Chapter 8
Sepsis and Septic Shock

Anand Kumar and Victor Tremblay

Case Study

A 67-year-old man is brought to the emergency department by his wife for fever and flank pain for 24 h. He has a previous medical history of type 2 diabetes, gout, and recurrent nephrolithiasis. His medications include glyburide and allopurinol. He has no known allergy. On physical examination, the patient is confused and cannot answer questions appropriately. His blood pressure is 85/40 mmHg and his heart rate is 128 beats per minutes. His respiratory rate is 26/min with an oxygen saturation of 97% on 2 L/min nasal prongs. He is febrile at 38.8 °C. He has costovertebral tenderness on the right. His extremities are warm with bounding pulses.

Laboratory studies show a white blood cell count of 23,000/mm^3, platelets of 98,000/mm^3, creatinine of 256 micromol/L, and lactate of 6.2 mmol/L. Urinalysis is positive for nitrite and numerous white blood cells. Chest x-ray is normal.

A. Kumar (✉)
Section of Critical Care Medicine, Section of Infectious Diseases, University of Manitoba, Winnipeg, MB, Canada

V. Tremblay
Section of Critical Care Medicine, University of Manitoba, Winnipeg, MB, Canada

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Diagnosis

The patient presents with hypotension and signs and symptoms compatible with an infection. The patient most likely has sepsis, and possibly septic shock, from a urinary tract infection.

Sepsis is a very common diagnosis. As many as 800,000 cases of sepsis are admitted every year to American hospitals. This is comparable to the incidence of first myocardial infarctions. The overall mortality is around 200,000 cases per year [1]. The incidence of septic shock seems to be increasing recently [2].

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection according to the 2016 Sepsis-3 consensus definition [3]. For clinical purposes, organ dysfunction is defined by an acute increase in SOFA score by 2 or more points. The baseline score can be assumed to be zero for patients with no known organ dysfunction.

Septic shock is a subcategory of sepsis with higher mortality and organ dysfunction. It can be defined as patient with sepsis with ongoing hypotension requiring vasopressors to maintain MAP greater than or equal to 65 mmHg *and* having a serum lactate equal or greater to 2 mmol/L *despite* adequate volume resuscitation. Mortality for patients with sepsis without septic shock is around 10%, while the mortality for patients with septic shock is around 40%. The term "severe sepsis" which was in the old definition has disappeared in the new Sepsis-3 definition.

The previous definition of sepsis as the presence of a suspected infection and two out of four systemic inflammatory response syndrome (SIRS) criteria has been abandoned.

The SIRS criteria were:

1. Temperature >38 °C or <36 °C.
2. Heart rate >90/min.
3. Respiratory rate >20/min or $PaCO_2$ < 32 mmHg.
4. White blood cell count >12,000/mm^3 or <4000/mm^3 or >10% immature bands).

The SIRS criteria were thought to reflect an inflammatory reaction to an insult, but not necessarily a sign of a dysregu-

lated response. It was found to be poorly sensitive. About 12% of patients admitted to ICU in Australia and New Zealand with sepsis and organ dysfunction did not have at least two out of four SIRS criteria [4]. The old definition of sepsis using SIRS criteria was also found to poorly predict mortality compared to the Sepsis-3 definition.

Diagnosing sepsis and septic shock in a timely fashion is important so that treatment can be initiated early. A score that can be used outside of the intensive care unit is the quick SOFA (qSOFA) score. It has three components that are each allocated 1 point, and a score of 2 or more is considered positive:

- Respiratory rate $\geq$ 22/min.
- Altered mentation.
- Systolic blood pressure $\leq$ 100 mmHg.

Clinical presentation and investigation: The differential diagnosis of shock includes cardiogenic shock, obstructive shock, hypovolemic shock, and distributive shock (see Table 8.1). Septic shock is a form of distributive shock which is characterized by a loss of venous tone and peripheral resistance. Clinically, the patient with fluid-resuscitated septic shock will present with tachycardia, tachypnea, and hypotension with a high or normal pulse pressure (systolic blood pressure at least double the diastolic blood pressure). The skin is usually warm and extremities well perfused as opposed to the nondistributive types of shock. The pulse pressure can be low, and skin can be poorly perfused in case of very severe or unresuscitated septic shock or a mixed shock like a patient with superimposed hypovolemic elements (due to venous pooling) along with septic shock.

The presentation of septic shock frequently involves elements of other forms of shock. Hypovolemia is common given that patient often have diarrhea or decreased their fluid intake prior to coming to hospital. Sepsis-induced cardiac dysfunction is also very common. Other forms of distributive shock, including adrenal insufficiency and anaphylaxis, are not uncommon.

Table 8.1 Classification of shock

1. Hypovolemic
Hemorrhagic
Fluid depletion (nonhemorrhagic)
Interstitial fluid redistribution
Thermal injury
Trauma
Anaphylaxis
Increased vascular capacitance (venodilatation)
Sepsis
Anaphylaxis
Toxins/drugs
2. Cardiogenic
Myopathic
Myocardial infarction
Myocardial contusion (trauma)
Myocarditis
Cardiomyopathy
Septic myocardial depression
Pharmacologic
Mechanical
Valvular failure
Hypertrophic cardiomyopathy
Ventricular septal defect
Arrhythmic
3. Extracardiac obstructive
Tension pneumothorax
Pulmonary embolus
Cardiac tamponade

(continued)

Table 8.1 (continued)

Status asthmaticus/auto-PEEP
Constrictive pericarditis
Intrathoracic obstructive tumors (direct vena cava obstruction)
4. Distributive
Septic
Toxic shock syndrome
Anaphylactic
Neurogenic
Endocrinologic
Adrenal crisis
Thyroid storm

Adapted with permission from Parrillo and Dellinger [21]

Post-fluid resuscitation, septic shock is hemodynamically characterized by a hyperdynamic circulatory profile, decreased systemic vascular resistance (<900 dynes per second/cm^5), normal or increased cardiac index (>4.2 L/min/m^2), normal or decreased pulmonary capillary wedge pressure (<15 mmHg), and normal or high SvO2 or ScvO2 (>65 or 70%). Before fluid resuscitation, however, severe septic shock may exhibit a hypodynamic profile similar to hypovolemic shock with narrow pulse pressures and low central filling pressures, cardiac output, and SvO2 with reduced cardiac output.

Given that right heart catheterizations are used less often given their invasive nature and multiple studies showing absence of clinical benefit for their use, bedside ultrasonography has emerged as a useful way of assessing shock in a non-invasive way. Many clinicians now use it as part of their physical examination in critically ill patients. There have been several protocols (RUSH, ACES) on bedside ultrasonography in undifferentiated shock [5, 6].

On bedside ultrasonography, septic shock will classically present with normal heart function (although both increased and decreased contractility can be seen in some circumstances), small to normal inferior vena cava with normal inspiratory variation, and absence of bilateral B-lines in lungs (localized B-lines could point out to a diagnosis of pneumonia). Cardiac output as measured by left ventricular outflow tract velocity time integral (LVOT VTI) method should be preserved or high in the majority of cases.

Laboratory results are useful to identify organ dysfunction. White blood cells can be either elevated or decreased. Elevation in creatinine, bilirubin, and INR and decrease in PaO_2/FiO_2 ratio and platelets are associated with organ dysfunction and worse outcomes and are included in SOFA score. Glucose is often elevated even in patients without diabetes. C-reactive protein is often elevated more than two standard deviations. Procalcitonin is elevated in bacterial sepsis, but its ability to differentiate between sepsis and other causes of SIRS is questioned [7].

Lactate is a very important laboratory test. An elevated serum lactate (>2 mmol/L) is associated with poor outcome. The pathophysiology of lactate elevation in septic shock is complex. While local or global tissue hypoxia can be responsible, often, the rise in lactate can be due factors other than anaerobic metabolism. Impaired microcirculation, increased glycolytic flux through beta2-adrenergic receptor activation due to the activation of endogenous catecholamine systems, and decreased lactate clearance are other causes of increased lactate [8].

Nevertheless, failure to clear lactate despite fluid resuscitation is part of the diagnostic criteria for septic shock and portends a high mortality. Its use is therefore important in the initial evaluation of patients with potential sepsis or septic shock. Even in the setting of normal blood pressure, an elevated lactate (>4 mmol/L) is associated with a poor prognosis [9].

Collection of cultures from all potential sites of infection is important. If possible these cultures should be obtained prior to antimicrobials. Every patient with suspected sepsis or septic shock should get blood cultures from at least two sites

(including at least one peripheral site). Site cultures, including sputum, urine, cerebrospinal fluid, abscess, or pleural effusion, should be obtained depending on the clinical picture and clinical suspicion.

Approximately one-third to one-half of sepsis patients do not have any positive culture. It is thus not absolutely necessary for the diagnosis, but it can help guide management and treatment.

Management

The most important part of management of sepsis and septic shock is early recognition. Delayed recognition is frequent and leads to delay in treatment. The diagnosis of sepsis is primarily based on clinical criteria. The qSOFA score can be used to identify patients with infection at greater risk of poor outcome and does not require any laboratory test. The full SOFA score is more accurate at predicting mortality but requires laboratory tests. An elevated lactate is also useful in recognizing sepsis and potential septic shock.

Once the empiric diagnosis of sepsis is made, treatment should be rapidly instituted. It is useful to separate management of sepsis in five different categories:

1. Early antimicrobials.
2. Hemodynamic management (fluid and vasopressors).
3. Source control.
4. Adjunctive therapies.
5. De-escalation.

While they are discussed separated here, it is important to remember that in real life clinical environment, these things should be happening rapidly and simultaneously.

Early Antimicrobials

Early administration of appropriate antimicrobials is a keystone of sepsis care. Several studies have shown that delays in administrating antimicrobials in septic shock are associated

with worse outcome. Each hour delay in antimicrobials in septic patient with hypotension was associated with a 7.6% decrease in survival [10]. These results have been validated in numerous newer studies [11].

When considering the delay in antimicrobials, it is important to realize that there can also be a substantial delay between the time of the order to give the antimicrobials and the actual time it is administered. At least one study has shown that delay to be in the order of hours for various reasons [12]. Every effort should be made to ensure that the antimicrobials are given as soon as possible. This requires that the doctors, nurses, and pharmacists are aware of the importance of giving antimicrobials early and good communication between different health-care professionals.

While it is critical to give antimicrobials early, the physician should ensure that the appropriate antimicrobials are given. This choice has to take into account the suspected anatomic site of infection, past medical history of the patient (including receipt of antimicrobials within the preceding 3 months), and previous documented infection of the patient. Studies have shown that if inadequate antimicrobials are given initially, mortality increases in critically ill patients [13]. It is better to give broad-spectrum antimicrobials initially and narrow it down once the patient is more stable and/or an organism has been identified in culture.

Consequently, most patients with sepsis and septic shock are treated with a broad-spectrum beta-lactam such as piperacillin-tazobactam, ceftriaxone, ceftazidime, cefepime, or meropenem. Coverage for MRSA should be strongly considered if the patient has risk factors or if the local flora mandates. If the patient has pneumonia, atypical coverage particularly for Legionella should be initially considered. If the patient is immunocompromised in any way or has a health-care-associated infection, pseudomonas coverage should be included. During influenza season, patient presenting with respiratory symptoms and flu-like illness should generally also be covered with oseltamivir empirically until tests are negative.

Antifungal treatment should not be routinely used if risk factors are absent. If the patient has risk factors for invasive

Candida infection such as neutropenia, abdominal perforation, long-standing central venous access, chemotherapy, transplant, or total parenteral nutrition, it may be appropriate to consider the addition of an echinocandin (particularly for septic shock) pending culture results. If aspergillus is suspected, such as a profoundly neutropenic patient with new lung opacities, empiric voriconazole or amphotericin B can be considered.

Another factor to consider when choosing empiric coverage of antimicrobials is whether one should double cover the most likely bacterial pathogens. While studies have failed to show benefit in sepsis of double coverage of the most likely organism, meta-analysis seems to show benefit for the sickest patients: the ones with septic shock [14]. The Surviving Sepsis Campaign Guidelines of 2016 thus permits the use of two different antibiotics of different mechanistic classes (e.g., a β-lactam with an aminoglycoside or a fluoroquinolone) to cover the most likely organism only in patients with septic shock [15].

Often multiple antimicrobials have to be given to cover multiple potential organisms. In this situation, it is preferable to start with the antimicrobial with the highest likelihood of covering the offending organism. This will often be a broad-spectrum β-lactam which also has the advantage that they can be administered fairly rapidly.

When the frontline clinician is confronted with complex case and unsure of the correct empiric treatment, he should get an infectious disease or intensivist consultation as soon as possible as timely administration of the correct antimicrobials is one of the most important things that need to be done in the care of septic patients.

Hemodynamic Management

Shock and hypotension is often found in patient with sepsis. It is important to ensure that patients with sepsis and septic shock are adequately monitored. Peripheral venous access should be established. Arterial cannulation for accurate

blood pressure monitoring should be done in unstable patients. A urinary catheter should be inserted for adequate urine output monitoring. Vital signs should be taken frequently, and the patient should be monitored in a resuscitation room or the intensive care unit if they have septic shock. Intubation might be required for hypoxemia, increased work of breathing, or decreased level of consciousness.

Central venous cannulation should be performed for most patients who require vasopressor medications. While it is possible to give vasopressors peripherally for a short period of time, there is a risk of extravasation and soft tissue necrosis. Additionally, the central venous line can give useful information such as the central venous pressure (CVP) and central venous oxygen saturation (ScvO2). Right heart catheterization should be reserved only for cases where the diagnosis of distributive shock is in doubt or in mixed shock (for example septic and cardiogenic shock). It should not be a routine part of management of sepsis or septic shock.

Initial management of hypotension should almost always begin with fluid resuscitation. While there is no consensus on the amount of fluid needed, 30 mL/kg of crystalloid is a good starting point and is recommended by Surviving Sepsis Guidelines.

In 2001 a study showed that early management (<6 h post-presentation) with a protocol targeting a mean arterial pressure ≥65 mmHg, CVP 8–12 mmHg, ScvO2 > 70%, and a hemoglobin of ≥90 g/L using fluids, vasopressors, blood transfusion, and dobutamine had been shown to improve outcome in severe sepsis and septic shock. However, three more recent randomized controlled trials have shown that this protocol is not superior to standard treatment [16–19].

If the patient is still hypotensive after initial fluid resuscitation, the patient should be reassessed. Crystalloid infusion until a CVP of 8–12 mmHg is reached or based on dynamic assessment of fluid responsiveness is appropriate. Fluid responsiveness is defined as an increase in cardiac output by 10–15% following a bolus of 500 mL of crystalloid. There are multiple ways of assessing fluid responsiveness, but a detailed discussion is beyond the scope of this chapter.

Crystalloids, either balanced solutions such as ringers lactate or normal saline, are the fluid of choice initially. Colloids have not been shown to improve outcome in sepsis, and starch solution seems to be associated with increase in renal failure and possibly mortality. Albumin has been shown to be safe with no increase in mortality. Its use might be indicated if several liters of crystalloid have already been given and the physician wants to minimize the amount of fluids given. But given the much higher cost of albumin, the risks of giving a blood products and lack of benefit, crystalloid remains the fluid of choice.

Once the physician has optimized preload and the patient is still hypotensive, the next step is to add vasopressors to maintain a MAP above 65 mmHg. Norepinephrine is the usual first-line vasopressor. It is an endogenous catecholamine with both powerful inotropic (cardiac alpha- and beta-1 receptors) and peripheral vasoconstriction effects (alpha-receptors). In a randomized controlled trial of shock, norepinephrine was found to have less side effects as compared to dopamine (mostly tachyarrhythmia). Dopamine has thus generally fallen out of favor. Phenylephrine (alpha-receptors agonist) can be used if trying to avoid tachycardia.

Vasopressin has been used in sepsis usually as an add-on to norepinephrine at a low dose (2.4 unit/h). It acts to increase systemic vascular resistance through peripheral V1 receptors with no increase in heart rate. Use of vasopressin decreases the amount of norepinephrine given but does not seem to affect mortality.

Some international regions utilize epinephrine more frequently. The main difference with norepinephrine is stronger activation of beta-1 and beta-2 receptors resulting in a stronger inotropic and chronotropic effects. It is worth noting that epinephrine tends to increase lactate, glucose, and lower potassium through its beta-2 activity. A modest lactate rise might be due to epinephrine and not an inadequate resuscitation.

In cases where bedside ultrasonography, low ScvO2, or physical examination show that there is an element of low

cardiac output or sepsis-induced myocardial dysfunction, pure inotropes such as dobutamine or milrinone might be needed. There is no utility in increasing cardiac output to supraphysiologic level as studies have failed to show any benefit of this strategy. The goal of inotropes should be to increase cardiac output to normal to normalize tissue perfusion.

Dobutamine is a beta-1 agonist with powerful inotropic and chronotropic but also peripheral vasodilatory effects. Milrinone is a phosphodiesterase inhibitor that acts by blocking the degradation of cyclic AMP. It also has inotropic and chronotropic with peripheral and pulmonary vasodilatory effects. Their effect on blood pressure is variable; sometimes the increase in cardiac output will offset the peripheral vasodilatation, and the blood pressure will increase. Reduced blood pressure may result if the peripheral vasodilatation is more important and central venous pressures are low. The physician should be ready to increase other vasopressors when starting either dobutamine or milrinone in septic shock.

The usual MAP target of 65 mmHg can also be individualized. A randomized controlled trial of MAP target in septic shock failed to show a benefit of MAP target higher than 65 mmHg. A subset of patients with chronic hypertension showed a decreased acute kidney injury with the higher target. Similarly, a patient with signs of good perfusion (good mentation, capillary refill, urine output $\geq$0.5 mL/kg/h, and decreasing lactate) at lower MAP might benefit from a lower blood pressure target.

Source Control

Several infections only need antimicrobials and hemodynamic support, but there are also many who will not get better unless the infectious burden is decreased with source control. Empyema, abscesses, cholangitis, ruptured intra-abdominal infections, obstructed urinary tract infections, or necrotizing fasciitis are examples of infections requiring source control. Antimicrobials penetration is often poor leading to bad outcome with antimicrobials alone. Depending on

the type and anatomical location of infection, source control can be done using surgery, chest tube, endoscopic retrograde cholangiopancreatography, or interventional radiology-guided drainage.

Studies have also shown that survival decrease with delay in achieving source control [20]. It is therefore important to aggressively look for source of infection that might need source control right away when the diagnosis of sepsis or septic shock is made. This will often require additional imaging, such as ultrasound or CT scan. A target of 6–12 h to obtain definitive source control is reasonable.

All intravascular devices should be considered potential source of infection in a septic patients and, if feasible, should be removed as soon as possible.

Adjunctive Therapies

Since sepsis is thought to be a dysfunctional host response to infection, there have been numerous pharmacological attempts to treat this dysfunctional host response. Unfortunately, the vast majority of these attempts have been unsuccessful. The most well-known is activated protein C. While an early study showed improved 28 days survival in the subgroup of patients with severe sepsis and septic shock, this result could not be replicated in a larger randomized controlled trial.

There is no evidence of benefit using early blood purification techniques such as high-volume hemofiltration or hemoperfusion, plasma exchange, or coupled plasma filtration adsorption. The indication for renal replacement therapy is the same as for every other critically ill patient.

There is no role for targeting higher hemoglobin level in septic patients. The target is the same as for general ICU patients: ≥70 g/L although a higher hemoglobin target of 90 g/L is appropriate for patients with septic shock (or those with concurrent acute coronary syndromes).

The only adjunctive therapy still being recommended is corticosteroids. They are recommended only in situation of

septic shock with hypotension despite fluids and vasopressors for more than an hour. However, they only reduce pressor requirements but do not appear to improve outcome. They should not be used in other less sick patients.

There are multiple potential adjunctive therapies being studied at this time, including esmolol, anticoagulants, and the combination of vitamin C, hydrocortisone, and thiamine. But the clinical utility of these therapies remains to be proven.

De-escalation

Initial treatment of sepsis and septic patients include broad-spectrum antimicrobials and aggressive fluid resuscitation and vasopressors. Once patients have stabilized and start to improve, it is important to de-escalate to minimize harms. Antimicrobials should be narrowed based on culture or the most likely organism if culture negative. Antimicrobials may also be de-escalated on the basis of clinical improvement despite negative cultures. Duration of antimicrobial therapy should be no more than 7–10 days except for certain circumstances.

Vasopressors should be decreased as the blood pressure tolerates.

Fluid administration should slow down as soon as the patient is deemed euvolemic. Once the sepsis resolves, patients often end up in fluid overload, and diuresis may be required.

Every line or catheter should be reassessed daily and removed as soon as safe. They are sources of infection and discomfort. If the patient is intubated, sedation should be minimized and spontaneous breathing trial done daily as soon as it is safe to do so.

Case Conclusion

The patient was diagnosed with sepsis and possible septic shock. Piperacillin-tazobactam and vancomycin were administrated within 1 h of the clinical diagnosis. A bedside

ultrasonography showed normal LV and RV function, no B-lines in the lungs, and a normal sized inferior vena cava but with greater than 50% inspiratory collapse.

30 mL/kg of crystalloid was given initially, but blood pressure remained low and norepinephrine was started. Lactate was still elevated at 5.9 mmol/L after the fluid bolus thus confirming the diagnosis of septic shock. A radial arterial cannula, a central venous line, and a urinary catheter were installed. Further fluid was administrated based on a low CVP. The patient had to be intubated for progressive increase work of breathing and hypoxemia. Vasopressin was added when norepinephrine had to be increased to 0.3 mcg/kg/min. Hydrocortisone was also administered for ongoing hypotension. The patient maintained warm extremities, ScvO2 was 76%, and bedside ultrasonography showed normal left ventricular function so inotropes were not given.

Given the history of renal stone and the hemodynamic instability, the diagnosis of obstructed urinary tract infection was entertained. A CT scan showed an obstructed stone in the distal right ureter and signs of right-sided pyelonephritis. Urology was consulted, and the stone was removed with ureteroscopy 5 h after ED admission. Pus was seen coming out of the ureter following stone removal.

The patient improved once the obstruction was lifted. Culture showed pan sensitive *Klebsiella* pneumonia in the urine and blood. Antimicrobials were narrowed down to ciprofloxacin for 7 days. Vasopressor requirements decreased, lactate decreased to normal, and renal function eventually returned to normal after several weeks although the patient needed renal replacement therapy for 1 week due to oliguria and fluid overload. He was extubated on day 5 and discharged home after 2 weeks.

Future Aims

- The optimal hemodynamic and fluid management strategy is still elusive. Early goal-directed therapy has been shown to not be better than usual management.

The decision to stop giving fluids is not yet defined. There are several studies showing harm of excess fluid administration. The patient should receive as much fluids as needed but not more; there is little agreement on what the amount is and how to individualize these decisions.

- The use of bedside ultrasound is growing as a tool to diagnose shock, assess fluid responsiveness, and monitor treatment response. Whether this will lead to better patient's outcome remains to be seen.
- Studies of adjunctive therapies in sepsis: esmolol, anticoagulations, or the combination of vitamin C, hydrocortisone, and thiamine.

Key Points

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction is defined as an increase of SOFA score by 2 or more (assume baseline SOFA = 0 if no known organ dysfunction).
- Quick SOFA (qSOFA) is a quick screen to detect patients with potential sepsis. It is positive if two or more of the following are positive: (1) respiratory rate $\geq$22/min, (2) altered mental status, and (3) systolic blood pressure $\leq$100 mmHg.
- Septic shock is defined by hypotension requiring vasopressors *and* lactate greater than 2 mmol/L *after* adequate fluid resuscitation.
- Early adequate antimicrobials are extremely important. Delays in antimicrobials administration have been shown to increase death.

- Early source control in infections where it is required has also been shown to improve outcomes.
- Crystalloid administration, vasopressor administration, and sometimes inotropes are part of the hemodynamic management. Resuscitation targets are usually MAP greater than 65 mmHg and normalization of lactate.
- Corticosteroids can be added for vasopressors-dependent septic shock.

References

1. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29:1303–10.
2. Kadri SS, Rhee C, Strich JR, Morales MK, Hohmann S, Menchaca J, et al. Estimating ten-year trends in septic shock incidence and mortality in United States academic medical centers using clinical data. Chest. 2017;151(2):278.
3. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA. 2016;315(8):801–10.
4. Kaukonen KM, Bailey M, Pilcher D, Cooper DJ, Bellomo R. Systemic inflammatory response syndrome criteria in defining severe sepsis. N Engl J Med. 2015;372(17):1629–38.
5. Atkinson PR, McAuley DJ, Kendall RJ, et al. Abdominal and cardiac evaluation with sonography in shock (ACES): an approach by emergency physicians for the use of ultrasound in patients with undifferentiated hypotension. Emerg Med J. 2009;26:87–91.
6. Perera P, Mailhot T, Riley D, Mandavia D. The RUSH exam: rapid ultrasound in SHock in the evaluation of the critically lll. Emerg Med Clin North Am. 2010;28:29–56, vii.

7. Tang BM, Eslick GD, Craig JC, McLean AS. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. Lancet Infect Dis. 2007;7(3):210.
8. Suetrong B, Walley KR. Lactic acidosis in Sepsis : it's not all anaerobic: implications for diagnosis and management. Chest. 2016;149(1):252–61.
9. Casserly B, Phillips GS, Schorr C, Dellinger RP, Townsend SR, Osborn TM, et al. Lactate measurements in sepsis-induced tissue hypoperfusion: results from the surviving sepsis campaign database. Crit Care Med. 2015;43(3):567.
10. Kumar A, Roberts D, Wood KE, Light B, Parillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34(6):1589–96.
11. Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, et al. Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med. 2017;376:2235–44.
12. Kanji Z, Dumaresque C. Time to effective antibiotic administration in adult patients with septic shock: a descriptive analysis. Intensive Crit Care Nurs. 2012;28(5):288–93.
13. Paul M, Shani V, Muchtar E, et al. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. Antimicrob Agents Chemother. 2010;54:4851–63.
14. Kumar A, Zarychanski R, Light B, Parrillo J, Maki D, Simon D, et al. Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis. Crit Care Med. 2010;38(9):1773–85.
15. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43:304.
16. 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;345:1368–77.
17. The Arise Investigators and Anzics Clinical Trials Grou. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014;371:1496. https://doi.org/10.1056/NEJMoa1404380.
18. ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014;371:1683–93.
19. 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.

20. Bloos F, Thomas-Rüddel D, Rüddel H, et al. Impact of compliance with infection management guidelines on outcome in patients with severe sepsis: a prospective observational multicenter study. Crit Care. 2014;18:1.
21. Parrillo JE, Dellinger RP. Critical care medicine: principles of diagnosis and management in the adult. 4th ed. Philadelphia: Elsevier; 2014.