19, 2025. For personal use only. All other uses require permission. Downloaded from DUGAR AND COLLEAGUES viving Sepsis Campaign care bundle.7,8,17 Even though lactate is not a direct surrogate of tis sue hypoperfusion, it is a mainstay for assess ing end-

organ hypoperfusion. Central venous oxygen saturation-guided resuscitation (requiring central vascular ac cess) does not offer any advantage over lac tate-guided resuscitation.38 Microvascular as sessment devices are promising tools to guide resuscitation, but their use is still limited to clinical research. Although optimal resuscitation end points are not known, key variables to guide resus citation include a composite of physical ex amination fi ndings plus peripheral perfusion, lactate clearance,

and dynamic preload re sponsiveness.17,39 Balanced crystalloids are preferred over isotonic solutions Crystalloid solutions (isotonic saline or bal anced crystalloids) are recommended for vol ume resuscitation in sepsis and septic shock. The best one to use is still debated, but over the last decade, balanced solutions have come to be favored for

critically ill patients. Grow ing evidence indicates that balanced crystal loids (lactated Ringer solution, Plasma-Lyte) are associated with a lower incidence of renal injury, less

need for renal replacement therapy, and lower mortality in critically ill patients. Moreover, isotonic saline is associated with hyperchloremia and metabolic acidosis, and it can reduce renal cortical blood fl ow.40–42 No proven benefi t from colloids The rationale for using colloids is to increase intravascular oncotic pressure, reducing cap illary leak and consequently reducing the amount of fl uid required for resuscitation. But in vivo studies have failed to demonstrate this benefi t. One can consider using albumin in sepsis if a

signifi cant amount of resuscitative fl uid is required to restore intravascular volume.17 But comparisons of crystalloids and albumin, either for resuscitation or as a means to in crease serum albumin in critically ill patients, have found no benefi t in terms of morbidity or mortality.43–45 When considering albumin to treat sepsis or septic shock, clinicians should remember its lack of benefi t and its substantial cost—20 to 100 times as much as crystalloids, TABLE 1 Randomized controlled trials of volume replacement in sepsis and

septic shock Author and year Finfer et al,43 2004 Perner et al,47 2012 Annane et al,45 2013 Caironi et al,44 2014 Young et al,41 2015 Number of patients Major fi ndings 6,997 804 2,587 1,818 No reduction in mortality with albumin compared with saline Higher risk of death and renal replacement therapy with hydroxy ethyl starch compared with Ringer solution No reduction in mortality, need for renal replacement therapy, dura tion of

resuscitation, or length of stay with colloids compared with crystalloids No reduction in mortality, need for renal replacement therapy, or length of stay with albumin replacement 2,278 Semler et al,40 2018 15,802 No difference in incidence of acute kidney injury, need for renal re placement therapy, or length of stay with balanced solution compared with saline Lower rates of mortality and need for renal replacement therapy with balanced solutions compared with saline with an additional cost greater than $30,000 per case with

use of albumin.46 Hydroxyethyl starch, another colloid, was associated with a higher mortality rate and a higher incidence of renal failure in septic pa tients and should not be used for resuscitation (Table 1).47 ■ EARLY SOURCE CONTROL Source control is imperative in managing sep sis and septic shock. Inadequate source con trol may lead to worsening organ function and hemodynamic instability despite appropriate resuscitative measures.17 A thorough exami nation and appropriate imaging studies should be

performed to determine the optimal way to control the source and assess the risks associ ated with each intervention.

If appropriate, source control should be achieved within 6 to 12 hours of diagnosis, once initial resusci tation is completed.48 The source control can range from removal of infected

intravascular devices to a chest tube for empyema to per cutaneous or surgical intervention in cases of cholecystitis and pyelonephritis. ■ RESTORING BLOOD PRESSURE Persistent hypotension and tissue hypoper fusion after adequate fl uid resuscitation are caused by loss of normal sympathetic vascular tone, leading to vasodilation, neurohormonal imbalances, myocardial depression, micro circulatory dysregulation, and mitochondrial dysfunction. Vasopressors and inotropes re store oxygen delivery to tissues

by increasing arterial pressure and cardiac output respec tively. The passive leg-raise test has excellent sensitivity and specifi city for determining f l uid responsiveness Mean arterial pressure is the preferred blood pressure to target during resuscitation. The recommended initial goal is 65 mm Hg. A higher goal of 80 to 85 mm Hg may help patients with chronic hypertension,49 while a lower target may be better tolerated in patients with reduced systolic function, older patients, and patients with end-stage liver disease. These

recommendations are based on our understanding of autoregulation of blood fl ow in the vascular beds of central organs (brain, heart, kidneys). After blood pressure falls be low a critical threshold, tissue perfusion de creases linearly. That critical threshold can vary between organ systems and individuals, and the target can later be personalized based on global and regional perfusion as assessed with urine output, mental status, or lactate

clearance.50 Decisions to titrate vasopressors to achieve mean arterial pressure goals should be bal anced against potential adverse effects, in cluding arrhythmias, cardiovascular events, and ischemia. Norepinephrine is the fi rst-line vasopressor Few large, multicenter randomized controlled studies have been done to determine the most effective initial and adjunctive vasoactive agents for septic shock. Norepinephrine has

shown survival benefi t with lower risk of ar rhythmia than dopamine.51–53 On the other hand, 2 systematic reviews found no differ ence in clinical outcomes and mortality with norepinephrine vs epinephrine, vasopressin, terlipressin, or phenylephrine.53,54 Without convincing evidence to support other agents as fi rst-line therapy for septic shock, norepinephrine remains the preferred vasopressor for achieving the target mean ar terial pressure and is strongly recommended by the Surviving Sepsis Campaign guidelines, albeit

supported by only moderate-quality data.17,55 Adding a second vasopressor or inotrope Another sympathomimetic drug such as vaso pressin or epinephrine can be used to either achieve target mean arterial pressures or de crease the norepinephrine requirement. A second vasopressor is routinely added when norepinephrine doses exceed 40 or 50

μg/min. Vasopressin. Septic shock involves rela tive vasopressin defi ciency. Adding vasopres sin as a replacement hormone has been shown to have a sparing effect on

norepinephrine, re sulting in a lower dose needed. A randomized controlled trial comparing vasopressin plus norepinephrine vs vasopressin monotherapy failed to show any survival benefi t or reduc tion in kidney failure.56,57 Evidence supporting the use of vasopressin over norepinephrine as a fi rst-line agent remains limited, but va sopressin remains the preferred adjunct with norepinephrine.56,57 Epinephrine is recommended by the Surviving Sepsis Campaign guidelines as a second-line vasopressor. It has potent alpha- and beta-

adrenergic activity, which increases mean arterial pressure by increasing cardiac output and vasomotor tone. Use of epineph rine is limited by signifi cant risk of tachycar dia, arrhythmia, and transient lactic acidosis.58 Dopamine use is discouraged in sepsis ow ing to its propensity to induce tachyarrhyth mia and signifi cantly worsen outcomes in this setting.51,52 Phenylephrine is a pure alpha-adrenergic agonist that is routinely used in septic shock, albeit with limited data on its effi cacy and safety. Vail et al59 found

increased mortality associated with phenylephrine use in septic shock in a multicenter cohort study conduct ed during a norepinephrine shortage. Phenyl 58 CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 87 • NUMBER 1 JANUARY 2020 www.ccjm.org on September 19, 2025. For personal use only. All other uses require permission. Downloaded from DUGAR AND COLLEAGUES ephrine use should be limited to septic shock complicated by signifi cant tachyarrhythmia or as an adjunct for refractory vasodilatory

shock until there is more evidence of its benefi ts.17 Angiotensin II was recently approved as a vasopressor for use in septic shock. It activates angiotensin type 1a and 1b receptors to in crease intracellular calcium in smooth muscle, promoting vasoconstriction. Clinical data re lated to its use are limited to a recent trial that showed that the addition of angiotensin II im proved blood pressure in patients with refrac tory vasodilatory shock

receiving high-dose vasopressors.60 The data are still sparse on its safety, and its precise role in refractory shock treatment algorithms has yet to be defi ned. Inotropic agents may be required for pa tients with inadequate cardiac output after f l uid resuscitation due to sepsis-induced car diomyopathy or combined shock. Data are limited suggesting an optimal inotropic agent in septic shock, but epinephrine and dobuta mine are most commonly used.61,62 A compari son of norepinephrine plus dobutamine vs epi nephrine in septic shock found no difference in mortality, side effects, or shock duration.62

Milrinone and levosimendan (not approved in the United States) have been studied, with limited data to support their use over dobu tamine.63,64 The response to use of inotropes should be monitored by measuring changes in cardiac output, central venous oxygen

satura tion, or other indices of tissue perfusion (Ta ble 2). ■ ROLE OF CORTICOSTEROIDS IS QUESTIONED Corticosteroids downregulate the maladaptive infl ammatory response seen in sepsis and help address relative adrenal insuffi ciency caused by adrenal suppression or

glucocorticoid tissue resistance.65 In septic shock, they have a vaso pressor-sparing role and reduce the duration of shock, ventilator use, and ICU stay. However, the evidence is not conclusive that giving corticosteroids for sepsis improves clinical outcomes or survival,66–71 and so they are not recommended in sepsis or severe sepsis if fl uid resuscitation and vasopressors are suffi cient to restore hemodynamic stability. Rath er, they can be added as adjunctive therapy for TABLE 2 Randomized controlled trials of vasopressors and inotropes in septic shock Author and year Annane et al,62 2007 Russell

et al,57 2008 De Backer et al,51 2010 Gordon et al,56 2016 Number of patients Major fi ndings 330 780 1,679 No difference in mortality with epi nephrine vs norepinephrine ± dobu tamine; higher lactate elevation and lower pH in epinephrine group No reduction in mortality with addition of vasopressin to norepi nephrine Survival benefi t in patients with septic shock requiring norepineph rine < 15 µg/min Vasopressin had norepinephrine sparing effect. Higher rates of mortality and ar rhythmia with dopamine than with norepinephrine 409 Khanna et al,60 2017 344 No improvement in kidney failure free days,

use of renal replacement therapy, or mortality with vasopres sin Angiotensin II increased blood pres sure in refractory vasodilatory shock patients requiring higher doses of vasopres sors.17,65 Adverse events in studies of corticoste roids were limited to hyperglycemia, hyperna tremia, and hypertension, with no increase in superinfections.71 The limited adverse events, along with a uniform demonstration of shorter shock duration, ventilator duration, and ICU stay, suggest steroids may have a role in man aging refractory septic

shock.66–69 If corticosteroids are used in septic shock, current guidelines recommend hydrocortisone 200 mg per day intravenously as a continu ous drip or 50 mg bolus in 4 divided doses for at least 3 days, based on a systematic review showing a longer course of low-dose steroids is associated with a lower mortality rate.72 There is no clear consensus

on whether ste roids should be tapered or if abrupt cessation is appropriate, as larger randomized clinical tri CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 87 • NUMBER 1 JANUARY 2020 www.ccjm.org on September 19, 2025. For personal use only. All other uses require permission. 59 Downloaded from SEPSIS AND SEPTIC SHOCK TABLE 3 Randomized controlled trials of corticosteroids in septic shock Author and year Annane et al,68 2002 Sprung et al,69 2008 Keh et al,70 2016 Annane et al,66 2018 Venkatesh et al,67

2018 Number of patients Major fi ndings 300 499 380 Lower mortality rate and shorter duration of shock in corticotropin nonresponders with hydrocortisone + fl udrocortisone,

but not in all patients No difference in mortality rate, but shorter duration of shock and no increased risk of superinfection with hydrocortisone No benefi t of hydrocortisone in preventing septic shock or decreas ing mortality in severe sepsis 1,241 3,800 Lower mortality rate and shorter duration of shock and mechanical ventilation with addition of

hydro cortisone + fl udrocortisone. No reduction in mortality with addition of hydrocortisone, but reduced duration of shock, mechani cal ventilation and length of stay in intensive care unit als did not use a tapering strategy and found no difference in shock recurrence.66,67 In most cases, steroids are stopped after cessation of vasopressors.65 Future research should focus on appropri ate timing of glucocorticoid initiation after onset of shock and comparing a fi xed duration regimen to a clinically guided one. Etomidate as an induction agent for intu bation has been associated with suppression of cortisol synthesis and a reduced response to exogenous steroids. Whether it affects outcomes is

unclear. Nonetheless, clinicians should practice extreme caution with etomi date use in septic shock (Table 3).73 ■ BIOMARKERS Biomarkers facilitate early diagnosis, identify patients at high risk, and monitor disease pro gression to guide resuscitation goals and tailor management. C-reactive protein and erythrocyte sedi mentation rate have been used in the past, but with limited success.74 Procalcitonin has emerged as a method to help detect bacterial infections early and to guide de-escalation or discontinuation of anti biotics.75,76 Procalcitonin-guided de-escalation of antibiotics reduces duration of

antibiotic exposure, with a trend toward decreased mor tality.77,78 Galactomannan and beta-D-glucan can be used to detect infections with fungi, specially Aspergillus. Beta-d-glucan is more sensitive for invasive Aspergillus, while galactomannan is more specifi c.79 Cytokines such as interleukins (eg, IL 6, IL-8, IL-10), tumor necrosis factor alpha, acute-phase proteins, and receptor molecules are currently being studied to determine their utility in sepsis care. The limited sensitivity and specifi city of single biomarkers may be overcome by using a combination of biomarkers, which is a cur rent focus of research.80

For now, the decision to initiate, escalate, and de-escalate therapy should be based on clinical assessment, with procalcitonin or other biomarkers used as an adjunct to other clinical factors.17 ■ USUAL CARE VS PROTOCOLIZED INITIAL RESUSCITATION In 2001, Rivers et al61 compared usual care for severe sepsis or septic shock with a pro tocolized targeting of physiologic end points as goals of resuscitation for the 6 hours before admission to the ICU in a single center. They found a signifi cantly lower mortality rate in the goal-directed therapy group. This fi nding heavily infl uenced the bundle-based, goal directed management strategy recommended by the Surviving Sepsis Campaign in 2004.81

However, the protocolized approach has been challenged since then, with 3 large mul ticenter trials fi nding that usual care was not inferior to protocolized care in sepsis, with no difference in mortality or length of stay.82–84 Further, usual care was associated with signifi cantly reduced need for central vascular ac cess, blood transfusions, and dobutamine. A meta-analysis involving nearly 4,000 patients at 138 hospitals in 7 countries found that usu 60 CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 87 • NUMBER 1 JANUARY 2020 www.ccjm.org on September 19, 2025. For personal use only. All other uses

require permission. Downloaded from DUGAR AND COLLEAGUES al care emphasizing detecting sepsis early and rapidly implementing appropriate antimicro bial therapy and adequate fl uid resuscitation was not only equivalent to protocolized care in outcomes but was more cost-effective.85 (Table 4). Is SEP-1 appropriate? In January 2013, the State of New York man dated that all state hospitals initiate processes for early detection and treatment of sepsis. In October 2015, the National Quality Forum and CMS implemented these processes na tionwide.7 The resultant CMS SEP-1 quality measure standardizes early

management of se vere sepsis and septic shock, with the goal of improving outcomes. Its elements are based on the Surviving Sepsis Campaign guidelines and consist of a series of steps that need to be completed within 3 and 6 hours after sepsis is recognized. Steps to be performed within 3 hours in clude measuring the serum lactate level, draw ing blood cultures, and starting appropriate antibiotics, intravenous fl uid resuscitation, and vasopressor support if needed. A lactate level is repeated within 6 hours, and static and

dynamic assessment of perfusion must be done to determine the need for additional fl uid or vasopressors to improve end-organ perfusion. SEP-1 overall hospital performance is pub licly available on the CMS website (medicare. gov/hospitalcompare/search.html?) and has the potential to be used for fi nancial incen tives centered on SEP-1 measure compliance performance.86 Although SEP-1 has been adopted as a quality measure, some question its clinical relevance, as many of the core recommenda tions are not supported by strong evidence.86,87 Three major trials found that the mortality rate was no lower with bundled sepsis care than with usual care.82–84 Seymour et al28 col lected New York State Department of Health data for 49,331 patients with sepsis and septic shock and found that

more rapid completion of the 3-hour bundle—particularly of antibi otic administration but

not of fl uids—was as sociated with decreased hospital mortality. A multicenter retrospective cohort study88 found TABLE 4 Randomized controlled trials evaluating early goal-directed care in septic shock Author and year Rivers et al,61 2001 Peake et al,82 2014 Rowan et al,85 2014 Mouncey et al,83 2015 Number of patients Major fi ndings 268 1,600 1,351 Signifi cantly lower mortality rate with protocolized care No reduction in mortality,

need for advanced respiratory or renal sup port, or intensive care unit length of stay with protocolized care No reduction in mortality, need for advanced respiratory or renal sup

port, or intensive care unit length of stay with protocolized care 1,260 No reduction in

mortality, need for advanced respiratory, cardiovas cular or renal support, or intensive care unit length of stay with proto colized care that failure to meet SEP-1 criteria for any step

other than giving antibiotics did not translate to poor outcomes. A major concern about mandating SEP-1 is that fl uids and broad-spectrum antibiotics will be overprescribed as healthcare systems try to meet CMS-mandated quality measures. Indiscriminate use of these therapies has the potential to cause harm and puts an undue strain on healthcare resources.89 A call to refi ne guidance Sepsis is a multifaceted disease, and its man

agement is complex. Simplifi ed guidelines and quality measures based on sound evidence

are needed. Electronic medical record systems show promise for assisting with early and ac curate detection of sepsis and have the poten tial to play an important role.90,91

Checklists that allow bedside caregivers to exercise their clinical acumen are another approach. The success of optimal care initiatives requires sustained, collaborative quality

improvement across different specialties in medicine, nurs ing, and hospital administration.92 ■ The lactate level remains an objective guide to assess response to resuscitation CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 87 • NUMBER 1

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Department of Critical Care Medicine, Respiratory Institute, G62, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, Ohio. 44195; duggala2@ccf.org 64 CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 87 • NUMBER 1 JANUARY 2020 www.ccjm.org on September 19, 2025. For personal use only. All other uses require permission. Downloaded from