

CHAPTER 3

Shock and Multiple Organ Dysfunction Syndrome

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LEARNING OUTCOMES: After completing this e-chapter you will be able to:

1. Identify characteristics that are common to all types of shock.
2. Classify the various etiologies of shock as belonging to one of the following categories: hypovolemic, cardiogenic, distributive, or obstructive shock.
3. Explain the cellular, metabolic, and hemodynamic alterations occurring in shock and relate them to alterations in oxygen delivery.
4. Understand the pathophysiological basis for the progression of shock from the initial stage through the compensatory, progressive, and refractory stages.
5. Explain the etiology, pathophysiology, and clinical manifestations of cardiogenic shock.
6. Attribute the treatment strategies for cardiogenic, hypovolemic, anaphylactic, neurogenic, and septic shock to the underlying pathophysiology involved.
7. Explain the etiology, pathophysiology, and the clinical manifestations of mild, moderate, and severe hypovolemic shock.
8. Relate the etiology, pathophysiology, prevention, and the clinical manifestations of anaphylactic shock to the immune mechanisms involved.

9. Explain the etiology, pathophysiology, and clinical manifestations of neurogenic shock and differentiate neurogenic from spinal shock.
10. Differentiate the criteria for systemic inflammatory response syndrome, sepsis, severe sepsis, and septic shock.
11. Explain how microorganisms activate host defense systems, how those host defense systems function in the pathophysiology of septic states, and how they produce the clinical manifestations in septic states.
12. Describe the criteria for multiple organ dysfunction syndrome, the pathophysiological mechanisms responsible for organ dysfunction, and the clinical indicators of dysfunction of various organs.

CHAPTER OVERVIEW

Shock is a clinical condition that can result from several causes including injury, trauma, infection and severe bleeding, and represents an imbalance between oxygen supply and demand. **Shock** is characterized by hypoxia and inadequate cellular function that can lead to organ system failure and death. There are several distinct types of shock including cardiogenic, hypovolemic, anaphylactic, neurogenic, and septic shock. Despite having different etiologies, all of the shock states have similar manifestations of inadequate peripheral tissue perfusion, impaired cellular function, and impaired organ perfusion.

Although compensatory mechanisms, including the sympathetic nervous system and neurohormonal responses, attempt to maintain cardiac output and perfusion, hypoxic injury and cellular and organ damage can occur. Recognizing the signs of shock and instituting treatment measures can help reestablish perfusion and prevent further detrimental effects. This e-chapter

presents the pathophysiology of shock, common signs and symptoms, and management strategies to promote best outcomes for patients in shock.

INTRODUCTION OF CHAPTER CASES

Case Study One: A 69 year old female is brought to the emergency room by a neighbor who reports that she found the patient in an incoherent state in her apartment after the neighbor had noticed that the patient had not checked her mail for 3 days. The patient is currently awake and responsive, but is lethargic. She is Russian and speaks little English.

Current vital signs: Bp: 88/50mmHg Hr: 125bpm Temp: 97.4 (°C) Respirations: 34bpm

Initial physical exam reveals a thin white female, ill in appearance. The skin is cool to touch and the skin and mucous membrane color are pale. Lungs have bibasilar rales to auscultation posteriorly. Abdomen is soft with hyperactive bowel sounds. She has no jugular vein distention. Slight pedal edema is present, capillary refill is sluggish. The EKG reveals sinus tachycardia. A Foley's catheter was inserted for 60 cc dark yellow urine return.

Details about her past medical history are unavailable. An IV is started and lab work is drawn. A Russian translator arrives in the ER and begins interpretation. The patient relates that she is very weak and dizzy but denies pain. She states that she has had a "flu bug" for the past week, has not kept much food down and has been having diarrhea.

Case Study Two: *A 75 year old male with a 6 year history of hypertension and a 30 pack per year cigarette history was admitted to the ICU with a diagnosis of cirrhosis secondary to biliary obstruction. He underwent an exploratory laparotomy and cholecystectomy 3 days ago. Postoperatively, he was relatively stable, experiencing an episode of hypotension 12 hours postoperatively which was corrected by fluid administration. He remains intubated at TV 800 FIO2 40%, IMV 8 Peep +5 and attempts at weaning have been delayed due to periodic hypoxemia.*

He currently has an arterial line, CVP, T-tube drain and foley catheter. He is alert and oriented, moving in bed with little assistance. Physical exam reveals that his skin is pale pink, warm to touch, lungs have a few bibasilar rales, 1+ pedal edema is present bilaterally. His abdomen is nondistended, no active bowel sounds. His 5 inch midline abdominal wound requires tid dressing changes and is approximated with retention sutures. His hourly urine output has decreased from 100 to 50 cc/hr. He is currently receiving total parenteral nutrition via the CVP.

Current vital signs: Temp: 101.0(°C) HR: 122bpm, Sinus tachycardia, Respirations: 34bpm, BP: 90/60 mm Hg. He required several liters of lactated ringers and was started on low dose norepinephrine, a vasoconstrictive agent to increase his blood pressure and improve perfusion.

CATEGORIES OF SHOCK

Shock results when oxygen balance is disturbed and demand exceeds supply and is the body's response to physiologic injury, trauma, or infection (Medline Plus Health Information, 2015). The major types of shock include cardiogenic, hypovolemic, anaphylactic, neurogenic, and septic shock (Pasman & Corden, 2015). Shock is commonly classified into 4 main categories based on cardiovascular characteristics including hypovolemic, cardiogenic, distributive, which occurs when peripheral vascular dilation results in a decrease in systemic vascular resistance (which includes anaphylactic and septic shock) and obstructive shock, in which the flow of blood is obstructed which impedes blood flow, occurs with tension pneumothorax, cardiac tamponade, constrictive pericarditis, or massive pulmonary embolism (Zimmerman, 2012).

ALTERATIONS IN HEMODYNAMICS, OXYGEN DELIVERY, AND CELL METABOLISM IN SHOCK

Shock is a clinical syndrome that results from inadequate oxygenation and tissue perfusion (Medline Plus Health Information, 2015; Pasman & Corden, 2015; Wedro, 2014; Zimmerman, 2012). Shock occurs when the blood supply to the organs, tissues, and cells of the body is decreased. Inadequate blood supply impairs cellular function. When shock occurs, systemic hypotension, acidosis, and impairment of vital organ functioning result (Pasman & Corden, 2015). An imbalance between the delivery and the uptake of oxygen leads to cellular dysfunction. Regardless of the specific type and cause of shock, the end result is impaired tissue perfusion, which leads to inadequate oxygenation to the cell, causing cellular damage and

eventually, hypoperfusion to organs (Wedro, 2014). Clinical signs include hypotension, tachycardia, tachypnea, cool skin, altered level of consciousness, and oliguria (Wedro, 2014). Additional clinical changes relate to the hemodynamic profiles of shock as outlined in **Table 1**.

TABLE 1. Hemodynamic Profiles of Shock

Type of Shock	Heart Rate	Cardiac Output	Ventricular Filling Pressures	Systemic Vascular Resistance	Pulse Pressure	S _v O ₂
Cardiogenic	↑	↓	↑	↑	↓	↓
Hypovolemic	↑	↓	↓	↑	↓	↓
Distributive	↑	↑ or N ^a	↓ or N ^b	↓	↑	↑ or N ^a
Obstructive	↑	↓	↑	↑	↓	↓

S_vO₂, mixed venous oxyhemoglobin saturation; N, normal

^a May be decreased prior to or early in resuscitation

^b Left ventricular filling pressures may be normal or low in massive pulmonary embolism

Adapted from Zimmerman JL (Zimmerman, 2012).

In shock, oxygen delivery to the mitochondria of the cell is decreased, leading to stalled energy production and failure of ion pumps (Na^+ , K^+ , and Ca^+). As a result, sodium accumulates within the cell, changing the osmotic gradient and causing cellular swelling (Walshe & D'Amore, 2008; Zimmerman, 2012).

Tissue hypoperfusion results in cellular hypoxia. At the cellular level, the body switches to metabolism that doesn't require oxygen (**anaerobic metabolism**), which is insufficient to maintain cellular energy needs (Walshe & D'Amore, 2008; Zimmerman, 2012). Anaerobic glycolysis results, with depletion of adenosine triphosphate (ATP) and intracellular energy reserves (Pasman & Corden, 2015; Walshe & D'Amore, 2008; Zimmerman, 2012). Energy that is required for cellular processes is stored in the phosphate bonds of the ATP molecule, and the breakdown of ATP results in the release of energy. With cellular hypoxia, the normal process of ATP breakdown is altered, resulting in increased hydrogen ion concentration (Pasman & Corden, 2015). Anaerobic glycolysis also causes accumulation of lactic acid, resulting in intracellular acidosis.

A brief review of oxygen delivery can help explain the effects of altered tissue perfusion and impaired oxygen delivery in shock. Oxygen delivery (DO_2) is defined as the amount of oxygen delivered to the tissues of the body per minute. DO_2 is dependent upon the cardiac output (CO), or the amount of blood pumped per minute, and the arterial oxygen content of that blood (CaO_2) (Pasman & Corden, 2015). Oxygen delivery is defined by the following equation: DO_2 (mL O_2 /min) = CaO_2 (mL O_2 /L blood) X CO (L/min). The CaO_2 is dependent upon how much oxygen-carrying capacity is available in terms of hemoglobin (Hb) content as well as by how much oxygen the patient's hemoglobin contains, defined as the arterial oxygen saturation

(SaO₂) (Xiushui & Lenneman, 2014). The CaO₂ is defined by the following formula²: $CaO_2 = Hb \text{ (g/100 mL)} \times SaO_2 \times 1.34 \text{ mL O}_2/\text{g}$.

A state of clinical shock may exist when CaO₂ is impaired either by hypoxia, which decreases SaO₂, or by anemia, which reduces the amount of hemoglobin (Hb) and hence reduces the body's total oxygen-carrying capacity (Pasman & Corden, 2015). Often, this is why patients in shock are given increased oxygenation, many times through intubation and mechanical ventilation. In addition, blood transfusions can be used to increase the oxygen-carrying capacity of the blood.

Cardiac output is the amount of blood pumped each minute, and is determined by the patient's stroke volume (SV) and heart rate (HR). The cardiac output is defined by the following formula: $CO = HR \text{ (beats/min)} \times SV \text{ (mL/beat)}$ (Pasman & Corden, 2015).

SV is dependent upon the ventricular end-diastolic filling volume (commonly referred to as ventricular preload), myocardial contractility, and the afterload (Pasman & Corden, 2015). These factors can be impaired in clinical shock states and impact the cardiac output (Pasman & Corden, 2015).

These principals are used to provide treatment measures to the patient in shock. Often, intravenous fluids are administered in order to increase preload, vasopressors are used to decrease afterload, and inotropes are given to improve contractility.

STAGES OF SHOCK

There are several distinct stages of shock. These include the initial, compensatory, progressive, and refractory stages of shock (Pasman & Corden, 2015). In the **initial stage of shock** the cardiac output is decreased, leading to decreased blood supply. Clinical evidence of

decreased cardiac output includes cool clammy skin, decreased urinary output, altered level of consciousness, cyanosis, pallor, and hypotension (Pasman & Corden, 2015).

When tissue perfusion is impaired, changes in the normal functioning of the cell occur. As the blood supply to cells decreases, cells switch from aerobic to anaerobic metabolism as a source of energy. Anaerobic metabolism produces minimal energy and leads to a buildup of lactic acid, which is detrimental to the functioning of a cell. Lactic acidemia develops, causing more cellular damage as the body is unable to buffer the increased levels of acid. The degree of lactic acidosis can be determined by monitoring serum lactate levels. Normal serum lactate levels are less than 1 mmol/L (Pasman & Corden, 2015; Wedro, 2014). Lactic acidosis is associated with high levels of serum lactate (greater than 5 mmol/L). In some patients with shock, neither the arterial pH nor bicarbonate may reflect the presence of lactic acidosis. Therefore, the most accurate assessment of the severity of lactic acidosis is the serum lactate level (Walshe & D'Amore, 2008; Zimmerman, 2012). However, the arterial pH and serum bicarbonate might not indicate acidosis in the presence of lactic acidosis as factors such as the degree of hyperlactatemia, the buffering capacity of the body, and conditions such as tachypnea and alkalosis may affect pH levels simultaneously.

In Case Study One, the patient presented to the emergency room with signs of the initial stage of shock as she had tachycardia and hypotension as well as pale skin, demonstrating clinical evidence of decreased cardiac output.

In the compensatory stage of shock, the body's homeostatic mechanisms attempt to improve tissue perfusion. The compensatory mechanisms are mediated by the sympathetic nervous system (SNS) and consist of neural, hormonal, and chemical responses. Neurohormonal

responses attempt to maintain cardiac output in shock. The neurohormonal responses include catecholamine release, causing increased contractility and rennin release by the kidneys which cause the formation of angiotensin I, which is then converted to angiotensin II that causes vasoconstriction, shunting blood to vital organs. Aldosterone is released, causing water conservation. Capillary hydrostatic pressure decreases and shifts fluid to the intravascular space. Antidiuretic hormone release causes conservation of sodium and water leading to decreased urine output. Additionally, release of epinephrine and norepinephrine by the sympathetic nervous system results in increased heart rate (HR) (Pasman & Corden, 2015; Wedro, 2014).

These neurohormonal compensatory mechanisms are triggered in shock to help maintain arterial blood pressure despite a fall in cardiac output (Pasman & Corden, 2015; Walshe & D'Amore, 2008).

Progressive stage of shock: As shock progresses, these compensatory mechanisms are not able to sustain adequate perfusion to tissues and impaired oxygen delivery results. A decreased cardiac output results in impaired oxygenation that causes hypoxic injury to the cells. Metabolic acidosis with severe electrolyte imbalance and respiratory acidosis with hypoxemia can occur. Under anaerobic metabolism, toxic metabolites can accumulate, including lactic acid (Gunnerson & Harvey, 2014) The acid-base status of the arterial blood (pH) is normally between 7.35 and 7.45 (Gunnerson & Harvey, 2014; Walshe & D'Amore, 2008). The blood pH decreases when lactic acid production increases (termed lactic acidosis). Profound acidosis (a pH less than 7.0) results in altered cellular functioning and cellular damage (Gunnerson & Harvey, 2014).

In Case Study Two, the patient has signs of progressive shock as he has episodes of hypotension, sustained tachycardia, tachypnea and impaired oxygenation requiring continued mechanical

ventilation. In addition, his urine output has decreased, demonstrating decreased tissue perfusion. Although lab test results are pending, he most likely has a developing state of acidosis.

Refractory shock: In refractory shock, systemic hypoperfusion causes multiple organ damage. At this stage of shock, end-organ damage and cellular necrosis occur as shock becomes unresponsive to treatment. Ultimately, death occurs from impaired tissue perfusion.

CHECK YOUR PROGRESS: Assess your understanding of key points from the previous sections.

- Inadequate tissue perfusion resulting in impaired cellular oxygenation is characteristic of all shock states.
- If shock is not treated or does not respond to treatment it progresses through the following stages: initial, compensatory, progressive, and irreversible.
- Classic manifestations of shock include hypotension, tachycardia, tachypnea, decreased level of consciousness, cool skin, and oliguria.
- As a result of decreased oxygen delivery to cells in shock states, metabolism switches from aerobic with adequate amounts of ATP produced, to anaerobic metabolism in which there is an inadequate amount of ATP produced to support cell functions.

1. Clinical signs of shock include all but which of the following?
 - A. Tachycardia
 - B. Tachypnea

C. Oliguria

D. Hypertension

Answer: D: Clinical signs include hypotension, tachycardia, tachypnea, cool skin, altered level of consciousness, and oliguria

2. What factors influence the cardiac output?

A. Heart rate and stroke volume

B. Heart rate and rhythm

C. Intravascular volume and contractility of the heart

D. Contractility of the heart and stroke volume

Answer: A. The cardiac output is defined by the following formula: $CO = HR \text{ (beats/min)} \times SV$

3. Multiple organ damage can occur in which type of shock?

A. Initial

B. Compensatory

C. Progressive

D. Refractory

Answer: D. In refractory shock, systemic hypoperfusion causes multiple organ damage.

CARDIOGENIC SHOCK

Cardiogenic shock results when the heart no longer functions as an effective pump, often because of acute myocardial infarction (MI). Other causes include pulmonary edema, cardiomyopathies, dysrhythmias, pericardial tamponade, or valvular regurgitation (Medline Plus Health Information, 2015; Pasma & Corden, 2015). The estimated incidence of cardiogenic shock in hospitalized patients is 5-10% of patients (Medline Plus Health Information, 2015;

Pasman & Corden, 2015). In cardiogenic shock, forward blood flow is inadequate due to cardiac pump failure and loss of functional myocardium (ischemia, cardiomyopathy), a mechanical or structural defect (valvular failure, septal defect) or arrhythmias (Zimmerman, 2012). Cardiogenic shock results in decreased cardiac output, altered oxygen delivery, and reduced tissue perfusion.

Specifically, cardiogenic shock is defined as a decrease in cardiac output along with evidence of tissue hypoxia in the presence of adequate blood volume (Medline Plus Health Information, 2015; Pasman & Corden, 2015). In cardiogenic shock; the heart is unable to effectively contract, leading to ineffective emptying of blood. Right or left ventricular dysfunction can result because of diminished or ineffective contractility. Cardiogenic shock is often characterized by both systolic and diastolic myocardial dysfunction. Inadequate tissue perfusion results from myocardial dysfunction, which leads to cellular hypoxia and ischemia, the end results of shock (Gorman, Calhoun, & Carasco, 2008; Xiushui & Lenneman, 2014).

Clinical Manifestations of Cardiogenic Shock

Clinical signs and symptoms of cardiogenic shock include pale, cool clammy skin, hypotension, tachycardia, oliguria, low cardiac output and cardiac index (less than 2.2 L/minute/m²), distended neck veins, pulmonary edema and S3 gallop (Medline Plus Health Information, 2015; Pasman & Corden, 2015; Wedro, 2014; Zimmerman, 2012). Cardiogenic shock is diagnosed based on clinical signs and symptoms as well as specific hemodynamic criteria that indicate inadequate cardiac functioning. These include sustained hypotension (SBP 30 mm Hg below baseline for at least 30 minutes) and reduced cardiac index, (less than 2.2 L/minute/m²) with pulmonary artery occlusion pressure (PAOP) (more than 15 mm Hg) (Medline Plus Health Information, 2015). The cardiac index is a more specific vasodynamic parameter that is related to the body surface area. It is calculated by dividing the cardiac output

by the body surface area. The PAOP, also termed pulmonary capillary wedge pressure, provides an indirect measure of the left atrial pressure.

Linking Treatment to Pathophysiology of Cardiogenic Shock

In cardiogenic shock, the myocardial dysfunction is difficult to treat because the underlying cellular damage is often irreversible (Gorman et al., 2008; Xiushui & Lenneman, 2014). Treatment goals for cardiogenic shock include increasing contractility, decreasing oxygen demands, increasing myocardial oxygen supply and increasing cardiac output. However, these goals are difficult to achieve, as interventions to increase CO tend to increase myocardial oxygen demands (TS Ahrens, D Prentice, & RM Kleinpell, 2008a; Kar, Basra, Shar, & Loyolka, 2012). The management of cardiogenic shock is aimed at optimizing myocardial function.

Common treatments for cardiogenic shock include supplemental oxygen or endotracheal intubation and mechanical ventilation and hemodynamic support. The initial approach should include fluid resuscitation only if pulmonary edema is not present (Pasman & Corden, 2015; Wedro, 2014; Zimmerman, 2012). Other indicated aspects of treatment can include diuretic therapy to decrease preload and pulmonary congestion; medications, such as intravenous inotropes (e.g., amrinone or dobutamine) to increase the force of contraction; vasodilator medications such as nitroglycerin or nitroprusside to decrease left ventricular afterload; or the use of vasopressors such as norepinephrine when hypotension remains refractory. Catecholamine infusions such as epinephrine must be carefully titrated in patients with cardiogenic shock to maximize coronary perfusion pressure with the least possible increase in myocardial O₂ demand. Vasopressin, a hormone, has been used with a good response for

refractory vasodilatory shock when administered as an intravenous infusion to promote vasoconstriction (TS Ahrens et al., 2008a; Gorman et al., 2008).

Mechanical support devices such as the intra-aortic balloon pump (IABP) can be used to augment coronary artery perfusion and systolic ejection. The IABP is inserted through the femoral artery and positioned in the descending thoracic aorta. It inflates during diastole to improve blood flow to the heart by supplying the coronary arteries with freshly oxygenated blood (TS Ahrens et al., 2008a; Gorman et al., 2008). The balloon then deflates at the end of diastole just prior to ventricular systole (contraction of the left ventricle) to decrease left ventricular afterload (resistance to ejection) to improve cardiac output. The IABP is used for temporary support for patients in cardiogenic shock until either myocardial function improves or surgical intervention can be performed. There are two major complications associated with the use of the IABP: compromised circulation to the leg inferior to the insertion site and balloon rupture. Monitoring of perfusion including pulses, temperature and appearance of the leg below the insertion site is therefore important.

Other assist devices, known as a ventricular assist device, whether percutaneous or surgically inserted, decreases the heart's workload and increases cardiac output to restore adequate systemic perfusion pressure while allowing time to address the underlying cause of myocardial pump failure (Kar et al., 2012). Other indicated treatment may include reperfusion interventions such as percutaneous transluminal angioplasty or coronary artery bypass surgery. These interventions reestablish perfusion to improve ventricular function after myocardial infarction. The use of reperfusion measures in patients with cardiogenic shock after myocardial infarction has increased survival rates (TS Ahrens et al., 2008a; Kar et al., 2012).

HYPOVOLEMIC SHOCK

Hypovolemic shock is considered the most common form of shock (Kolecki & Menchhoff, 2014). **Hypovolemic shock** results from loss of blood, from loss of plasma volume of greater than 20% of the circulating volume, or from profound dehydration (Medline Plus Health Information, 2015). Commonly, hypovolemic shock is due to rapid blood loss (Kolecki & Menchhoff, 2014). Other causes of hypovolemic shock include massive gastrointestinal losses, capillary leak, and tissue third spacing, which results in leakage of fluid out of the intravascular space into the interstitial tissues, which can occur in such conditions as pancreatitis, bowel obstruction, and ascites (TS Ahrens, D Prentice, & RM Kleinpell, 2008b; Kolecki & Menchhoff, 2014).

The clinical signs of hypovolemic shock include pale, cool clammy skin, systolic blood pressure 30 mmHg less than baseline, tachycardia, oliguria, and decreased level of consciousness (TS Ahrens et al., 2008b; Kolecki & Menchhoff, 2014). There is wide variation in the clinical symptoms depending upon the amount of volume loss, the rate of loss, and the underlying illness or injury causing the loss (Kolecki & Menchhoff, 2014). With blood volume loss, the hemoglobin and hematocrit will be reduced. Hypovolemia results in shock caused by decreased blood volume, leading to decreased cellular oxygen supply and impaired tissue perfusion (TS Ahrens et al., 2008b; Kolecki & Menchhoff, 2014). As outlined in **Table 2**, the symptoms of hypovolemic shock are similar to cardiogenic shock with low blood pressure, tachycardia, low urine output, cool clammy skin, weak pulse and altered level of consciousness. The two shock states are differentiated in that cardiogenic shock is characterized by low oxygenation and high pulmonary artery occlusion pressures and often pulmonary vascular congestion.

TABLE2. Clinical Manifestations of Shock

Clinical Manifestations in Common	Hypovolemic Shock	Cardiogenic Shock	Septic Shock	Anaphylactic Shock
Blood pressure	Low	low	low	low
Heart rate	tachycardia	tachycardia	tachycardia	Tachycardia
Urine Output	low (< 0.5 ml/Kg/hr)	low	Low	Low
Level of consciousness	Altered	altered	altered	altered
Skin	Cool, clammy	Cool, clammy	warm	warm
Pulse quality	Weak	weak	weak early strong later	weak
Differentiating Clinical Manifestations				
PaO ₂	Normal	low	low	normal or low
SaO ₂	Normal	low	low	normal or low
Cyanosis	Absent	May be present	absent	absent
a/A ratio	Normal	low	low	low
PAOP	low (<10)	high (> 18)	normal or low	normal or low
Orthopnea	Minimal	present	possible	present
Crackles	Minimal	present	possible	possible
Dependent edema	Absent	present	absent	absent

Clinical Manifestations in Common	Hypovolemic Shock	Cardiogenic Shock		
Blood pressure	Low	low		
Heart rate	tachycardia	tachycardia		
Urine Output	low (< 0.5 ml/Kg/hr)	low		
Level of consciousness	Altered	altered		
Skin	Cool, clammy	Cool, clammy		
Pulse quality	Weak	weak		
Differentiating Clinical Manifestations				
PaO ₂	Normal	low		
SaO ₂	Normal	low		
Cyanosis	Absent	May be present		
a/A ratio	Normal	low		

PAOP	low (<10)	high (> 18)		
Orthopnea	Minimal	present		
Crackles	Minimal	present		
Dependent edema	Absent	present		

Adapted with permission, Ahrens et al 2008

Stages of Hypovolemic Shock

There are several distinct stages of hypovolemic shock (see **Table 3**). In the initial stage where approximately 15% (750 ml) volume is lost, compensatory mechanisms maintain cardiac output and the patient is asymptomatic (Kolecki & Menchhoff, 2014). In the second or compensatory stage, 15-30% (750-1500 ml) of volume is lost and the cardiac output falls, resulting in compensatory increase in heart rate and respiratory rate, low urine output, and altered level of consciousness (Kolecki & Menchhoff, 2014). Hypoxemia develops as perfusion to tissues is reduced as a result of the decreased cardiac output. Sympathetic nervous system compensatory mechanisms are activated with resulting vasoconstriction. However, if volume loss continues the third or progressive stage develops in which 30% to 40% (1500 to 2000ml) volume loss occurs and impaired tissue perfusion develops as compensatory mechanisms become overwhelmed (Kolecki & Menchhoff, 2014). Arrhythmias can develop and cause myocardial ischemia and metabolic acidosis and respiratory distress can occur. In the fourth or refractory stage, over 40% (more than 2000 ml) volume loss occurs which is immediately life-threatening. Severe tachycardia, hypotension and organ failure can occur and cardiac arrest may ensue. (TS Ahrens et al., 2008b; Kolecki & Menchhoff, 2014).

Table 3 Stages of Hypovolemic Shock

Mild (less than 20% blood volume loss)	Moderate (20 to 40%) blood volume loss	Severe (over 40% blood volume loss)
Cool extremities	Same as mild plus:	Same as moderate plus:
Increased capillary refill time	Tachycardia	Hemodynamic instability
Diaphoresis	Tachypnea	Marked tachycardia
Anxiety	Oliguria	Hypotension
	Orthostatic Changes	Mental status deterioration

Adapted from Harrison's Online Shock. Available at: www.harrisonsonline.com. (May 4, 2013).

Pathophysiology of Hypovolemic Shock

In hypovolemic shock, venous return to the heart (preload) decreases, resulting in decreased cardiac output (Kolecki & Menchhoff, 2014). Compensatory mechanisms respond by increasing heart rate, systemic vascular resistance (SVR), cardiac output, and tissue perfusion owing to catecholamine release (TS Ahrens et al., 2008b; Kolecki & Menchhoff, 2014). Blood volume is increased in several ways, including through neurohormonal mechanisms including the renin-angiotension-aldosterone system that promotes conservation of sodium and water and a shifting of the interstitial fluid into the vasculature in response to the decreased circulating volume. Additionally, the liver and spleen release stored red blood cells and plasma. With continued blood loss, the compensatory mechanisms are unable to maintain perfusion to the tissues and organs, and the end result of shock can result: profound acidosis, altered cellular functioning, and cellular damage (Kolecki & Menchhoff, 2014).

Linking Pathophysiology to the Treatment of Hypovolemic Shock

The treatment goals for hypovolemic shock are to treat the underlying cause, control additional fluid loss, and replace fluid losses (TS Ahrens et al., 2008b; Kolecki & Menchhoff,

2014). Treatment is aimed at reestablishing normal blood pressure, pulse and organ perfusion (Zimmerman, 2012). Volume expanders including crystalloid solutions (e.g., lactated Ringer's solution, normal saline) and colloids (e.g., albumin, hetastarch [Hespan]) are used for fluid resuscitation of patients with hypovolemic shock. Crystalloids are effective at expanding intravascular volume and interstitial fluid (Kolecki & Menchhoff, 2014). Lactated Ringer's solution and normal saline are the two most commonly used isotonic solutions due to the osmolality needed to restore intravascular volume (Kolecki & Menchhoff, 2014). Volume resuscitation with large amounts of normal saline can result in hyperchloremic metabolic acidosis (Zimmerman, 2012). The advantage of using lactated Ringer's solution is that it is metabolized by the liver and kidneys to generate bicarbonate, which provides a buffer against the lactic acid generated by tissue hypoperfusion, thereby promoting normal pH balance (Kolecki & Menchhoff, 2014). Colloids expand the intravascular space by pulling fluid from the interstitial spaces (Kolecki & Menchhoff, 2014). Although colloids are more effective than crystalloids at increasing intravascular fluid, data suggest an increased incidence of complications and risk of death with the use of colloids, particularly albumin (Kolecki & Menchhoff, 2014).

Blood and blood products are used for patients who are hemodynamically unstable, for patients with greater than 1500 cc blood loss, and patients with ongoing uncontrolled sources of bleeding (TS Ahrens et al., 2008b; Kolecki & Menchhoff, 2014). Transfusion of blood and blood products are usually indicated for a hematocrit less than 28% (Kolecki & Menchhoff, 2014). Whole blood is used to replace large blood loss, while packed red blood cells (PRBCs) are used to replace moderate blood loss (Kolecki & Menchhoff, 2014). Platelets are administered when platelet levels are decreased (thrombocytopenia), which occurs in hemorrhage. Fresh

frozen plasma (FFP) is used to correct plasma deficits and restore osmotic pressure (Kolecki & Menchhoff, 2014).

Type-O PRBCs are used for initial resuscitation in emergent situations, until cross-matched blood is available (Kolecki & Menchhoff, 2014). In the presence of coagulopathy, hypothermia, or when PRBC transfusion exceeds six units, platelets and FFP should be administered (Kolecki & Menchhoff, 2014). With massive hemorrhage, in which the volume of blood lost equals the patient's total blood volume, a 70-kg adult may require 10 units of PRBCs in 24 hours (Kolecki & Menchhoff, 2014). New artificial red blood cells that are more like RBCs are being developed (Kar et al., 2012). Red blood cell (RBC) substitutes, often referred to as hemoglobin-based O₂ carriers (HBOCs), consist of extracted hemoglobin from lysed RBCs (Kolecki & Menchhoff, 2014). Most RBC substitutes have a hemoglobin concentration of 10-15%, compared to a typical hemoglobin concentration of PRBCs of 20-25 g/dl (Kar et al., 2012). RBC substitute solutions are typically hypertonic colloids and expand blood volume more than the volume of the infused solution (Kolecki & Menchhoff, 2014).

Other aspects of treatment include determining the cause of blood or volume loss and preventing further volume loss (Kar et al., 2012). Vasopressor medications such as phenylephrine, and dobutamine may be required to increase blood pressure and cardiac output, and should be used only as a temporizing measure while fluid resuscitation is ongoing or when hypotension persists despite adequate volume resuscitation (Zimmerman, 2012). Vasopressors should not be given without adequate fluid replacement because they can cause cardiac decompensation and hemodynamic deterioration, especially in patients with ischemic heart disease (TS Ahrens et al., 2008b; Kolecki & Menchhoff, 2014). Cardiac output and oxygen supply are dependent on adequate intravascular volume and cardiac function, therefore adequate

fluid replacement is required to ensure adequate tissue perfusion when administering vasopressors as these agents can cause vasoconstriction. Other interventions may include insertion of a urinary catheter to monitor urine output and hemodynamic monitoring to evaluate cardiac output and metabolic consumption (SVO₂). A central venous catheter may be inserted to monitor central venous pressure.

In Case Study One, the patient presented to the emergency room with signs of shock including altered vital signs with a low blood pressure of 88/50 mm Hg, an elevated heart rate of 125 bpm with sinus tachycardia and an elevated respiratory rate of 34bpm. Her physical exam revealed pale skin and sluggish capillary refill, indicating vasoconstriction to the skin. A foley catheter insertion resulted in 60 cc of dark yellow urine, indicating possibly dehydration. She had no jugular venous distention, which if present, can be a sign of cardiogenic shock.

The patient reported that she was weak and dizzy and had a “flu bug” for the past week with diarrhea. Although lab work was pending, the possible cause of her beginning shock state was dehydration or blood loss with diarrhea. A diagnosis of hypovolemic shock was made with a low hemoglobin and hematocrit and Helicobacter pyloric guiac positive stool (FOBT) confirmed the GI bleeding. A nasogastric tube was inserted with bright red blood return and the patient was taken for endoscopic treatment of a gastrointestinal bleed which was corrected, the patient stabilized and was eventually discharged home.

ANAPHYLACTIC SHOCK

Anaphylactic shock results from an allergic reaction that causes systemic release of IgE (antibody formed as part of immune response) and causes mast cell activation and histamine release (Balentine, 2014; Medline Plus Health Information, 2014). Anaphylaxis affects up to 15% of the U.S. population (Medline Plus Health Information, 2014; Stern, 1997) It is estimated that a total of 3.29 million to 40.9 million individuals are at risk of anaphylaxis (Medline Plus Health Information, 2014; Stern, 1997). Many substances known as allergens can cause anaphylaxis. Allergens may include foods, food additives, drugs, and insect-stings. Insect stings present the greatest number of cases of anaphylaxis (American Association of Allergy Asthma and Immunology, 2015; Stern, 1997) (see **Table 4**). Routes of entry for an allergen can include injection, ingestion, inhalation, and skin absorption. Clinical signs of anaphylaxis include generalized pruritis, respiratory distress, syncope, and apprehension (see **Table 5**) (American Association of Allergy Asthma and Immunology, 2015; Stern, 1997). The signs and symptoms of anaphylaxis can appear within several minutes of exposure to the antigen. The severity of the reaction is directly related to the onset of symptoms, with early signs appearing with a severe reaction. Occasionally, biphasic reactions occur in which symptoms recur several hours after the initial reaction. Anaphylaxis is a life-threatening hypersensitivity reaction that can develop rapidly (within seconds) or occur as a delayed reaction (12 or more hours after initial exposure) (American Association of Allergy Asthma and Immunology, 2015; Stern, 1997).

Table 4: Common Anaphylaxis Allergens

Foods	Food Additives	Medications	Other
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Eggs	Monosodium Glutamate	Antibiotics	latex
Peanut butter	Autolized Yeast	Aspirin	Exercise
Fish	Natural Flavorings	Contrast Dye	Insect venom
Shellfish	Yeast Extract	Blood products	Animal hair
Milk	Food coloring	Vaccines	Dust
Cheese		Narcotics	Pollen
Tomatoes		Local anesthetics	
Chocolate			
Nuts and seeds			

Table 5: Clinical Signs and Symptoms of Anaphylaxis

Generalized Signs & Symptoms	Life-threatening Signs & Symptoms
Itching (any part of the body)	Respiratory distress/stridor
Swelling (of any body parts)	Bronchospasm
Red, watery eyes	Laryngeal edema
Nausea, vomiting, diarrhea	Shock
Stomach cramps	
Change of voice	
Coughing	
Wheezing	
Difficulty swallowing	
Sense of doom	
Dizziness	

Adapted from American Academy of Allergy, Asthma and Immunology

http://www.aaaai.org/members/academy_statements/position_statements/ps34.asp

Pathophysiology of Anaphylaxis

Anaphylaxis, caused by an antibody-antigen response, results in an extensive immune and inflammatory response (Balentine, 2014; Medline Plus Health Information, 2014; Stern, 1997). Anaphylactic shock results from an allergic reaction that causes release of immunoglobulin E (IgE), an antibody that is formed as part of the immune response. Leukocytes, including mast cells, basophils, and eosinophils, release mediators such as histamine, prostaglandins, kinins, and complement that cause vasodilation, increased vascular permeability, hypotension, bronchoconstriction, and coronary vasoconstriction (American Association of Allergy Asthma and Immunology, 2015; Stern, 1997). The result is peripheral pooling of blood, tissue edema, airway constriction, and myocardial depression. A state of relative hypovolemia occurs, with altered tissue perfusion and impaired cellular metabolism. If untreated, anaphylaxis results in a shock state and can lead to cardiac, renal, pulmonary, and multisystem organ failure (American Association of Allergy Asthma and Immunology, 2015; Stern, 1997). Death may result from cardiovascular or respiratory distress.

Linking Pathophysiology to the Treatment of Anaphylactic Shock

The treatment goals for anaphylactic shock include the “ABC’s” (airway, breathing, and circulation) of emergency care, along with volume expansion (American Association of Allergy Asthma and Immunology, 2015; Balentine, 2014; Medline Plus Health Information, 2014; Stern, 1997). Hypotension should be managed with intravenous fluids to promote intravascular volume expansion. Colloid solutions (e.g., 5% albumin, 6% hetastarch) better facilitate volume expansion than crystalloid solutions (e.g., lactated Ringer’s solution, 5% dextrose in normal saline). Vasoconstrictor agents such as norepinephrine (Levophed), phenylephrine (Neo-Synephrine), and dopamine HCL (Intropin) may be administered to reverse the effects of severe vasodilation and myocardial depression (American Association of Allergy Asthma and

Immunology, 2015; Balentine, 2014; Medline Plus Health Information, 2014; Stern, 1997). Epinephrine is a first-line drug administered to patients with anaphylaxis to promote vasoconstriction and further inhibit mediator release. The standard dose of epinephrine is 1:1000, 0.3 ml given subcutaneously(American Association of Allergy Asthma and Immunology, 2015; Balentine, 2014; Medline Plus Health Information, 2014; Stern, 1997). Antihistamines, such as diphenhydramine (Benadryl) are useful as second-line drug therapy to block the histamine response and stop the inflammatory reaction. Antihistamines should not be administered without epinephrine (American Association of Allergy Asthma and Immunology, 2015; Balentine, 2014; Medline Plus Health Information, 2014; Stern, 1997). Additional treatment measures include Aminophylline and inhaled beta 2 agonists to reverse Bronchospasm and corticosteroids to help stabilize capillary membranes and prevent a delayed reaction (American Association of Allergy Asthma and Immunology, 2015; Balentine, 2014; Medline Plus Health Information, 2014; Stern, 1997).

Prevention of anaphylactic shock through identification of patients at risk and careful monitoring of patient response to drugs, blood products, and blood are important components of nursing care (American Association of Allergy Asthma and Immunology, 2015; Balentine, 2014; Medline Plus Health Information, 2014; Stern, 1997). Important measures include obtaining a complete allergy history and identifying potential allergens. Patients experiencing an episode of anaphylaxis should be instructed to avoid the allergen. Teaching about the importance of seeking prompt medical attention when symptoms of anaphylaxis occur is an important part of patient education (Balentine, 2014; Medline Plus Health Information, 2014; Stern, 1997). Early identification and prompt medical treatment are essential in preventing a life-threatening reaction. The American Academy of Allergy and Immunology stresses that education of the lay

and professional public is important to promote the prompt administration of measures such as administration of epinephrine for the emergency treatment of anaphylaxis (Stern, 1997).

NEUROGENIC SHOCK

Neurogenic shock results from loss of peripheral sympathetic vasomotor tone.

Neurogenic shock is commonly seen in trauma and results from a change in systemic vascular resistance, mediated by a neurologic injury (e.g., head injury or high thoracic or cervical spinal cord injury) (Chin, 2014). Neurogenic shock is considered the rarest form of shock (Chin, 2014; Guly, Bouamra, Lecky, Trauma, & Research, 2008). Neurogenic shock, sometimes called vasogenic shock, results from the disruption of autonomic nervous system control over vasoconstriction (Chin, 2014). After spinal cord injury, neurogenic shock can occur immediately after injury or can exhibit a delayed response for up to weeks or months after the initial injury (Chin, 2014). Although the terms are sometimes used interchangeably, neurogenic shock is distinguished from spinal shock, which refers to an acute, transient neurologic syndrome of sensorimotor dysfunction that develops with spinal cord injury at any level (American Association of Allergy Asthma and Immunology, 2015). Neurogenic shock is a hemodynamic syndrome associated with upper thoracic and cervical spinal cord injury and is characterized by bradycardia and decreased systemic vascular resistance. The two patterns may or may not occur concurrently (Chin, 2014). Neurogenic shock is suggested by a pattern of decreased heart rate, blood pressure, and systemic vascular resistance (Guly et al., 2008) The classic signs of shock may not be present in neurogenic shock because of alteration in sympathetic tone (Chin, 2014). As a result, bradycardia is commonly seen and the skin is warm, dry, and pink, rather than cool; and pale—at least below the level of spinal cord injury (Chin, 2014; Guly et al., 2008).

Pathophysiology of Neurogenic Shock

In neurogenic shock, sympathetic nervous system deregulation occurs. As vasomotor tone is lost, systemic arteriolar resistance decreases profoundly and venous capacitance increases, resulting in decreased afterload and preload and subsequent massive vasodilation and decreases in cardiac output (Chin, 2014). Unopposed vagal tone results in significant bradycardia.

The loss of normal sympathetic tone also results in an inability to shunt blood from the periphery to the core, and heat loss through the skin becomes excessive, resulting in hypothermia (Chin, 2014). Decreased tissue perfusion results primarily from arterial hypotension caused by a reduction in systemic vascular resistance (Chin, 2014). In addition, a reduction in effective circulating plasma volume often occurs because of a decrease in venous tone that leads to vasodilation and a resultant decrease in blood pressure (Chin, 2014). A decrease in cardiac output leads to decreased cellular oxygen supply and impaired cellular metabolism. The clinical signs and symptoms of neurogenic shock include hypotension and pale, cool, clammy skin with warm extremities above the level of injury. Bradycardia and decreased level of consciousness can also be present (Chin, 2014; Guly et al., 2008).

Linking Pathophysiology to the Treatment of Neurogenic Shock

The treatment of neurogenic shock includes the ABCs of emergency care. Fluid resuscitation is given with caution, as the blood volume is sufficient but blood distribution is altered (Chin, 2014). The administration of a large volume of IV fluids to increase central venous return may cause heart failure. The Trendelenburg position can be used temporarily to increase the blood pressure. Insertion of a Foley catheter may be required, as bladder function may be lost. Atropine may be administered to block dominant vagal effects that cause bradycardia (Chin,

2014). Vasoconstrictive intravenous agents may be used to increase blood pressure that is resistant to fluid replacement (Chin, 2014). Positive inotropic agents such as dopamine and dobutamine at lower dosages (1-5 mcg/kg/min) can enhance cardiac output, increase perfusion pressure, and improve renal hemodynamics (Chin, 2014). However, vasopressors are used with caution, as vasoconstriction may decrease spinal cord blood flow, which can ultimately influence the extent of secondary cord injury. In rare cases, a pacemaker may be required for refractory bradyarrhythmias (Chin, 2014).

SEPTIC SHOCK

Sepsis and **septic shock** are common, pathophysiologically complex, clinical conditions that are associated with high morbidity, mortality, and cost of care (Mayr et al 2014). Sepsis occurs in response to infection and results in sepsis related organ system dysfunction and/or circulatory shock, resulting in high morbidity and mortality rates for hospitalized patients (Cohen et al 2015). While estimates show trends toward decreasing in hospital and case fatality rates, the incidence of sepsis cases is increasing at a larger rate. These developments have resulted in a large number of sepsis related fatalities and a larger number of survivors who require post hospital care and/or are unable to resume their prior occupation (Kempker and Martin 2016). Although a growing number of potential biomarkers have been studied to improve the capability of diagnosing sepsis, most lack specificity (McLean 2015; Faix 2013; Kibe et al 2011; Marshall et al 2009; Rivers et al 2013; Gibot et al 2012). Clinicians are currently using clinical criteria for sepsis surveillance and identification based on prior consensus definitions (Levy et al 2003). However these definitions have limitations. Recently, a 3rd Sepsis Definitions Conference

published new definitions and clinical criteria for the diagnosis of sepsis and septic shock (Singer et al 2016).

Epidemiology of Sepsis

In the United States, sepsis is the most common cause of death in noncardiac intensive care units and the 10th leading cause of death overall. The incidence of sepsis is increasing because of a number of factors (see **Table 6**). The rise in the number of cases of sepsis is expected to continue because of the number of elderly patients in health care facilities; an increased number of patients with compromised immune status, chronic illness, or malnutrition; an increased number of patients having invasive and surgical procedures; and an increased number of resistant microorganisms, among other factors (Balk, 2000; Vincent et al., 2002).

Table 6: Risk Factors for Sepsis

Extremes of age: under age 1 and over age 65 years
Surgical/invasive procedures
Malnutrition
Broad-spectrum antibiotics
Chronic illness
Diabetes mellitus
Chronic renal failure
Hepatitis
Increased number of patients with compromised immune status
Acquired immunodeficiency syndrome
Increased use of cytotoxic and immunosuppressant agents
Alcoholism
Malignancy
Increased number of transplant recipients and transplantation procedures
Increased number of resistant microorganisms
Increased number of elderly patients
Increased awareness and sensitivity for the diagnosis

Adapted from Balk RA. Severe sepsis and septic shock. Definitions, epidemiology, and clinical manifestations. *Critical Care Clinics* 2000; 16:179-192.

In Case Study Two, the patient had several risk factors for infection including increased age, and status post a surgical procedure with a midline incision requiring frequent dressing changes. In addition, he had several invasive lines including an arterial line and central venous catheter, a foley catheter and a t-tube drain, all of which can predispose to infection risk. Special Consideration for the Aged: As the patient was age 76, a consideration with respect to the presentation of sepsis is that due to altered immune system response, he may not have demonstrated a classic presentation with an elevated temperature. Often, the aged patient with developing sepsis presents with a normal temperature. Additionally, aged patients may present with altered level of consciousness or confusion

While early recognition of sepsis is important and influences survival, the clinical signs of sepsis can be difficult to identify. Signs of sepsis include changes in vital signs (decreased blood pressure, increased heart rate, increased respiratory rate, and increased temperature), along with signs of altered perfusion to vital organs (e.g., decreasing urine output from the development of acute renal failure). Septic shock is characterized by hemodynamic changes including high cardiac output and decreased peripheral resistance due to dilation of systemic resistance vessels and dysfunction of one or several organs (Alves-Filho, de Freitas, Spiller, Souto, & Cunha, 2008; Salomao et al., 2008). Often, patients with sepsis exhibit signs of the systemic inflammatory response or SIRS criteria: alteration in temperature (most often elevation), elevated heart rate (more than 90 beats/minute), elevated respiratory rate (more than 20 breaths/minute or a PCO_2 less than 32 mm Hg), and an altered white blood cell count (less than 12,000 cells/mm³, less than 4000 cells/mm³, or more than 10% immature (band) forms) (Balk, 2000). Several terms specifically define the progression from infection to severe sepsis to septic shock and are outlined in Table 7.

Table 7: Sepsis Terms and Definitions

Infection: Microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms

Bacteremia: The presence of viable bacteria in the blood

Sepsis: Life-threatening organ dysfunction caused by a dysregulated host response to infection

Septic shock: A subset of sepsis in which circulatory, cellular, and metabolic alterations are associated with a higher mortality rate than sepsis alone

Hypotension: A systolic blood pressure of <90 mm Hg or a reduction of >40 mm Hg from baseline in the absence of other causes for hypotension.

Multiple organ dysfunction syndrome: Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

(*Singer et al 2016; Rhodes et al 2017*)

Pathophysiology of Sepsis

The pathophysiology of sepsis is complex and is associated with three integrated responses: activation of inflammation, activation of coagulation mediators, and procoagulant factors and inhibition of fibrinolysis (C. J. Fernandes, Jr. et al., 2008). Gram-negative and gram-positive bacteria, fungi, parasites, and viruses all contain pathogen (or microorganism) associated molecular patterns (PAMPs) that can initiate a septic response (Dellinger & Vincent, 2005; Levy et al., 2010).

The known mechanisms by which various microbiologic organisms trigger a septic

response appear to vary. For example, lipopolysaccharide (LPS) is released from the cell wall of gram-negative bacteria. LPS can then bind to LPS-binding protein (LBP) found in plasma. The LPS:LBP complex can then bind with the opsonic receptor *CD14*, predominately expressed on the cell wall of monocytes and macrophages, or with soluble *CD14* (*sCD14*) found in plasma, which is necessary for activation of cells without membrane-bound *CD14*, such as dendritic cells. Antigen-presenting cells (APCs) such as monocytes, macrophages, neutrophils, and dendritic cells can all be activated to release cytokines in response to the protein toll like receptor 4 (TLR4) to further stimulate the release of other cytokines and effector molecules, leading to a cascade effect of increasing inflammation and continued stimulation of the innate immune system response (Dellinger & Vincent, 2005; Levy et al., 2010).

Gram-positive bacteria may also utilize *CD14* and *TLR2* to stimulate cytokine and effector molecule release (Dellinger & Vincent, 2005; Levy et al., 2010). Unlike gram-negative bacteria, gram-positive bacteria do not produce endotoxins such as LPS. Therefore, it is believed that the peptidoglycans and lipoteichoic acid found on the cell walls of gram-positive bacteria are proinflammatory and maybe involved in binding to the above cell-surface receptors, though they are not nearly as potent as LPS (Dellinger & Vincent, 2005; Levy et al., 2010).

The antigen (eg. bacteria) is recognized by a monocyte which immediately releases inflammatory mediators. These mediators include factors such as interleukin-1 (IL-1, IL-6, tumor necrosis factor alpha (TNF α) and tissue factor. These mediators result in a series of responses including initiation of the coagulation cascade, decreased fibrinolysis, and endothelial changes. Toll-like receptors (TLRs), are transmembrane proteins expressed by cells of the innate immune system in response to infection. TLR activation induces the cytokine/chemokine release (ie. TNF α , IL-8) and activation of inflammatory responses. Activation of TLRs in neutrophils

can impair the migration of neutrophils and alter immune function (Aitken et al., 2011). Up-regulation of inducible nitric oxide synthase (i-NOS) (NOS-2) protein expression and the consequent enhanced production of nitric oxide is believed to result in excessive vasodilation, vascular hypo reactivity and vascular leak (Alves-Filho et al., 2008).

Although the immune system response is protective in nature, aimed at combating infection in sepsis, increased responsiveness of mediators has been cited as a causal factor in contributing to endothelial cell damage, micro capillary permeability changes, capillary leak, and profound vasodilation and hypotension. Common theories that have been proposed are that sepsis represents an uncontrolled inflammatory response, failure of the immune response to infection, and genetic polymorphisms causing hyper inflammatory or hypoinflammatory responses to infection (C. J. Fernandes, Jr. et al., 2008). More recent theories propose that sepsis results due to a severely compromised immune system response that is dependent on a number of factors including the virulence of the infecting organism, a patient's current health status and severity of illness, nutritional status, age and polymorphisms in cytokine genes or variations in genes that are genetically determined which have been implicated in the pathogenesis of infectious diseases (Salomao et al., 2008). Sepsis is associated with activation of coagulation and impairment of fibrinolysis, which contribute to further impairment in perfusion. Proinflammatory cytokines *IL1* and *TNF α* stimulate the release of tissue factor from monocytes and endothelial cells that directly stimulate the coagulation cascade (Linde-Zwirble & Angus, 2004). A procoagulant state results with increased generation of thrombin and significantly reduced levels of protein C and antithrombin III, which are normal constituents of the anticoagulation system (Linde-Zwirble & Angus, 2004). The resultant microthrombi impairs blood flow and organ perfusion. Thrombocytopenia and disseminated intravascular coagulation can also result. Simultaneously, the

normal processes of fibrinolysis are impaired, leading to persistence of microvascular thrombosis that can lead to multiple organ dysfunction (**Figure 1**)(**Balk, 2000**).

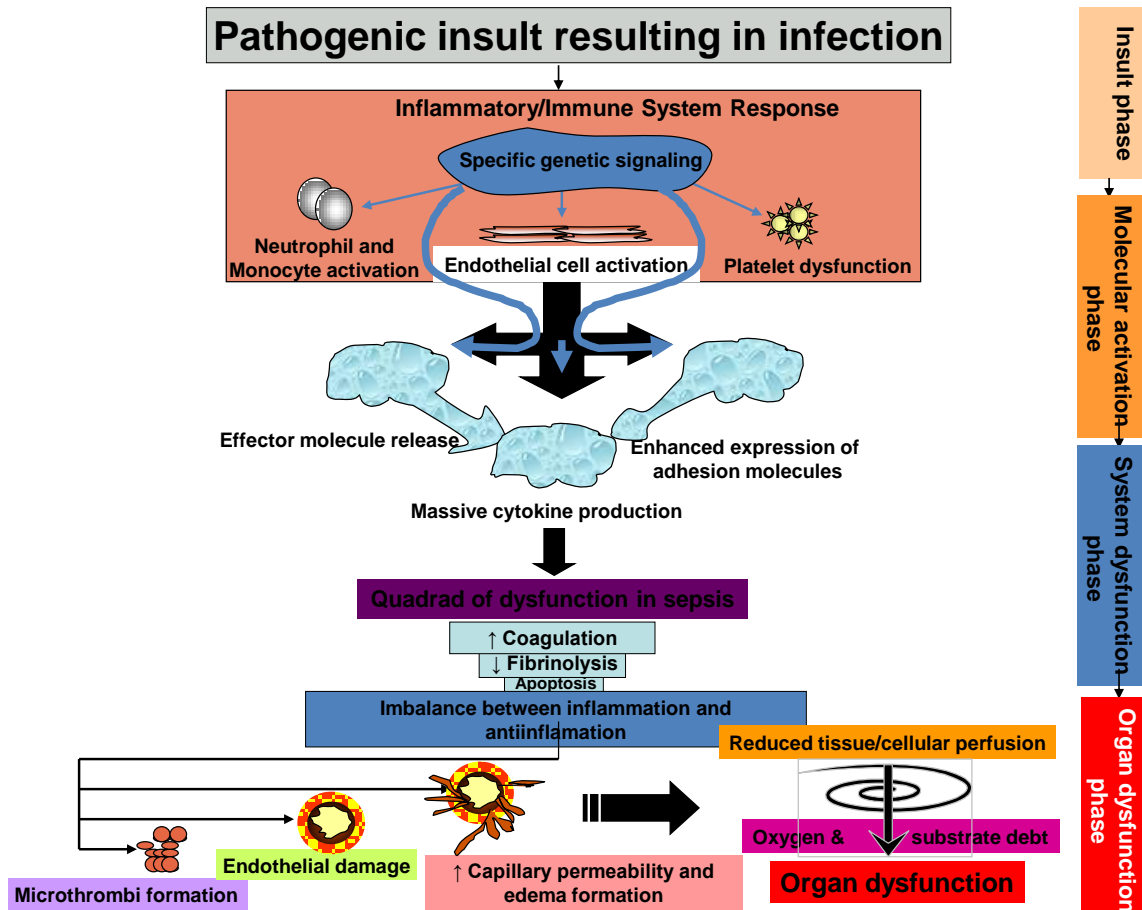


Figure 1

Linking Pathophysiology to Treatment of Septic States

Essential treatment goals for sepsis include antibiotic therapy, supportive treatment with oxygenation and ventilation; and circulatory support with fluid and inotropic administration. The goal of fluid resuscitation is to restore tissue perfusion, and fluid infusion should be titrated to clinical end points, such as heart rate, blood pressure, and urine output (Rhodes et al 2017). Vasopressive agents such as norepinephrine or phenylephrine are indicated if volume infusions do not normalize blood pressure and organ perfusion, as judged by a mean arterial pressure (MAP) of greater than 60 mm Hg and adequate urine output (Rhodes et al 2017).

The Surviving Sepsis Campaign Guidelines provides strategies for targeting treatment of

patients at risk of developing sepsis and septic shock (Rhodes et al 2017). The guidelines outline several evidence-based guidelines for the treatment of patients with sepsis. The focus of the Surviving Sepsis Campaign Guidelines are aimed at providing resuscitation for sepsis-induced hypoperfusion and enhancing perfusion; antibiotic administration to combat infection; cultures to identify the source of infection; mechanical ventilation to optimize oxygenation; and source control to identify and contain the infection. The guidelines also advocate for the use of evidence-based treatment practices for critically ill patients including glucose control; prophylaxis measures for deep vein thrombosis and stress ulcer prevention, renal replacement therapies, nutritional support; and blood product administration as indicated. Sedation and analgesia are promoted for patient comfort, and setting goals of care for critically ill patients is advocated to promote realistic treatment goals including decision-making regarding less-aggressive support or withdrawal of support (Rhodes et al 2017).

The sepsis bundles form the main components for implementation. A “bundle” is a group of interventions that when implemented, produce better outcomes than when implemented individually (www.survivingsepsis.org). The Sepsis Resuscitation Bundle (outlined in **Table 8**), which outline several indicated interventions aimed at stabilizing and further managing the critically ill patient, are advocated to promote optimal management of sepsis.

Table 8: Surviving Sepsis Campaign Care Bundles.

WITHIN 3 HOURS OF SEPSIS:

1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30ml/kg crystalloid for hypotension or lactate ≥ 4 mmol/L

WITHIN 6 HOURS OF INITIAL SYMPTOMS FOR SEPTIC SHOCK:

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mmHg
6. In the event of persistent hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactate was ≥ 4 mmol/L, re-assess volume status and tissue perfusion and document findings
7. Re-measure lactate if initial lactate elevated.

DOCUMENT REASSESSMENT OF VOLUME STATUS AND TISSUE PERFUSION WITH:

EITHER • Repeat focused exam (after initial fluid resuscitation) by licensed independent practitioner including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings. OR
TWO OF THE FOLLOWING: • Measure CVP • Measure ScvO₂ • Bedside cardiovascular ultrasound • Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge

Source: Adapted from www.survivingsepsis.org.²⁰¹⁷

The Surviving Sepsis Campaign recommendations are graded based on the degree of support from research and focus on improving perfusion, treating the infection, and providing organ system support such as oxygenation and mechanical ventilation, renal replacement therapy for acute renal failure, among other measures to prevent complications of critical illness (Rhodes et al 2017). As nurses are often involved in providing treatment measures to patients, the

implications of the guidelines for nursing care are important considerations (Kleinpell, Aitken, & Schorr, 2013).

Several processes can be targeted to ensure successful adoption of the guidelines. Discussion of the guidelines should be incorporated in venues such as daily rounds, grand rounds, and Critical Care Conferences. Other measures to address sepsis as a priority area for ICU care include promoting early identification of sepsis to help in ensuring prompt treatment (Kleinpell et al., 2013). The use of tracking systems such as daily sepsis rounds, use of check sheets to monitor patients for signs of sepsis, or automated computer-based sepsis alert programs can enhance identification of patients with sepsis (Aitken et al., 2011).

Sepsis prevention measures can be instituted, including the use of oral care, head of bed positioning, hand hygiene, and infection control measures. The use of oral care, including tooth brushing, is an essential aspect of care for the critically ill patient to reduce accumulation and colonization of dental plaque that can lead to nosocomial infection risk (Kleinpell et al., 2013). Providing oral care is a direct nursing care measure, yet recent research indicates that inadequate oral care is provided to patients in the ICU. Patient positioning is a key component of nursing care (Aitken et al., 2011). Research evidence suggests that the use of semi recumbent positioning in critically ill patients may reduce ventilator-associated pneumonia. However, the use of recommended levels of backrest elevation (head of bed is 45) can be inconsistent in the critical care environment (Aitken et al., 2011). Hand hygiene measures remain the single most effective means to prevent, control, and reduce infection, as it effectively interrupts microbial transmission from person to person and person to object to person. Infection prevention measures remain critical for limiting infection spread and instituting infection control precautions on the basis of suspected or confirmed infections in critically ill patients is an indicated component of nursing care.

In Case Study Two, the patient was at increased risk for infection due to having had recent surgery with an abdominal incision that required frequent dressing changes, several intravenous lines and invasive catheters. He was also at risk for developing pneumonia as he required prolonged intubation and had difficulty being weaned from the ventilator. He developed low blood pressure requiring fluid therapy and his urine output began to decline – both signs of altered perfusion. His vital signs changed and his physical exam findings revealed additional signs of progressive shock.

He also began to manifest signs of sepsis including tachycardia, tachypnea, and elevated temperature. Postoperative lab results revealed an elevated white blood cell count, indicating a potential infection.

When he began to exhibit signs of shock, the most likely etiology was sepsis. His state of impaired oxygenation, hypotension which required fluids and vasopressor therapy, and his decreased urine output demonstrated signs of altered perfusion, classifying him as being in severe sepsis. This was confirmed; and he was started on broad spectrum antibiotic therapy. He required supportive therapy with continued oxygen and mechanical ventilation and on post operative day three. he was afebrile and his vital signs stabilized. By postoperative day five, he was extubated and was transferred to the surgical floor and was ultimately discharged home with home health follow up for assistance with surgical dressing changes.

MULTIPLE ORGAN DYSFUNCTION SYNDROME

A number of factors contribute to multiple organ dysfunction syndrome, the eventual cause of death in sepsis, severe trauma, or hepatic dysfunction, among other causes including: inadequate

tissue/organ perfusion, cellular injury, apoptosis-related cell death, ischemia, and diffuse endothelial cell injury (Aird, 2001; Balk, 2000). In addition, end organ damage may be further exacerbated by cardiac and endocrine dysfunction. Impaired cardiac contractility has been linked to the release of myocardial depressant substances early in sepsis (Alves-Filho et al., 2008). Diminished contractility results in increased left ventricular dilation, requiring greater filling pressures in order to meet the delivery demands of the tissues. If compensatory left ventricular dilation does not occur, risk of death from sepsis increases (Dellinger et al., 2013). Adrenal insufficiency and vasopressin deficiency in sepsis contribute to loss of vasomotor control. Insulin deficiency results in hyperglycemia and all its respective sequelae, including impaired wound healing, reduced granulocyte function, and increased risk for infections. Furthermore, insulin deficiency impairs inhibition of both proinflammatory cytokine TNF and proinflammatory intracellular signal transduction by *NF-B*, and may impair macrophage function (Dellinger et al., 2013).

Patients with sepsis have an average of two organ systems that are affected or become dysfunctional (Al-Khafija, 2015). This is associated with a mortality of up to 40%. As other organ systems are affected, mortality rates increase by 15-20% with each additional failure (Al-Khafija, 2015). The implication for clinical practice is significant, as early detection and treatment of organ system dysfunction can prevent increasing rates of mortality in patients with severe sepsis. Clinical criteria and laboratory markers can be used to assess the development and progression of MODS in severe sepsis (see **Table 9**).

Table 9: Commonly Employed Markers of Acute Organ System Dysfunction

ORGAN SYSTEM	MARKER OF DYSFUNCTION	UNDERLYING MECHANISM
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Cardiovascular	Tachycardia Dysrhythmias Hypotension Elevated central venous and pulmonary artery pressures	Myocardial depression; altered hemodynamics
Respiratory	Tachypnea Hypoxemia	Altered oxygenation due to capillary leak and impaired gas exchange
Renal	Oliguria Anuria Elevated serum creatinine	Reduced renal perfusion and the onset of acute renal failure/acute kidney injury
Hepatic	Jaundice Elevated serum level of liver enzymes Decreased serum albumin Coagulopathy	Onset of hepatic failure; impaired perfusion; coagulopathies
Hematologic	Thrombocytopenia Coagulopathy Decreased Protein C levels Increased D-dimer levels	Low platelet count is often due to decreased production; coagulopathies develop due to stimulation of the coagulation cascade by proinflammatory mediators or cytokines; Platelet aggregation and thrombi form because of the increased viscosity of the blood.
Neurologic	Altered consciousness Confusion Psychosis	A depressed level of consciousness may occur with sepsis; the specific cause is unknown but may be related to altered perfusion or the effects of cytokines

Adapted from Balk RA. Severe sepsis and septic shock. Definitions, epidemiology, and clinical manifestations. Critical Care Clinics 2000; 16:179-192.

International Considerations

The incidence of sepsis in low middle income countries (LMICs), and its consequent burden of mortality are currently not known (Adhikari et al, 2010). Epidemiological studies of sepsis in the USA and elsewhere were slow to emerge, considering the burden of illness and mortality. In LMICs, no population studies of sepsis exist to date. However, groups at risk of sepsis in LMICs are:

- HIV (Odd Ratio for BSI=3.4, Reddy et al, 2010)
- Maternal complications (approx. 10% of all maternal mortality, Khan et al, 2006)
- Diabetes (25-75% increased risk of sepsis, Hall et al, 2011)
- Hospital Acquired Infections (15% In-patients will contract a nosocomial infection in LMICs, Allegranzi et al, 2010)

LMIC mortality data

- Median (and mean) mortality rates for sepsis and septic shock can be calculated for LMIC's as 44.95% (45.67%) and 53.35% (62.86%) respectively, compared to a severe sepsis mortality rate of 28.6% in the US.
- Brazil – Overall mortality vs. sepsis mortality (21-29% for all cause in hospital mortality vs. 51.6 – 56.8% with severe sepsis; Kauss et al, 2011, Silva et al, 2004).
- Uganda – all cause in-hospital mortality of 15.4% compared to an in-hospital mortality of 23.7% and a 28 day-mortality of 43.0% for patients with sepsis (Jacob et al, 2009).

Specific considerations relate to the ability to confirm a clinical diagnosis in LMICs as there is limited availability to diagnose by blood or other microbiological cultures and the clinical coding may be unreliable or unavailable in many LMICs. Sepsis presents an extraordinary medical and economic challenge for LMICs. With early recognition, aggressive fluid resuscitation and early goal directed therapy; outcome of sepsis can be improved. However, in resource poor settings this can be quite challenging (Kabara et al 2013). The key concepts of sepsis management are potentially translatable to LMIC's and health personnel should be educated in recognition of sepsis early and appropriate antibiotic use. Simple and low-cost standardised laboratory testing should be available, and evidence-based interventions and treatment algorithms tailored to LMIC countries should be developed and validated.

CHECK YOUR PROGRESS: Assess your understanding of key points from the previous sections.

- Cardiogenic shock is caused by inability of the heart to pump adequate amounts of blood to meet cellular needs. It is most often caused by a massive myocardial infarction. Pulmonary edema occurs in cardiogenic shock because blood backs up into the lungs and increases hydrostatic pressure in the pulmonary capillaries.
- Hypovolemic shock is caused by loss of whole blood or plasma from the body or shifting of large amount of fluid out of the vascular space into the interstitial space. The decreased blood volume results in decreased venous return to the heart, decreased cardiac preload, and decreased

cardiac output.

- Anaphylactic shock occurs as a result of a severe systemic allergic reaction. Hypotension in anaphylactic shock is due to massive vasodilation and loss of circulating blood volume caused by increased vascular permeability resulting in fluid leakage out of the vascular compartment.
- Neurogenic shock, which is also called vasogenic shock, occurs when there is disruption of the neural output from the central nervous system to the blood vessels. Head injury or spinal cord injury is a common cause of neurogenic shock.
- Septic shock is caused by a serious systemic infection. In many individuals, septic shock is associated with an intense inflammatory response caused by the infection with cell injury resulting from the inflammation as well as activation of the complement and coagulation systems. However, septic shock can also cause immune paralysis leaving the individual susceptible to a variety of nosocomial infections.
- Multiple organ dysfunction syndrome can occur as an end result of altered perfusion. Mortality rates increase as the number of organ system failures increase. Shock is difficult to reverse once multiple organ dysfunction occurs. Therefore early recognition and treatment to improve organ system perfusion are key components to managing multiple organ dysfunction.

1. What is the most common form of shock?

- a. Cardiogenic
- b. Neurogenic
- c. Septic
- d. Anaphylactic

e. Hypovolemic

Answer: E, hypovolemic shock is the most common form of shock

2. Signs of sepsis include changes in vital signs. Which of the following is not seen in patients with sepsis?

- a. Decreased blood pressure
- b. Increased heart rate
- c. Decreased respiratory rate
- d. Elevated temperature

Answer: C. An increase in respiratory rate is often seen in sepsis due to the development of hypoxemia and a compensatory response to increase oxygenation.

3. Which type of shock can progress rapidly to a life-threatening state?

- a. Cardiogenic
- b. Neurogenic
- c. Septic
- d. Anaphylactic
- e. Hypovolemic

Answer: D, anaphylactic shock can progress rapidly to a life-threatening state due to profound hypotension and airway compromise that can result from bronchoconstriction.

CHAPTER SUMMARY

Shock is a clinical syndrome that results from inadequate oxygenation and tissue perfusion.

Shock is classified based on the etiology into several categories including hypovolemic,

cardiogenic, distributive, or obstructive shock. In shock, a number of cellular, metabolic and hemodynamic alterations occur that result in alterations in oxygen delivery and perfusion. Shock can progress from the initial stage through the compensatory, progressive and refractory stages if compensatory mechanisms are unable to maintain perfusion to vital organs. Cardiogenic shock results from inadequate tissue perfusion from myocardial dysfunction, which leads to cellular hypoxia and ischemia. Cardiogenic shock is often characterized by both systolic and diastolic myocardial dysfunction. Hypovolemic shock, the most common form of shock, results from loss of blood, loss of plasma volume of greater than 20% of the circulating volume, or from profound dehydration. Anaphylactic shock results from an allergic reaction that causes systemic release of IgE (antibody formed as part of immune response) and causes mast cell activation and histamine release

Neurogenic shock, the rarest form of shock, results from loss of peripheral sympathetic vasomotor tone and changes in systemic vascular resistance mediated by a neurologic injury, often due to spinal cord injury.

Sepsis is systemic infection that can progress to septic shock, in which severe hypotension results that is unresponsive to fluid therapy and medical treatment. Multiple organ system dysfunction can result which has a high mortality rate in patients with shock. Treatment goals for shock are focused on improving perfusion along with the ABC's of shock management: airway, breathing and circulation. Additional specific treatment measures based on the type of shock include: fluid and blood replacement for hypovolemic shock; reversal of severe vasodilation due to histamine and mediator release in anaphylactic shock; and antibiotic therapy for septic shock, along with organ support measures such as supplemental oxygenation and

mechanical ventilation, renal replacement therapy for acute renal failure, and other measures to prevent the complications of critical illness.

Key clinical care priority areas include: monitoring patients for evidence of developing shock and organ dysfunction, identifying patients at risk for shock and sepsis, promoting early identification, and instituting treatment measures (Kleinpell et al 2013).

End of Chapter Multiple Choice Questions

1) All of the following except which condition can lead to a state of shock?

- A. Allergic reaction
- B. Severe myocardial infarction
- C. Systemic infection
- D. Pregnancy

Answer: D.

Rationale: While complications of pregnancy such as bleeding can predispose a patient to shock, pregnancy in and of itself does not lead to a state of shock. An allergic reaction can lead to anaphylactic shock. A severe myocardial infarction can predispose a patient to developing cardiogenic shock. A systemic infection can progress to sepsis and septic shock.

2) Which of the following is NOT considered a sign of shock?

- A. Tachycardia
- B. Pale skin
- C. Decreased urine output
- D. Hypertension

Answer: D

Rationale: Hypertension is not considered a sign of shock; rather, hypotension is commonly seen in shock.

Other signs of shock include tachycardia as a compensatory response and a result of sympathetic nervous system activation, pale skin which occurs due to vasoconstriction to maintain perfusion to vital organs, and decreased urine output which results from a decreased cardiac output to the kidneys.

3) What is the primary aim of treatment in shock states?

- A. Increase blood pressure
- B. Decrease heart rate
- C. Increase perfusion
- D. Decrease acidosis

Answer: C

Rationale: The primary aim in the treatment of shock is to increase perfusion. Shock results due to an alteration of perfusion. While hypotension is commonly seen in shock, increasing the blood pressure may not sufficiently increase perfusion. Acidosis may be present in shock but is often a late manifestation.

4) Which of the following is a sign of neurogenic shock that is not seen in other forms of shock?

- A. Hypotension
- B. Hyperthermia
- C. Tachypnea
- D. Bradycardia

Answer: D

Rationale: Bradycardia occurs in neurogenic shock as a result of the loss of normal sympathetic nervous system response and a resultant unopposed vagal tone.

Neurogenic shock is a distributive type of shock resulting in hypotension, occasionally with bradycardia, that is attributed to the disruption of the autonomic pathways within the spinal cord.

5) Which of the following is a first-line agent for treating anaphylactic shock?

- A. Steroids
- B. Antihistamines
- C. Bronchodilators
- D. Epinephrine

Answer: D

Rationale: Epinephrine is a first-line agent for anaphylaxis because it promotes vasoconstriction, along with inhibiting the further release of mediators

Antihistamines, which block the release of histamine, are considered second line agents for treating anaphylactic shock.

Bronchodilators and corticosteroids are also considered second-line agents that reduce additional symptoms including respiratory stridor and wheezing and potentially late-phase reactions.

6) What type of shock is associated with the highest mortality rate?

- A. Cardiogenic
- B. Anaphylactic
- C. Neurogenic
- D. Septic

Answer: D

Rationale: Septic shock is associated with the highest mortality rate – 28% to 50% or more depending on the number of organ systems involved with altered perfusion.

While cardiogenic shock has a high mortality up of to 50%, septic shock mortality rates can exceed 60% or more when 3 or more organs are involved in multiple organ dysfunction syndrome.

7) Which of the following is NOT considered a sign of sepsis?

- A. Tachycardia

- B. Tachypnea
- C. Hypertension
- D. Elevated white blood cell count

Answer: C

Rationale: Hypertension is not considered a sign of sepsis.

The signs of sepsis include tachycardia, or an elevated heart rate, tachypnea, or an elevated respiratory rate, an elevated temperature (or hypothermia) and an elevated white blood cell count and/or greater than 10% bands or immature neutrophils, also termed bandemia.

8) Which of the following is NOT a cause of cardiogenic shock?

- A. Cardiomyopathy
- B. Dysrhythmias
- C. Pericardial tamponade
- D. Cardiac transplant rejection

Answer: D

Rationale: Recognized causes of cardiogenic shock include cardiomyopathies, dysrhythmias and pericardial tamponade.

Cardiac transplant rejection is not associated with cardiogenic shock

9) What term describes sepsis with acute organ dysfunction?

- A. Septic shock
- B. Septicemia

C. Sepsis

D. Multiple organ dysfunction syndrome

Answer: A

Rationale: Septic shock designates progression of sepsis with the manifestation of organ dysfunction.

Septic shock is caused by decreased tissue perfusion and oxygen delivery as a result of severe infection and sepsis and often is manifested by severe hypotension that is unresponsive to treatment.

Septicemia is the medical term referring to the presence of pathogenic organisms in the bloodstream.

Multiple organ dysfunction syndrome (MODS) signifies the involvement of more than one organ system dysfunction due to altered perfusion in severe sepsis. MODS is associated with high mortality rates.

10. Which of the following is NOT a commonly employed marker of acute organ system dysfunction?

A. Jaundice

B. Thrombocytopenia

C. Hypotension

D. Decreased creatinine levels

Answer: D.

Rationale: Increased creatinine levels are a sign of acute organ system dysfunction, specifically acute renal failure or acute kidney injury. Jaundice may be seen due to hepatic dysfunction.

Thrombocytopenia or a decrease in platelets may occur due to decreased production, due to bone marrow suppression. Hypotension is a common presenting sign of acute cardiovascular organ system dysfunction in shock states.

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