

# Pathophysiology and management of different types of shock

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## ABSTRACT

More than 1 million cases of shock are estimated to present to U.S. hospital EDs each year. (1) The presentation may be cryptic, as in the patient with compensated heart failure, or obvious as in the ultimate shock state of cardiac arrest. Despite aggressive treatment, mortality from shock remains high. Approximately 30 to 45 percent of patients in septic shock, and 60 to 90 percent for those with cardiogenic shock, die within 1 month of presentation. (2,3) The definition and treatment of shock continues to evolve. With a contemporary understanding of the disease and new evolving technology, the emergency physician can recognize shock at an earlier stage and initiate expert, timely intervention. The general approach to a patient in the initial stages of shock follows similar principles regardless of the inciting factors or etiology.

**Keywords:** Shock, peripheral circulatory failure, cardiogenic shock ,anaphylactic shock.

### Definition

Shock is defined as circulatory insufficiency that creates an imbalance between tissue oxygen supply and oxygen demand. The result of shock is global tissue hypoperfusion and is associated with a decreased venous oxygen content and metabolic acidosis (lactic acidosis).<sup>(4)</sup>

### Pathophysiology<sup>(4)</sup>

Shock is classified into four categories by etiology:

- (1) Hypovolemic (caused by inadequate circulating volume),
- (2) Cardiogenic (caused by inadequate cardiac pump function),

- (3) Distributive (caused by peripheral vasodilatation and mal distribution of blood flow),
- (4) Obstructive (caused by extra cardiac obstruction to blood flow).

Clinically, shock may have a predominant cause, but as the shock state persists or progresses to irreversible end organ damage, other pathophysiologic mechanisms become operative. Knowledge of the principles of oxygen delivery and consumption is important to the understanding of shock. A maximum of four molecules of oxygen is loaded onto each molecule of hemoglobin as it passes through the lungs. If all available oxygen sites are occupied (four per molecule of hemoglobin), arterial oxygen

saturation (Sao<sub>2</sub>) is 100 percent. Arterial oxygen content (Cao<sub>2</sub>) is the amount of oxygen bound to hemoglobin plus the amount dissolved in plasma. Oxygen is delivered to the tissues by the pumping function (cardiac output) of the heart. Systemic oxygen delivery (Do<sub>2</sub>) is the product of the Cao<sub>2</sub> and cardiac output (CO). Systemic oxygen consumption (Vo<sub>2</sub>) comprises a sensitive balance between supply and demand.

Normally, the tissues consume approximately 25 percent of the oxygen carried on hemoglobin, and venous blood returning to the right heart is approximately 75 percent saturated [mixed venous oxygen saturation (pulmonary artery) (Smvo<sub>2</sub>)].

When oxygen supply is insufficient to meet demand, the first compensatory mechanism is an increase in CO. If the increase in CO is inadequate, the amount of oxygen extracted from hemoglobin by the tissues increases, which decreases Smvo<sub>2</sub>. When compensatory mechanisms fail to correct the imbalance between tissue supply and demand, anaerobic metabolism occurs, resulting in the formation of lactic acid. Lactic acid is rapidly buffered, resulting in the formation of measured lactate; normally between 0.5 and 1.5 mM/L. An elevated lactate level is associated with an Smvo<sub>2</sub> < 50 percent. Most cases of lactic acidosis are a result of inadequate oxygen delivery, but lactic acidosis occasionally can develop from an excessively high oxygen demand, for example, in status epilepticus.

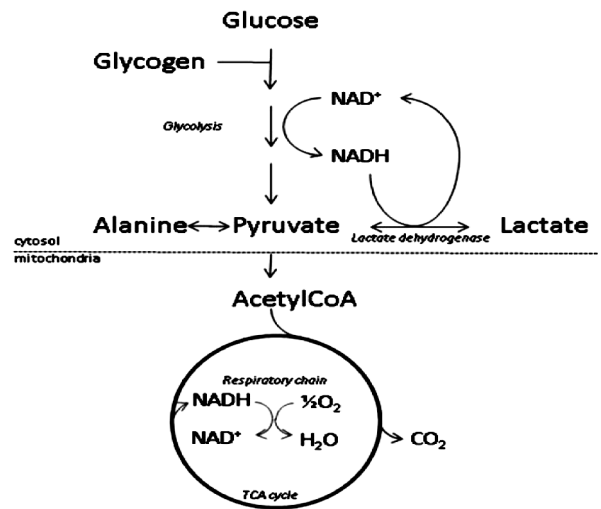
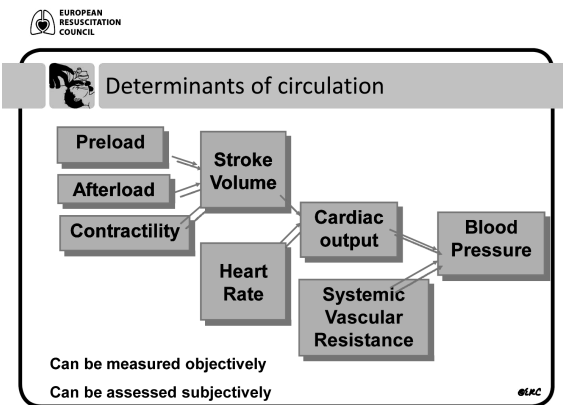


Figure (1) with insufficient oxygen supply, pyruvate will be diverted to lactate, thereby assuring regeneration of NAD<sup>+</sup> from NADH. This will enable glycolysis, and the accompanying ATP production to proceed.<sup>(5)</sup>

In other cases, lactic acidosis occurs because of an impairment in tissue oxygen utilization, as in septic shock and post resuscitation from cardiac arrest; a normal Smvo<sub>2</sub> with an elevated lactate indicates such an impairment. Elevated lactate is a marker of impaired oxygen delivery and/or utilization and correlates with short-term prognosis of critically ill patients in the ED. Smvo<sub>2</sub> can also be used as a measure of the balance between tissue oxygen supply and demand. Smvo<sub>2</sub> is obtained from the pulmonary artery catheter, but similar information can be obtained by central venous blood cannulation (Scvo<sub>2</sub>). Scvo<sub>2</sub> correlates well with Smvo<sub>2</sub> and can be more easily obtained in the ED setting.<sup>(6)</sup>

Shock is usually, but not always, associated with systemic arterial hypotension; i.e., systolic blood pressure less than 90 mm Hg. Pressure is the product of flow and resistance [mean arterial pressure(MAP) = CO X systemic vascular resistance (SVR)]. Blood pressure may not fall if there is increase in peripheral vascular resistance in the presence of decreased cardiac output, resulting in inadequate flow to the tissue or global tissue hypoperfusion. The insensitivity of blood pressure to detect global tissue hypoperfusion has been repeatedly confirmed. Thus, shock may occur with a normal blood pressure, and hypotension may occur without shock.



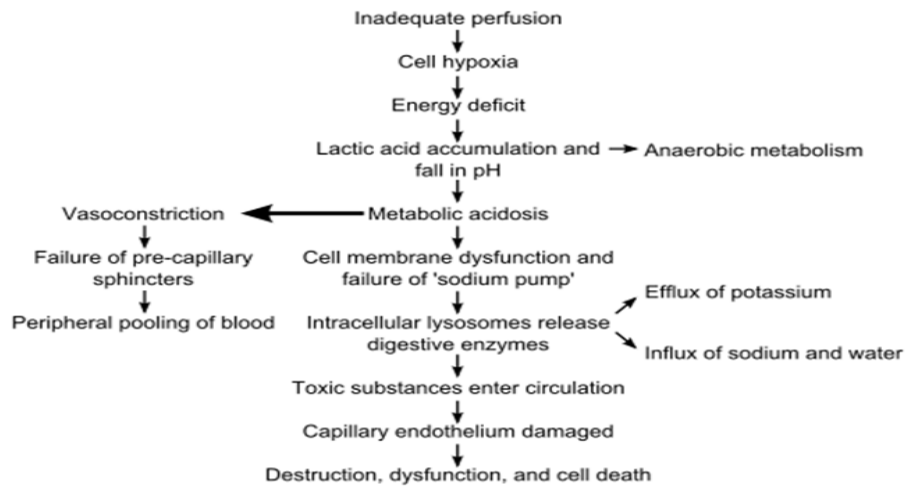
The onset of shock provokes a myriad of autonomic responses, many of which serve to maintain perfusion pressure to vital organs. Stimulation of the carotid baroreceptor stretch reflex activates the sympathetic nervous system leading to

- (1) Arteriolar vasoconstriction, resulting in redistribution of blood flow from the skin, skeletal muscle, kidneys, and splanchnic viscera;
- (2) an increase in heart rate and contractility that increases cardiac output;

- (3) constriction of venous capacitance vessels, which augments venous return;
- (4) release of the vasoactive hormones epinephrine, norepinephrine, dopamine, and cortisol to increase arteriolar and venous tone; and
- (5) release of antidiuretic hormone and activation of the renin-angiotensin axis to enhance water and sodium conservation to maintain intravascular volume. These compensatory mechanisms attempt to maintain Do<sub>2</sub> to the most critical organs—the coronary and cerebral circulation. During this process, blood flow to other organs such as the kidneys and gastrointestinal tract may be compromised.

The cellular response to decreased Do<sub>2</sub> is adenosine triphosphate depletion leading to ion-pump dysfunction, influx of sodium, efflux of potassium, and reduction in membrane resting potential. Cellular edema occurs secondary to increased intracellular sodium, while cellular membrane receptors become poorly responsive to the stress hormones insulin, glucagon, cortisol, and catecholamines.

As shock progresses, lysosomal enzymes are released into the cells with subsequent hydrolysis of membranes, deoxyribonucleic acid, ribonucleic acid, and phosphate esters. As the cascade of shock continues, the loss of cellular integrity and the breakdown in cellular homeostasis result in cellular death. These pathologic events give rise to the metabolic features of hemoconcentration, hyperkalemia, hyponatremia, prerenal azotemia, hyper- or hypoglycemia, and lactic acidosis.



Effects of inadequate perfusion on cell function.

In the early phases of septic shock, these physiologic changes produce a clinical syndrome called the systemic inflammatory response syndrome or SIRS, defined as the presence of two or more of the following features:

- (1) Temperature greater than 38°C (100.4°F) or less than 36°C (96.8°F);
- (2) Heart rate faster than 90 beats/min;
- (3) Respiratory rate faster than 20 breaths/min;
- (4) White blood cell count greater than 12.0 X 10<sup>9</sup>/L, less than 4.0 X 10<sup>9</sup>/L, or with greater than 10 percent immature forms or bands.(7)

As SIRS progresses, shock ensues, followed by multi organ dysfunction syndrome (MODS) manifested by myocardial depression, adult respiratory distress syndrome, disseminated intravascular coagulation, hepatic failure, or renal failure.

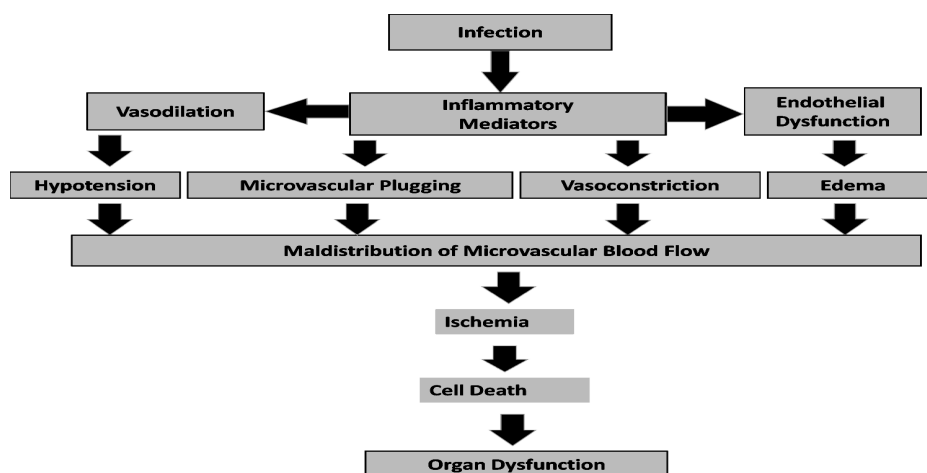


Figure (2) Mechanism of organ dysfunction in sepsis

The fulminate progression from SIRS to MODS is determined by the balance of anti-inflammatory and pro-inflammatory mediators or cytokines that are released from endothelial cell disruption. Global tissue hypoperfusion alone can independently activate the inflammatory response and serve as a co-morbid variable in the pathogenesis of all forms of shock. (8) The failure to diagnose and treat global tissue hypoperfusion in a timely manner leads to an accumulation of an oxygen debt, the magnitude of which correlates with increased mortality.

### **There are four stages of shock**

As it is a complex and continuous condition there is no sudden transition from one stage to the next. (9) At a cellular level, shock is the process of oxygen demand becoming greater than oxygen supply. (10)

#### **Initial**

During this stage, the state of hypoperfusion causes hypoxia. Due to the lack of oxygen, the cells perform lactic acid fermentation. Since oxygen, the terminal electron acceptor in the electron transport chain, is not abundant, this slows down entry of pyruvate into the Krebs cycle, resulting in its accumulation. Accumulating pyruvate is converted to lactate by lactate dehydrogenase and hence lactate accumulates (causing lactic acidosis) figure (1).

#### **Compensatory**

This stage is characterised by the body employing physiological mechanisms, including neural, hormonal and bio-chemical mechanisms in an

attempt to reverse the condition. As a result of the acidosis, the person will begin to hyperventilate in order to rid the body of carbon dioxide (CO<sub>2</sub>). CO<sub>2</sub> indirectly acts to acidify the blood and by removing it the body is attempting to raise the pH of the blood. The baroreceptors in the arteries detect the resulting hypotension, and cause the release of epinephrine and norepinephrine. Norepinephrine causes predominately vasoconstriction with a mild increase in heart rate, whereas epinephrine predominately causes an increase in heart rate with a small effect on the vascular tone; the combined effect results in an increase in blood pressure. The renin-angiotensin axis is activated, and arginine vasopressin (Anti-diuretic hormone; ADH) is released to conserve fluid via the kidneys. These hormones cause the vasoconstriction of the kidneys, gastrointestinal tract, and other organs to divert blood to the heart, lungs and brain. The lack of blood to the renal system causes the characteristic low urine production. However the effects of the renin-angiotensin axis take time and are of little importance to the immediate homeostatic mediation of shock.

#### **Progressive**

Should the cause of the crisis not be successfully treated, the shock will proceed to the progressive stage and the compensatory mechanisms begin to fail. Due to the decreased perfusion of the cells, sodium ions build up within while potassium ions leak out. As anaerobic metabolism continues, increasing the body's metabolic acidosis, the arteriolar smooth muscle and precapillary

sphincters relax such that blood remains in the capillaries.(11) Due to this, the hydrostatic pressure will increase and, combined with histamine release, this will lead to leakage of fluid and protein into the surrounding tissues. As this fluid is lost, the blood concentration and viscosity increase, causing sludging of the micro-circulation. The prolonged vasoconstriction will also cause the vital organs to be compromised due to reduced perfusion.(11) If the bowel becomes sufficiently ischemic, bacteria may enter the blood stream, resulting in the increased complication of endotoxic shock.(11,12)

## Refractory

At this stage, the vital organs have failed and the shock can no longer be reversed. Brain damage and cell death are occurring, and death will occur imminently. One of the primary reasons that shock is irreversible at this point is that much cellular ATP has been degraded into adenosine in the absence of oxygen as an electron receptor in the mitochondrial matrix. Adenosine easily perfuses out of cellular membranes into extracellular fluid, furthering capillary vasodilation, and then is transformed into uric acid. Because cells can only produce adenosine at a rate of about 2% of the cell's total need per hour, even restoring oxygen is futile at this point because there is no adenosine to phosphorylate into ATP.(12)

## Diagnosis

Signs and symptoms: The presentation of shock is variable with some people having only minimal symptoms such as confusion and weakness.(13) While the general signs for all types of shock are

low blood pressure, decreased urine output, and confusion these may not always be present.(14) While a fast heart rate is common, those on  $\beta$ -blockers, those who are athletic and in 30% of cases those with shock due to intra abdominal bleeding may have a normal or slow heart rate. Direct loss of effective circulating blood volume leading to:

- A rapid, weak, thready pulse due to decreased blood flow combined with tachycardia
- Cool, clammy skin due to vasoconstriction .
- Rapid and shallow breathing due to sympathetic nervous system stimulation and acidosis
- Hypothermia due to decreased perfusion and evaporation of sweat
- Thirst and dry mouth, due to fluid depletion
- Cold and mottled skin , especially extremities, due to insufficient perfusion of the skin

The shock index (SI), defined as heart rate divided by systolic blood pressure, is an accurate diagnostic measure that is more useful than hypotension and tachycardia in isolation.(15) Under normal conditions, a number between 0.5 and 0.8 is typically seen. Should that number increase, so does suspicion of an underlying state of shock. Blood pressure alone may not be a reliable sign for shock, as there are times when a person is in circulatory shock but has a stable blood pressure.(12)

Empirical criteria for diagnosis of circulatory shock regardless of the cause ,four of these six criteria should be met(16) :

1. Ill appearance or altered mental status.

2. Heart rate > 100 beat/min .
3. Respiratory rate >20 cycle/min .or paco<sub>2</sub> < 32 mm/hg
4. serum lactate level > 4 mmol/L.
5. Arterial base deficit ? -4meq/L.
6. Arterial hypotension > 20 minutes duration .

The first changes seen in shock is an increased cardiac output followed by a decrease in mixed venous oxygen saturation (SmvO<sub>2</sub>) as measured in the pulmonary artery via a pulmonary artery catheter. Central venous oxygen saturation (ScvO<sub>2</sub>) as measured via a central line correlates well with SmvO<sub>2</sub> and are easier to acquire. If shock progresses anaerobic metabolism will begin to occur with an increased blood lactic acid as the result. While many laboratory tests are typically performed there is no test that either makes or excludes the diagnosis. A chest X-ray or emergency department ultrasound may be

useful to determine volume state.

### Differential diagnosis <sup>(17)</sup>

Shock is a common end point of many medical conditions. It has been divided into four main types based on the underlying cause: hypovolemic, distributive, cardiogenic and obstructive. A few additional classifications are occasionally used including: endocrinologic shock.

**Hypovolemic:** This is the most common type of shock and is caused by insufficient circulating volume. Its primary cause is hemorrhage (internal and/or external), or loss of fluid from the circulation. Vomiting and diarrhea are the most common cause in children.. With other causes including burns, environmental exposure and excess urine loss due to diabetic ketoacidosis and diabetes insipidus.

Table (I): Classes of hemorrhage.

Class	Blood loss	Response	Treatment
I	<15 %(0.75 l)	min. fast heart rate, normal blood pressure	minimal
II	15-30 %(0.75-1.5 l)	fast heart rate, min. low blood pressure	intravenous fluids
III	30-40 %(1.5-2 l)	very fast heart rate, low blood pressure, confusion	fluids and packed RBCs
IV	>40 %(>2 l)	critical blood pressure and heart rate	aggressive interventions

## Cardiogenic

This type of shock is caused by the failure of the heart to pump effectively. This can be due to damage to the heart muscle, most often from a large myocardial infarction. Other causes of cardiogenic shock include dysrhythmias, cardiomyopathy/myocarditis, congestive heart failure (CHF), or cardiac valve problems.

### Obstructive

Obstructive shock is due to obstruction of blood flow outside of the heart.(18)Several conditions can result in this form of shock.

- Cardiac tamponade in which fluid in the pericardium prevents inflow of blood into the heart (venous return). Constrictive pericarditis, in which the pericardium shrinks and hardens, is similar in presentation.
- Tension pneumothorax Through increased intrathoracic pressure, blood flow to the heart is prevented (venous return).
- Pulmonary embolism is the result of a thromboembolic incident in the blood vessels of the lungs and hinders the return of blood to the heart.
- Aortic stenosis hinders circulation by obstructing the ventricular outflow tract

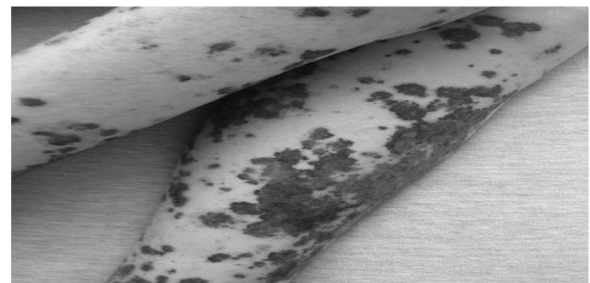
## Distributive

Distributive shock is due to impaired utilization of oxygen and thus production of energy by the cell. Examples of this form of shock are:

- Septic shock is the most common cause of distributive shock.(19) Caused by an overwhelming systemic infection resulting in vasodilation leading to hypotension. Septic shock can be caused by Gram negative bacteria such as (among others) Escherichia coli, Proteus species, Klebsiella

pneumoniae which release an endotoxin which produces adverse biochemical, immunological and occasionally neurological effects which are harmful to the body, and other Gram-positive cocci, such as pneumococci and streptococci, and certain fungi as well as Gram-positive bacterial toxins.

Septic shock also includes some elements of cardiogenic shock. Septic shock can be defined as "sepsis-induced hypotension (systolic blood pressure <90 mm Hg or a reduction of 40 mm Hg from baseline) despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may have a normalized blood pressure at the time that perfusion abnormalities are identified.



**Figure (1) petechial haemorrhage  
in case of sepsis.**

Early detection<sup>(20)</sup>

The qSOFA Score was introduced by the Sepsis-3 group in February 2016 as a simplified version of the SOFA Score as an initial way to screen for sepsis.

The qSOFA Score is an easy to use and apply score to help as an initial screening tool for poor outcome in infection patients.

qSOFA, ie, alteration in mental status, systolic



blood pressure  $\geq 100$  mm Hg, or respiratory rate  $\geq 22$ /min.

septic shock

- can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP  $\geq 65$  mm Hg and having a serum lactate level  $> 2$  mmol/L (18 mg/dL) despite adequate volume resuscitation.
- With these criteria, hospital mortality is in excess of 40%.

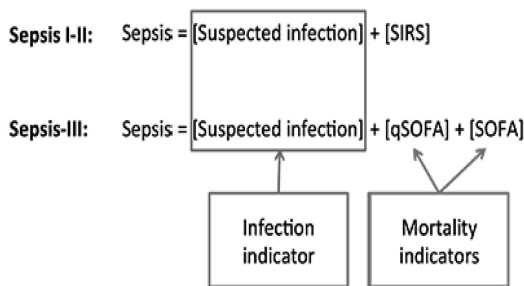


Figure (3) new definition of sepsis according to The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).

**Anaphylactic shock** (17,67):

Anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction. Characterized by rapidly developing life-threatening airway and or breathing and or circulation problems usually associated with skin and mucosal changes.



Figure (2,3) show skin and mucosal changes with anaphylaxis

Caused by a severe anaphylactic reaction to an allergen, antigen, drug or foreign protein causing the release of histamine which causes widespread vasodilation, leading to hypotension and increased capillary permeability.

- Neurogenic shock: High spinal injuries may cause neurogenic shock.<sup>(21)</sup> The classic symptoms include a slow heart rate due to loss of cardiac sympathetic tone and warm skin due to dilation of the peripheral blood vessels. (This term can be confused with spinal shock which is a recoverable loss of function of the spinal cord after injury and does not refer to the haemodynamic instability per se.)



Cervical spine MRI of a patient with SCI: C4 fracture and dislocation, spinal cord compression

Low blood pressure occurs due to decreased systemic vascular resistance resulting in pooling of blood within the extremities lacking sympathetic tone. The slowed heart rate results from unopposed vagal activity and has been found to be exacerbated by hypoxia and endobronchial suction.<sup>(22)</sup> Neurogenic shock can be a potentially devastating complication, leading to organ dysfunction and death if not promptly recognized and treated. It is not to be confused with spinal shock, which is not circulatory in nature.

**Causes:** Neurogenic shock can result from severe central nervous system damage (brain injury, cervical or high thoracic spinal cord).<sup>(23)</sup> In more simple terms: the trauma causes a sudden loss of background sympathetic stimulation to the blood vessels. This causes them to relax (vasodilation)<sup>(24)</sup> resulting in a sudden decrease in blood pressure (secondary to a decrease in peripheral vascular resistance). Neurogenic shock results from damage to the spinal cord above the level of the 6th thoracic vertebra.<sup>(25)</sup> It is found in about half of people who suffer spinal cord injury within the first 24 hours, and usually doesn't go away for one to three weeks.<sup>(25)</sup>

**Endocrine:** Based on endocrine disturbances such as:<sup>(26)</sup>

- Hypothyroidism (Can be considered a form of Cardiogenic shock) in critically ill

patients, reduces cardiac output and can lead to hypotension and respiratory insufficiency.

- Thyrotoxicosis (Cardiogenic shock)
  - may induce a reversible cardiomyopathy.
- Acute adrenal insufficiency (Distributive shock) is frequently the result of discontinuing corticosteroid treatment without tapering the dosage. However, surgery and inter current disease in patients on corticosteroid therapy without adjusting the dosage to accommodate for increased requirements may also result in this condition.
- Relative adrenal insufficiency (Distributive shock) in critically ill patients where present hormone levels are insufficient to meet the higher demands

SHOCK COMPARISON

Type of Shock	Causes:	Pathophysiology	Signs and Symptoms
Hypovolemic	Body Fluid Depletion— <ul style="list-style-type: none"> <li>• Hemorrhage Internal External</li> <li>• Dehydration</li> </ul>	Too little blood volume causes a MAP ↓ so that body's need for tissue oxygenation is not met.  (↓CO ↓CVP ↓PAP ↓PCWP)	↑ Respirations Weak, rapid pulse ↓ blood pressure ↓ O2 saturation Skeletal muscle weakness Cyanotic, cold, clammy skin Changes in H&H  Prolonged Capillary Refill ↓ or absent urine output Thirst, agitation, anxiety Confusion, lethargy Pain Respiratory Acidosis ↓ deep tendon reflexes
Cardiogenic	Direct Pump Failure <ul style="list-style-type: none"> <li>• MI, Cardiac Arrest</li> <li>• Ventricular Dysrhythmia</li> </ul>	Heart cannot contract effectively Fluid volume not affected  ↓ CO ↓ Afterload → ↓ MAP  (↓ CO ↑ CVP ↑ PAP ↑ PCWP)	Tachycardia Hypotension Tachypnea BP < 90 mm Hg, or 30 mm Hg less than baseline Cold, clammy skin with poor peripheral circulation Continuing chest discomfort  Urine output < 30 mL per hour Agitation, restlessness, or confusion Pulmonary Congestion
Distributive	Decreased Vascular Volume or Tone <ul style="list-style-type: none"> <li>• Neural Sympathetic stimulation of nerves controlling blood vessels is decreased, smooth vessel muscles relax causing vasodilation</li> <li>• Chemical Anaphylaxis Sepsis Capillary Leak Syndrome</li> </ul>	Vasodilation with pooling causes decreased preload and decreases in stroke volume and CO  Fluid shifted from central Vascular space  Anaphylactic: (↓CO ↓CVP ↓PAP ↓PCWP)  Early Sepsis: (↑CO normal or ↑ PAP + PCWP) Late Sepsis: (↓CO ↓CVP ↓PAP ↓PCWP)	Anaphylactic: damage to cells causes release of histamine which dilates vessels and increases capillary permeability causing severe hypovolemia and vascular collapse. Decreased contractility and dysrhythmias occur. Bronchial edema and pulmonary obstruction. Whole body hypoxia.  Septic: Associated with DIC. Toxins and endotoxins released into blood cause Systemic Inflammatory Response Syndrome. Metabolism becomes aerobic because of ↓ MAP, clot formation in capillaries and poor cell uptake of O2.  Capillary Leak: fluid shift from blood to interstitial space.
Obstructive	Indirect Pump Failure <ul style="list-style-type: none"> <li>• Cardiac tamponade</li> <li>• Pulmonary embolus</li> </ul>	Cardiac function decreased by non-cardiac factors Total body fluid volume not affected  (↓ CO ↑ CVP ↑ PAP ↑ PCWP)	Cardiac tamponade: JVD, Paradoxical Pulse, ↓CO, muffled heart sounds.  Pulmonary embolus: sudden onset dyspnea, pleuritic chest pain, apprehension, restlessness, cough, feeling of impending doom, hemoptysis, tachypnea, crackles, S3 or S4, diaphoresis, low grade fever, petechiae on chest and axillae, ↓ SaO2

<b>Hypovolemic</b>	Hypotension, tachycardia Weak thready pulse Cool, pale, moist skin U/O decreased	Decreased CO <b>Increased SVR</b>
<b>Cardiogenic</b>	Hypotension, tachycardia Weak thready pulse Cool, pale, moist skin U/O < 30 ml/hr Crackles, tachypnea	Decreased CO <b>Increased SVR</b>
<b>Neurogenic</b>	Hypotension, BRADYCARDIA <b>WARM DRY SKIN</b>	Decreased CO <b>Venous &amp; arterial vasodilation, loss sympathetic tone</b>
<b>Anaphylactic</b>	Hypotension, tachycardia Cough, dyspnea Pruritus, urticaria Restlessness, decreased LOC	Decreased CO <b>Decreased SVR</b>
<b>Septic</b>	Hypotension, Tachycardia Full bounding pulse, tachypnea <b>Pink, warm, flushed skin</b> Decreased U/O, fever	<b>Decreased CO,</b> <b>Decreased SVR</b>

### Initial Approach to the Patient in Shock(27)

As any critically ill patient follow ABCDE approach in our management (airway, breathing, circulation, disability, and exposure). Early, adequate hemodynamic support of patients in shock is crucial to prevent worsening organ dysfunction and failure. Resuscitation should be started even while investigation of the cause is ongoing. Once identified, the cause must be corrected rapidly (e.g., control of bleeding, percutaneous coronary intervention for coronary syndromes, thrombolysis or embolectomy for massive pulmonary embolism, and administration

of antibiotics and source control for septic shock). Unless the condition is rapidly reversed, an arterial catheter should be inserted for monitoring of arterial blood pressure and blood sampling, plus a central venous catheter for the infusion of fluids and vasoactive agents and to guide fluid therapy.

The initial management of shock is problem-oriented, and the goals are therefore the same, regardless of the cause, although the exact treatments that are used to reach those goals may differ. A useful mnemonic to describe the important components of resuscitation is the VIP rule(28) : ventilate (oxygen administration),



infuse (fluid resuscitation), and pump (administration of vasoactive agents).

## Ventilatory Support

The administration of oxygen should be started immediately to increase oxygen delivery and prevent pulmonary hypertension. Pulse oximetry is often unreliable as a result of peripheral vasoconstriction, and precise determination of oxygen requirements will often require blood gas monitoring. Mechanical ventilation by means of a mask rather than endotracheal intubation has a limited place in the treatment of shock because technical failure can rapidly result in respiratory and cardiac arrest. Hence, endotracheal intubation should be performed to provide invasive mechanical ventilation in nearly all patients with severe dyspnea, hypoxemia, or persistent or worsening acidemia (pH, <7.30).

Invasive mechanical ventilation has the additional benefits of reducing the oxygen demand of respiratory muscles and decreasing left ventricular afterload by increasing intrathoracic pressure. An abrupt decrease in arterial pressure after the initiation of invasive mechanical ventilation strongly suggests hypovolemia and a decrease in venous return. The use of sedative agents should be kept to a minimum to avoid further decreases in arterial pressure and cardiac output.

## Fluid Resuscitation

Fluid therapy to improve microvascular bloodflow and increase cardiac output is an essential part of the treatment of any form of shock. Even patients with cardiogenic shock may

benefit from fluids, since acute edema can result in a decrease in the effective intravascular volume. However, fluid administration should be closely monitored, since too much fluid carries the risk of edema with its unwanted consequences. Pragmatic end points for fluid resuscitation are difficult to define. In general, the objective is for cardiac output to become preload-independent (i.e., on the plateau portion of the Frank-Starling curve), but this is difficult to assess clinically.

In patients receiving mechanical ventilation, signs of fluid responsiveness may be identified either directly from beat-by-beat stroke-volume measurements with the use of cardiac-output monitors or indirectly from observed variations in pulse pressure on the arterial-pressure tracing during the ventilator cycle. However, such bedside inferences have some limitations (29)—notably, that the patient must receive ventilation with relatively large tidal volumes, have no spontaneous breathing effort (which usually requires the administration of sedatives or even muscle relaxants), and be free of major arrhythmia and right ventricular dysfunction. A passive leg-raising test is an alternative method (30) but requires a rapid response device, since the effect is transient. Regardless of the test used, there remains a gray zone in which it is difficult to predict a patient's response to intravenous fluids. A fluid-challenge technique should be used to determine a patient's actual response to fluids, while limiting the risks of adverse effects. A fluid challenge incorporates four elements that should be defined in advance. (31)

- First, the type of fluid must be selected.

Crystalloid solutions are the first choice, because they are well tolerated and cheap. The use of albumin to correct severe hypoalbuminemia may be reasonable in some patients.(32)

- Second, the rate of fluid administration must be defined. Fluids should be infused rapidly to induce a quick response but not so fast that an artificial stress response develops; typically, an infusion of 300 to 500 ml of fluids administered during a period of 20 to 30 minutes. (33)
- Third, the objective of the fluid challenge must be defined. In shock, the objective is usually an increase in systemic arterial pressure, although it could also be a decrease in heart rate or an increase in urine output.
- Finally, the safety limits must be defined. Pulmonary edema is the most serious complication of fluid infusion. Although it is not a perfect guideline, a limit in central venous pressure of a few millimeters of mercury above the baseline value is usually set to prevent fluid overload. (34)

Stimulation of the patient and any other change in therapy should be avoided during the test. Fluid challenges can be repeated as required but must be stopped rapidly in case of non-response in order to avoid fluid overload.

## Vasoactive Agents

### *Vasopressors*

If hypotension is severe or if it persists despite fluid administration, the use of vasopressors is indicated. It is acceptable practice to administer a vasopressor temporarily while fluid resuscitation is ongoing, with the aim of discontinuing it, if possible, after hypovolemia

has been corrected.

Adrenergic agonists are the first-line vasopressors because of their rapid onset of action, high potency, and short half-life, which allows easy dose adjustment. Stimulation of each type of adrenergic receptor has potentially beneficial and harmful effects. For example,  $\beta$ -adrenergic stimulation can increase blood flow but also increases the risk of myocardial ischemia as a result of increased heart rate and contractility. Hence, the use of isoproterenol, a pure  $\alpha$ -adrenergic agent, is limited to the treatment of patients with severe bradycardia.

At the other extreme,  $\beta$ -adrenergic stimulation will increase vascular tone and blood pressure but can also decrease cardiac output and impair tissue blood flow, especially in the hepatosplanchnic region. For this reason, phenylephrine, an almost pure  $\alpha$ -adrenergic agent, is rarely indicated.

We consider norepinephrine to be the vasopressor of first choice; it has predominantly  $\beta$ -adrenergic properties, but its modest  $\alpha$ -adrenergic effects help to maintain cardiac output. Administration generally results in a clinically significant increase in mean arterial pressure, with little change in heart rate or cardiac output. The usual dose is 0.1 to 2.0  $\mu$ g per kilogram of body weight per minute.

Dopamine has predominantly  $\beta$ -adrenergic effects at lower doses and  $\alpha$ -adrenergic effects at higher doses, but its effects are relatively weak. Dopaminergic effects at very low doses (<3  $\mu$ g per kilogram per minute, given intravenously) may selectively dilate the hepatosplanchnic and renal circulations, but controlled trials have not

shown a protective effect on renal function,(35) and its routine use for this purpose is no longer recommended.

Dopaminergic stimulation may also have undesired endocrine effects on the hypothalamic-pituitary system, resulting in immunosuppression, primarily through a reduction in the release of prolactin.

In a recent randomized, controlled, double blind trial, dopamine had no advantage over norepinephrine as the first-line vasopressor agent; moreover, it induced more arrhythmias and was associated with an increased 28-day rate of death among patients with cardiogenic shock.(36) Administration of dopamine, as compared with norepinephrine, may also be associated with higher rates of death among patients with septic shock.(37) Hence, we no longer recommend dopamine for the treatment of patients with shock. Epinephrine, which is a stronger agent, has predominantly  $\beta$ -adrenergic effects at low doses, with  $\alpha$ -adrenergic effects becoming more clinically significant at higher doses. However, epinephrine administration can be associated with an increased rate of arrhythmia(38,39) and a decrease in splanchnic blood flow(38) and can increase blood lactate levels, probably by increasing cellular metabolism.(38,40)

Prospective, randomized studies have not shown any beneficial effects of epinephrine over norepinephrine in septic shock.(39,40) We reserve epinephrine as a second-line agent for severe cases. (34)

The use of other strong vasopressor agents as continuous infusions (e.g., angiotensin or metaraminol) has largely been abandoned.

Non selective inhibition of nitric oxide has not been shown to be beneficial in patients with cardiogenic shock(41) and is detrimental in patients with septic shock. (42)

Vasopressin deficiency can develop in patients with very hyperkinetic forms of distributive shock, and the administration of low-dose vasopressin may result in substantial increases in arterial pressure. In the Vasopressin and Septic Shock Trial (VASST), investigators found that the addition of low-dose vasopressin to norepinephrine in the treatment of patients with septic shock was safe(43) and may have been associated with a survival benefit for patients with forms of shock that were not severe and for those who also received glucocorticoids. (44) Vasopressin should not be used at doses higher than 0.04 U per minute and should be administered only in patients with a high level of cardiac output.

Terlipressin, an analogue of vasopressin, has a duration of action of several hours, as compared with minutes for vasopressin. For this reason, we do not believe it offers an advantage over vasopressin in the ICU. Vasopressin derivatives with more selective V1-receptor activity are currently being studied.

### *Inotropic Agents*

We consider dobutamine to be the inotropic agent of choice for increasing cardiac output, regardless of whether norepinephrine is also being given. With predominantly  $\beta$ -adrenergic properties, dobutamine is less likely to induce tachycardia than isoproterenol. An initial dose of just a few micrograms per kilogram per minute may

substantially increase cardiac output. Intravenous doses in excess of 20 µg per kilogram per minute usually provide little additional benefit.

Dobutamine has limited effects on arterial pressure, although pressure may increase slightly in patients with myocardial dysfunction as the primary abnormality or may decrease slightly in patients with underlying hypovolemia. Instead of routine administration of a fixed dose of dobutamine to increase oxygen delivery to supranormal, predetermined levels, the dose should be adjusted on an individual basis to achieve adequate tissue perfusion. Dobutamine may improve capillary perfusion in patients with septic shock, independent of its systemic effects. (45) Phosphodiesterase type III inhibitors, such as milrinone and enoximone, combine inotropic and vasodilating properties.

By decreasing the metabolism of cyclic AMP, these agents may reinforce the effects of dobutamine. They may also be useful when β-adrenergic receptors are down regulated or in patients recently treated with beta-blockers. However, phosphodiesterase type III inhibitors may have unacceptable adverse effects in patients with hypotension, and the long half-lives of these agents (4 to 6 hours) prevent minute-to-minute adjustment. Hence, intermittent, short-term infusions of small doses of phosphodiesterase III inhibitors may be preferable to a continuous infusion in shock states. Levosimendan, a more expensive agent, acts primarily by binding to cardiac troponin C and increasing the calcium sensitivity of myocytes, but it also acts as a vasodilator by opening ATP sensitive potassium channels in vascular smooth muscle. However,

this agent has a half-life of several days, which limits the practicality of its use in acute shock states.

### *Vasodilators*

By reducing ventricular after load, vasodilating agents may increase cardiac output without increasing myocardial demand for oxygen. The major limitation of these drugs is the risk of decreasing arterial pressure to a level that compromises tissue perfusion. Nevertheless, in some patients, prudent use of nitrates and possibly other vasodilators may improve microvascular perfusion and cellular function. (46)

### *Mechanical Support*

Mechanical support with intraaortic balloon counterpulsation (IABC) can reduce left ventricular afterload and increase coronary blood flow. However, a recent randomized, controlled trial showed no beneficial effect of IABC in patients with cardiogenic shock, (47) and its routine use in cardiogenic shock is not currently recommended.

Venoarterial extracorporeal membrane oxygenation (ECMO) may be used as a temporary lifesaving measure in patients with reversible cardiogenic shock or as a bridge to heart transplantation. (48)

### **Goals of Hemodynamic Support**

#### **Arterial Pressure**

The primary goal of resuscitation should be not only to restore blood pressure but also to provide

adequate cellular metabolism, for which the correction of arterial hypotension is a prerequisite. Restoring a mean systemic arterial pressure of 65 to 70 mm Hg is a good initial goal, but the level should be adjusted to restore tissue perfusion, assessed on the basis of mental status, skin appearance, and urine output, as described above. In patients with oliguria, in particular, the effects of a further increase in arterial pressure on urine output should be assessed regularly, unless acute renal failure is already established. Conversely, a mean arterial pressure lower than 65 to 70 mm Hg may be acceptable in a patient with acute bleeding who has no major neurologic problems, with the aim of limiting blood loss and associated coagulopathy, until the bleeding is controlled.

### Cardiac Output and Oxygen Delivery

Since circulatory shock represents an imbalance between oxygen supply and oxygen requirements, maintaining adequate oxygen delivery to the tissues is essential, but all the strategies to achieve this goal have limitations. After correction of hypoxemia and severe anemia, cardiac output is the principal determinant of oxygen delivery, but the optimal cardiac output is difficult to define. Cardiac output can be measured by means of various techniques, each of which has its own benefits and drawbacks(49). Absolute measures of cardiac output are less important than monitoring trends in response to interventions such as a fluid challenge.

The targeting of a predefined cardiac output is not advisable, since the cardiac output that is needed will vary among patients and in the same patient over time. Measurements of

mixed venous oxygen saturation(SvO<sub>2</sub>) may be helpful in assessing the adequacy of the balance between oxygen demand and supply; SvO<sub>2</sub> measurements are also very useful in the interpretation of cardiac output.(50) SvO<sub>2</sub> is typically decreased in patients with low-flow states or anemia but is normal or high in those with distributive shock. Its surrogate, central venous oxygen saturation (ScvO<sub>2</sub>), which is measured in the superior vena cava by means of a central venous catheter, reflects the oxygen saturation of the venous blood from the upper half of the body only. Under normal circumstances, ScvO<sub>2</sub> is slightly less than SvO<sub>2</sub>, but in critically ill patients it is often greater. Rivers et al. (51) found that in patients presenting to the emergency department with septic shock, a treatment algorithm targeting an ScvO<sub>2</sub> of at least 70% during the first 6 hours was associated with decreased rates of death. The robustness of this finding is currently being evaluated in three multicenter trials. (ClinicalTrials.gov numbers, NCT00975793 and NCT00510835; and Current Controlled Trials number, ISRCTN36307479).

### Blood Lactate Level

An increase in the blood lactate level reflects abnormal cellular function. In low-flow states, the primary mechanism of hyperlactatemia is tissue hypoxia with development of anaerobic metabolism, but in distributive shock, the pathophysiology is more complex and may also involve increased glycolysis and inhibition of pyruvate dehydrogenase.

In all cases, alterations in clearance can be due to impaired liver function. The value of



serial lactate measurements in the management of shock has been recognized for 30 years. (52) Although changes in lactate take place more slowly than changes in systemic arterial pressure or cardiac output, the blood lactate level should decrease over a period of hours with effective therapy. In patients with shock and a blood lactate level of more than 3 mmol per liter, Jansen et al. (46) found that targeting a decrease of at least 20% in the blood lactate level over a 2-hour period seemed to be associated with reduced in-hospital mortality.

### Microcirculatory Variables

The development of hand held devices for orthogonal polarization spectral (OPS) imaging and its successor, side stream dark-field (SDF) imaging, is providing new means of directly visualizing the microcirculation and evaluating the effects of interventions on microcirculatory flow in easily accessible surfaces, such as the sublingual area. (53) Microcirculatory changes, including decreased capillary density, a reduced proportion of perfused capillaries, and increased heterogeneity of blood flow, have been identified in various types of circulatory shock, and the persistence of these alterations is associated with worse outcomes. (54)

Near-infrared spectroscopy is a technique that uses near-infrared light to determine tissue oxygen saturation from the fractions of oxyhemoglobin and deoxyhemoglobin. Analysis of the changes in tissue oxygen saturation during a brief episode of forearm ischemia can be used to quantify micro vascular dysfunction(55); such alterations are associated with worse outcomes.(56)

Various therapeutic interventions have been shown to have an effect on these microcirculatory variables, but whether therapy that is guided by monitoring or targeting the micro circulation can improve outcomes requires further study and cannot be recommended at this time.

### Therapeutic Priorities and Goals

There are essentially four phases in the treatment of shock, and therapeutic goals and monitoring need to be adapted to each phase.

- In the first (salvage) phase, the goal of therapy is to achieve a minimum blood pressure and cardiac output compatible with immediate survival. Minimal monitoring is needed; in most cases, invasive monitoring can be restricted to arterial and central venous catheters. Lifesaving procedures (e.g., surgery for trauma, pericardial drainage, revascularization for acute myocardial infarction, and antibiotics for sepsis) are needed to treat the underlying cause.
- In the second (optimization) phase, the goal is to increase cellular oxygen availability, and there is a narrow window of opportunity for intervention targeting hemodynamic status. (51) Adequate hemodynamic resuscitation reduces inflammation, mitochondrial dysfunction, and caspase activation. (57,58) Measurements of SvO<sub>2</sub> and lactate levels may help guide therapy, and monitoring of cardiac output should be considered.
- In the third (stabilization) phase, the goal is to prevent organ dysfunction, even after hemodynamic stability has been achieved. Oxygen supply to the tissues is no longer the key problem, and organ support becomes more relevant.

• Finally, in the fourth (de escalation) phase, the goal is to wean the patient from vasoactive agents and promote spontaneous polyuria or provoke fluid elimination through the use of diuretics or ultra filtration to achieve a negative fluid balance.

**Treatment goals**

The goal of treatment is to achieve a urine output of greater than 0.5 ml/kg/h, a central venous pressure of 8-12 mmHg and a mean arterial pressure of 65-95 mmHg. In trauma the goal is to stop the bleeding which in many cases requires surgical interventions.

For those with haemorrhagic shock the current evidence supports limiting the use of fluids for penetrating thorax and abdominal injuries allowing mild hypotension to persist

(known as permissive hypotension).(59)Targets include a mean arterial pressure of 60 mmHg, a systolic blood pressure of 70-90 mmHg.(60) or until their adequate mentation and peripheral pulses.(60)

**End Points of Resuscitation**

**Classic / Traditional**

- o Restoration of blood pressure
- o Normalization of heart rate and urine output
- o Appropriate mental status

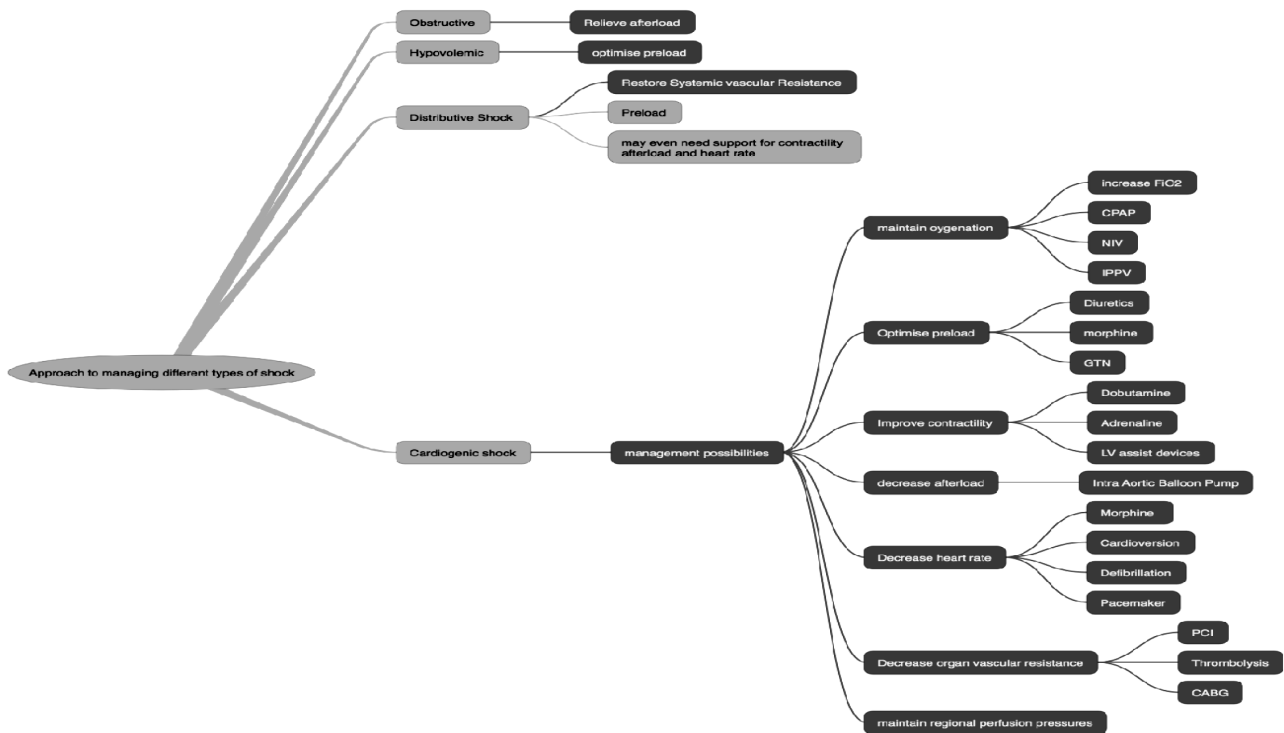
**Improved / Global**

- o All of the above plus
- o Normalization of serum lactate levels
- o Resolution of base deficit
- o Adequate - MVS

**Goal directed approach**

- o Urine output > 0.5 mL/kg/hr
- o CVP 5 -10 cm H2o
- o MAP 65 to 90 mmHg
- o Central venous oxygen concentration > 70%

**Specific treatment for different type of shock**



**Management Hypovolemic shock:**

Management may include securing the airway via intubation to decrease the work of breathing, oxygen supplementation, intravenous fluids and blood transfusions. It is important to keep the person warm as well as adequately manage pain and anxiety as these can increase oxygen consumption.

**Fluids** Aggressive intravenous fluids are recommended in most types of shock (e.g. 1-2 liter normal saline bolus over 10 minutes or 20ml/kg in a child) which is usually instituted as the person is being further evaluated(61) Which intravenous fluid is superior, colloids or crystalloids, remains undetermined. Thus as crystalloids are less expensive they are recommended.

If the person remains in shock after initial resuscitation packed red blood cells should be administered to keep the hemoglobin greater than 10gms/l. For those with hemorrhagic shock the

current evidence supports limiting the use of fluids for penetrating thorax and abdominal injuries allowing mild hypotension to persist (known as permissive hypotension). (62) Targets include a mean arterial pressure of 60 mmHg, a systolic blood pressure of 70-90 mmHg, or until their adequate mentation and peripheral pulses.

**Medications** Vasopressors may be used if blood pressure does not improve with fluids. There is no evidence of superiority of one vasopressor over another. (63) Vasopressors have not been found to improve outcomes when used for hemorrhagic shock from trauma, but may be of use in neurogenic shock. Activated protein C (Xigris) while once aggressively promoted for the management of septic shock has been found to improve survival ,thus recommended. (64) The use of sodium bicarbonate is controversial as it has not been shown to improve outcomes. (65) If used at all it should only be considered if the pH is less than 7.0.

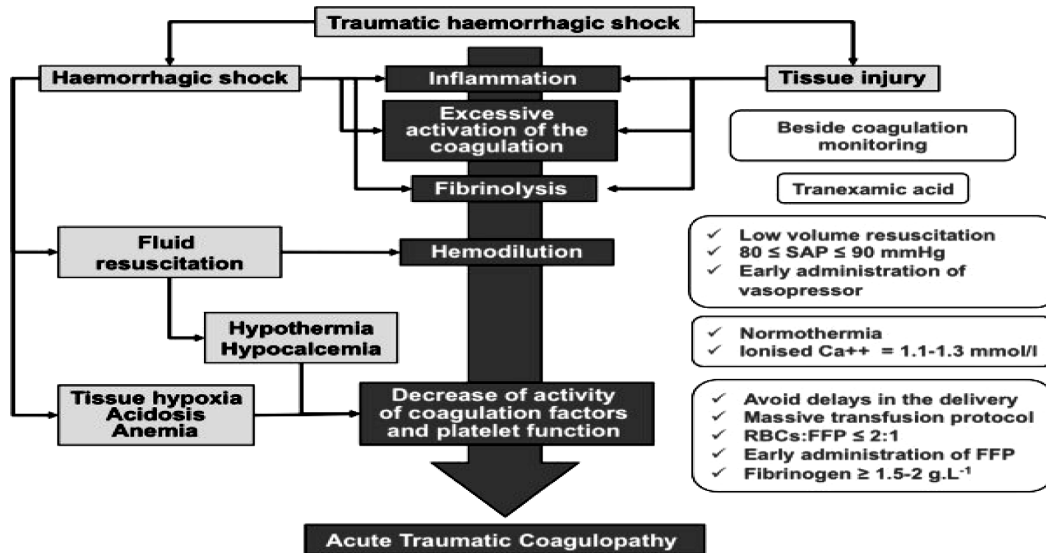


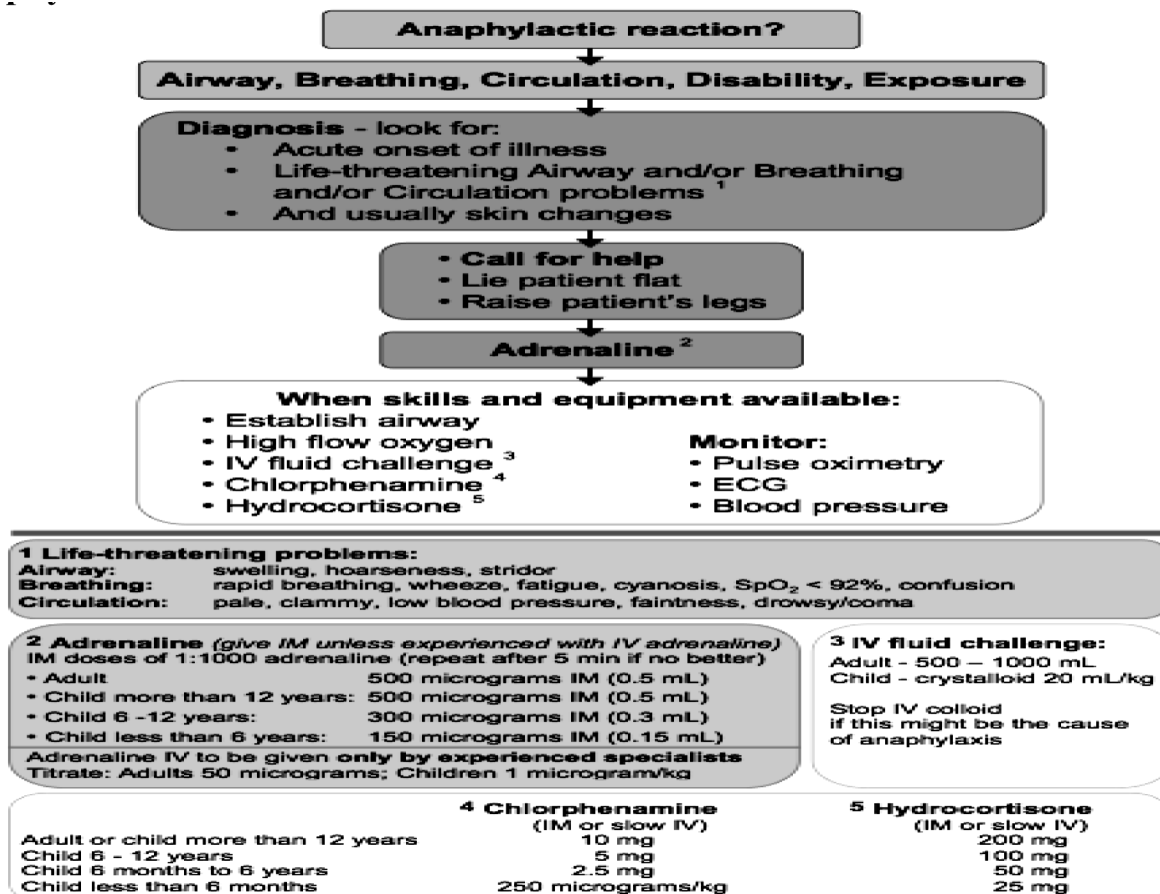
Figure (3) show The main pathophysiological mechanisms involved in acute traumatic coagulopathy and transfusion strategy. SAP, systolic arterial pressure; RBC, red blood cells; FFP, fresh-frozen plasma(66).

**Septic shock:(20)** The leadership of the Surviving Sepsis Campaign (SSC) has believed since its inception that both the SSC Guidelines and the SSC performance improvement indicators will evolve as new evidence that improves our

understanding of how best to care for patients with septic shock the SSC Executive Committee has revised the improvement bundles as follows:

- SURVIVING SEPSIS CAMPAIGN BUNDLES
- TO BE COMPLETED WITHIN 3 HOURS:
  - 1) Measure lactate level
  - 2) Obtain blood cultures prior to administration of antibiotics
  - 3) Administer broad spectrum antibiotics
  - 4) Administer 30 mL/kg crystalloid for hypotension or lactate 4mmol/L
- TO BE COMPLETED WITHIN 6 HOURS:
  - 5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) 65 mm Hg
  - 6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate 4 mmol/L (36 mg/dL):
    - Measure central venous pressure (CVP)\*
    - Measure central venous oxygen saturation (ScvO2)\*
  - 7) Remeasure lactate if initial lactate was elevated\*
    - \*Targets for quantitative resuscitation included in the guidelines are CVP of 8 mm Hg,
    - ScvO2 of 70%, and normalization of lactate.

## Anaphylaxis(67)



## Cardiogenic shock

Cardiogenic shock is defined by sustained low blood pressure with tissue hypo perfusion despite adequate left ventricular filling pressure. Signs of tissue hypoperfusion include low urine production (<30 mL/hour), cool extremities, and altered level of consciousness.

Treatment of cardiogenic shock depends on the cause. If cardiogenic shock is due to a heart attack, attempts to open the heart's arteries may help. An intra-aortic balloon pump or left ventricular assist device may improve matters until this can be done. Medications that improve the heart's ability to contract (positive inotropes) may help; however, it is unclear which is best. Norepinephrine may be better if the blood pressure is very low whereas dopamine or dobutamine may be more useful if only slightly low.(68)

## Treatment of Neurogenic shock

- Dopamine (Intropin) is often used either alone or in combination with other inotropic agents.
- Vasopressin (antidiuretic hormone [ADH])(69)
- Certain vasopressors (ephedrine, norepinephrine). Phenylephrine may be used as a first line treatment, or secondarily in people who do not respond adequately to dopamine.
- Atropine is administered for slowed heart rate.(70)

## Conclusions

Circulatory shock is associated with high morbidity and mortality. Prompt identification is essential so that aggressive management can be

started. Appropriate treatment is based on a good understanding of the underlying pathophysiological mechanisms. Treatment should include correction of the cause of shock and hemodynamic stabilization, primarily through fluid infusion and administration of vasoactive agents. The patient's response can be monitored by means of careful clinical evaluation and blood lactate measurements; microvascular evaluation may be feasible in the future.

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## List of Abbreviations

(a-v)CO<sub>2</sub> Arterial-central venous carbon dioxide difference

Cao<sub>2</sub> Arterial oxygen content

Cmvo<sub>2</sub> Mixed venous oxygen content

CI Cardiac index (cardiac output/body surface area)

CO Cardiac output

CPP Coronary perfusion pressure

CVP Central venous pressure

Do<sub>2</sub> Systemic oxygen delivery

DBP Diastolic blood pressure

Hb Hemoglobin

MAP Mean arterial pressure

MODS Multi organ dysfunction syndrome

OER Oxygen extraction ratio

Paco<sub>2</sub> Arterial carbon dioxide pressure

Pao<sub>2</sub> Arterial oxygen pressure

PAOP Pulmonary artery occlusion (wedge) pressure

Sao<sub>2</sub> Arterial oxygen saturation

Scvo<sub>2</sub> Central venous oxygen saturation

Smvo<sub>2</sub> Mixed venous oxygen saturation (pulmonary artery)

Srvo<sub>2</sub> Retinal venous oxygen saturation

SIRS Systemic inflammatory response syndrome

SVR Systemic vascular resistance

Vo<sub>2</sub> Systemic oxygen consumption