Critical Care

FAST FACTS

A brief refresher with useful tables, figures, and research summaries

Shock and Sepsis

Shock — most frequently caused by sepsis — is a common reason for ICU admission because of the need for close hemodynamic monitoring and nursing care. Patients with septic shock can be some of the sickest that you'll encounter during residency, and the complexities of management can seem overwhelming. In this section, we'll cover the basics of:

- Shock
- Sepsis and Septic Shock

Shock

Shock is defined as a state of tissue hypoxia due to decreased or dysregulated oxygen delivery or extraction resulting in end-organ damage. Clinical manifestations include:

ACUTE RESPIRATORY DISTRESS SYNDROME

RESUSCITATION FLUIDS AND BLOOD TRANSFUSION

ACID–BASE DISTURBANCES

SEDATION AND ICU DELIRIUM

NUTRITION IN THE ICU

- systemic arterial hypotension: in adults, typically systolic blood pressure (SBP) <90 mm Hg or mean arterial pressure (MAP) <70 mm Hg where MAP = (1/3) x SBP + (2/3) x diastolic blood pressure (DBP)
- clinical signs of tissue hypoperfusion: cool and clammy skin versus warm and flushed, low urine output (<0.5 mL/kg/hr), altered mental status
- metabolic acidosis: serum lactate level >2 mmol/L, possible elevated anion gap

Causes and Pathophysiology

Mean arterial pressure is the product of cardiac output (CO) multiplied by systemic vascular resistance (SVR); therefore, shock can be due to a decrease in SVR, CO, or both (see figure below for more details).

Septic shock, which is a form of distributive shock, is the most common etiology of shock in the ICU. However, other etiologies should be considered in the differential diagnosis. The four mechanisms listed in the table below are not mutually exclusive; for example, patients with sepsis commonly have myocardial depression that improves with resolution of sepsis.

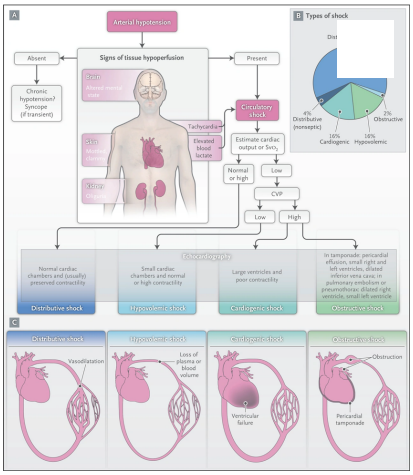
Causes of Shock Classified by Mechanism and Hemodynamics

Mechanism	Differential Diagnosis (examples)	Primary Hemodynamic Δ
Distributive	Sepsis, anaphylaxis	↓SVR
Hypovolemic	Hemorrhage, internal fluid losses (third spacing), external fluid losses (GI losses)	↓CO

Obstructive	Pulmonary embolism, cardiac tamponade, or tension pneumothorax	↓CO
Cardiogenic	Acute myocardial infarction, end-stage cardiomyopathy, advanced valvular heart disease, myocarditis, cardiac arrhythmias, pump failure or dysfunction	↓CO

Abbreviations: SVR, systemic vascular resistance; GI, gastrointestinal; CO, cardiac output

Initial Assessment of Shock States



(Source: Circulatory Shock. N Engl J Med 2013.)

Treatment

Treat the underlying cause: Identifying the etiology of shock is crucial for adequate treatment. Each of the diagnoses listed in the table aboves requires a specific management

strategy. For example:

- anaphylactic shock (a form of distributive shock): intramuscular (IM) epinephrine, identification of the cause of anaphylaxis and its removal
- septic shock (a form of distributive shock): broad spectrum intravenous (IV) antibiotics
- hemorrhagic shock: massive transfusion of blood products, definite hemostasis
- pulmonary embolism: systemic thrombolysis or embolectomy
- cardiogenic shock: percutaneous coronary intervention for myocardial infarction, inotropes, and sometimes mechanical support (e.g., intra-aortic balloon pump, percutaneous left ventricular assist device, venoarterial extracorporeal membrane oxygenation [ECMO])

Vasopressors:

- Patients with distributive, hypovolemic, and obstructive shock should be given IV fluid resuscitation prior to initiation of vasopressors. Use objective measures to assess how much and when to give more fluids (see Resuscitation Fluids and Blood Transfusion in this rotation guide for more information).
- Typically, vasopressors are titrated to a mean arterial pressure of 65 mm Hg, although decreasing lactate level and improving urine output are reassuring signs of adequate organ perfusion.
- Inotropes may be indicated in the treatment of cardiogenic shock from primary pump failure.
- The table below summarizes commonly used vasopressors and inotropes:

Commonly Used Vasopressors and Inotropes for the		
	Clinical	Receptor

Drug	Indication	Binding*
Norepinephrine (Levophed)	Shock (distributive, cardiogenic, mixed)	$\alpha 1 >> \beta 1 > \beta 2$
Phenylephrine (Neo-Synephrine)	Shock (distributive, hypovolemic)	$\alpha 1$
Vasopressin	Shock (distributive, cardiogenic)	V_1, V_2
Epinephrine	Shock (anaphylactic, cardiogenic, distributive), cardiac arrest, bronchospasm	$\alpha 1 > \beta 1 > \beta 2$
Dopamine	Bradycardia Shock (cardiogenic, distributive)	$D1 >> \beta 1 > \alpha 1 > \beta 2$
Dobutamine	Cardiogenic	$\beta 1 >> \beta 2 > \alpha 1$

	shock	
Milrinone	Cardiogenic shock	Phosphodiesterase (PDE) inhibitor

α1 = alpha-adrenergic receptors, β1 and β2 = beta-adrenergic receptors, V_1 and V_2 = vasopressin receptors, D1 = dopamine receptor; CO = cardiac output; HR = heart rate; SVR = systemic vascular resistance

*Receptor binding is shown for physiologic concentrations.

(Adapted from: Inotropes and Vasopressors. Circulation 2008.)

Sepsis and Septic Shock

Although sepsis has long been recognized as a systemic syndrome, precisely defining it has been challenging.

- In 1992, an international consensus conference introduced the term systemic inflammatory response syndrome (SIRS) and defined sepsis, severe sepsis, and septic shock (see table below).
- In 2003, a second international conference reaffirmed the definitions and acknowledged that SIRS may be nonspecific. (More-recent research suggests that SIRS-negative sepsis also is associated with high mortality and that the ≥2 criteria cutoff does not represent a transition in mortality.) The second group offered additional criteria to consider for diagnosing sepsis.

- In 2016, a third international conference defined sepsis (Sepsis-3) as life-threatening organ dysfunction caused by a dysregulated host response to infection.

Sepsis and Septic Shock Definitions

	1992/2003	2016 (Sepsis-3)
SIRS	≥2 of the following: 1. temperature >38°C or <36°C 2. heart rate >90 beats per min 3. respiratory rate >20 breaths per min or $PaCO_2$ <32 mm Hg 4. WBC >12,000 or <4000 or >10% bands	No longer used
Sepsis	SIRS and documented infection	Organ dysfunction as defined by an increase of ≥2 points in total SOFA score from baseline
Severe sepsis	Sepsis with organ dysfunction, hypoperfusion (e.g., lactic acidosis, oliguria, altered mental status), or hypotension	No longer used (considered redundant because sepsis is now defined by organ dysfunction)
Septic	Severe sepsis	Sepsis with hypotension

shock	and unexplained hypotension (SBP <90 mm Hg or 40 mm Hg reduction from baseline) despite adequate fluid resuscitation or requiring inotropic or vasopressor agents	requiring vasopressors to maintain MAP ≥65 mm Hg and having a serum lactate level >2 mmol/L despite adequate volume resuscitation

Abbreviations: SIRS, systemic inflammatory response syndrome; PaCO2, partial pressure of arterial carbon dioxide; WBC, white blood cell; SBP, systolic blood pressure; SOFA, sequential organ failure assessment; MAP, mean arterial pressure

To address the poor specificity of SIRS, the new definition shifts identification away from SIRS to the Sequential Organ Failure Assessment (SOFA, range 0–24, with higher scores indicating more-severe illness). The new definitions of sepsis and septic shock were based on studies and review of the literature for factors that best predicted mortality. Since publication, the 2016 definition has been criticized for the difficulty of incorporating into practice.

Sequential Organ Failure Assessment (SOFA) Score

System	Criteria	0	1	2	3	4
Respiratory	PaO_2/FiO_2 (partial pressure of oxygen in arterial blood divided by the fraction of inspired oxygen)	≥400 mm Hg (53.3 kPa)	<400 mm Hg (53.3 kPa)	<300 mm Hg (40 kPa)	<200 mm Hg (26.7 kPa) with res	
Coagulation	Platelets	≥150 x10^3/µL	<150 x10^3/µL	<100 x10^3/µL	<50 x10^3/µL	<20 x10^3/µL
Liver	Bilirubin	<1.2 mg/dL (20 µmol/L)	1.2–1.9 mg/dL (20-32 µmol/L)	2.5–5.9 mg/dL (33–101 µmol/L)	6–11.9 mg/dL (102–204 µmol/L)	>12 mg/dL (204 µmol/L)
Cardiovascular	Mean aterial pressure (MAP) or vasopressors requirement	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 µg/kg/min or dobutamine (any dose)*	Dopamine 5.1–15 µg/kg/min* or epinephrine ≤0.1 µg/kg/min or norepinephrine ≤0.1 µg/kg/min*	Dopamine >15 µg/kg/min or epinephrine >0.1 µg/kg/min or norepinephrine >0.1 µg/kg/min*
Neurologic	Glasgow coma scale score	15	13–14	10–12	6–9	<6
Renal	Creatinine (Cr) or urine output (UOP)	Cr <1.2 mg/dL (110 µmol/L)	Cr 1.2–1.9 mg/dL (110–170 µmol/L)	Cr 2.0–3.4 mg/dL (171–299 µmol/L)	Cr 3.5–4.9 mg/dL (300–440 µmol/L) or UOP <500 cc/day	Cr >5 mg/dL (440 µmol/L) or UOP <200 cc/day

*Doses given for at least 1 hour

NEJM Resident 360

(Source: NEJM Resident 360)

Treatment

Until 2001, sepsis was often not treated as a medical emergency and the approach to care was variable. In 2001, Dr. Emanuel Rivers studied a strict protocol of early goal-directed therapy (EGDT) for sepsis management, requiring central venous access to measure central venous pressure (CVP) and central venous oxygen saturation ($ScvO_2$) to guide fluid resuscitation, blood transfusions to prespecified goals, and administration of vasopressor drugs. This single-center study showed improved outcomes with EGDT and transformed sepsis care for the next 15 years.

However, concerns about the complex and resource-intensive EGDT led researchers to reexamine the results of the Rivers trial. In 2014 and 2015, three multicenter studies — Protocolized Care for Early Septic Shock (ProCESS), Australian Resuscitation in Sepsis Evaluation (ARISE), and Protocolized Management in Sepsis (ProMISe) — demonstrated that EGDT was not superior to current usual critical care practices, suggesting that a strict protocol of continuous CVP and $ScvO_2$ monitoring does not appear to add any benefit. Note: Between the time of the Rivers study and the three trials noted above, the "accepted practice" for patients with sepsis had changed such that patients in ProCESS, ARISE, and ProMISe received early antibiotics and fluids (>30 mL/kg) before randomization, so those

principles of EGDT are still very important.

The cornerstones of therapy for patients in septic shock are early initiation of appropriate antibiotics and adequate volume resuscitation.

Early antibiotic therapy:

- In a 2006 study, each hour of delay in delivery of appropriate antibiotics increased mortality by about 7%. These findings were demonstrated again in a 2014 study using data from the Surviving Sepsis Campaign (SCC) database. The 2021 Surviving Sepsis Campaign guideline recommends administration of effective IV antibiotics within one hour of recognizing sepsis or septic shock.
- Antibiotics should target all organisms most likely to cause infection in the suspected organ system; if the source of infection is not yet known, empiric broad-spectrum antibiotics are indicated.

Volume resuscitation:

- The 2021 Surviving Sepsis guidelines recommend choosing a balanced crystalloid solution, such as lactated Ringer solution, instead of saline.
- The 2021 Surviving Sepsis guidelines recommended that initial fluid challenge should be at ≥30 mL/kg (~2 liters in a 70-kg adult) for patients with sepsis-induced hypoperfusion. However, the optimum infusion makeup remains a subject of controversy based on the results of the following two studies published in 2022:
    - A large trial did not show a difference in deaths at 90 days with the use of intravenous fluid restriction versus standard intravenous fluid therapy.
    - A meta-analysis of all trials showed a small difference favoring balanced salt solutions versus saline.
- Withhold blood transfusions until a patient's hemoglobin concentration is <7 g/dL, unless there is evidence of

bleeding, severe hypoxemia, or myocardial ischemia.

- See Resuscitation Fluids and Blood Transfusion in this rotation guide for more on volume resuscitation.

Vasopressors:

- Start vasopressors if the patient's MAP is not responsive to fluid resuscitation.
- The goal MAP on vasopressors typically is ≥65 mm Hg. The 2014 SEPSISPAM trial showed no mortality difference between MAP goals of 65–70 mm Hg vs. 80–85 mm Hg, although among patients with chronic hypertension, those in the higher-goal group had less renal-replacement therapy but more atrial fibrillation.
- The safest way to deliver vasopressors is through central venous access (internal jugular, subclavian, femoral catheter, or peripherally inserted central catheter). Subclavian may cause less bloodstream infections and more pneumothorax than internal jugular or femoral. Lack of central access should not delay the initiation of vasopressors though, as recent studies have shown the safety of peripheral pressors.
- The 2021 Surviving Sepsis Campaign guideline recommends norepinephrine as the first-choice vasopressor in septic shock. See the table above for commonly used vasopressors in medical ICUs.

Other treatments:

- Many therapies that have been used in the treatment of septic shock are no longer part of clinical practice because high-quality trials have not shown benefit (and have sometimes shown harm). Examples include activated protein C, which was initially promising in the PROWESS trial but later disappointing in the PROWESS-SHOCK study, as well as vitamin C, which was associated with harm in the LOVIT trial.
- The use of glucocorticoids in sepsis remains

controversial. A 2002 French study showed that patients with relative adrenal insufficiency and septic shock had a mortality benefit from hydrocortisone, but this was not replicated by the CORTICUS trial for septic shock and the HYPRESS trial for severe sepsis. In 2018, two larger randomized controlled trials, APROCCHSS and ADRENAL, once again came to different conclusions. Following the publication of these new trials, guidelines now suggest IV glucocorticoids for adults with septic shock and an ongoing requirement for vasopressor therapy, as evidence suggests that it may accelerate resolution of shock. Although the optimal dose, timing, and duration remains uncertain, typically, IV hydrocortisone as 50 mg every 6 hours is administered.