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Review article

The Modern Concept of Etiopathogenesis and Diagnosis of Shock

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SUMMARY

Introduction/Aim. Shock is a life-threatening condition that occurs due to a mismatch in the supply and consumption of oxygen, which leads to cell and tissue hypoxia, resulting in cell death and dysfunction of vital organs. The effects of shock are reversible in the early stages, but delay in diagnosis and initiation of treatment can lead to irreversible changes. There are four main categories of shock: hypovolemic, distributive, cardiogenic, and obstructive. The aim of the paper is to present a new perception of viewing the etiopathogenesis and effectively establish the diagnosis of shock.
Etiology. Hypovolemic shock can occur due to hemorrhagic and non-hemorrhagic causes. Distributive shock is divided into septic, systemic inflammatory response syndrome (SIRS), anaphylactic, neurogenic, and endocrine. Cardiogenic shock occurs due to intracardiac causes, while obstructive shock occurs due to extracardiac causes.
Pathogenesis. The pathogenesis of each type of shock is different depending on the etiology. Generally speaking, shock has three phases: compensated, cellular distress phase, and decompensated. When the shock progresses into an irreversible phase, it usually ends with multiorgan failure (MODS) and death.
Clinical presentation. Symptoms may vary depending on the type and stage of shock. The most important changes during this syndrome are at the level of hemodynamics, so the most common clinical signs are hypotension, tachycardia, tachypnea, disturbed mental status, cold extremities, and oliguria.
Diagnosis. The diagnosis of shock is based on history, clinical presentation, physical examination, vital parameters and biochemical analyses, SOFA criteria (sequential organ failure assessment score), acid-base status, diuresis measurement, etc.
Conclusion. Understanding the etiopathogenesis of shock and recognizing its early signs are vital for timely interventions that lead to improved patient outcomes.

Keywords: **shock, hemodynamic disorder, sepsis, etiopathogenesis**

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INTRODUCTION

Shock is a condition manifested as circulatory failure that can lead to life-threatening outcomes (1). Shock is a state of hypoxia in cells, which can cause improper functioning of tissue and organs. Shock can lead to multiorgan failure (MODS) and death, but if timely diagnosis is made, it can be treated with positive outcome (2).

In the beginning, the emphasis was mainly on traumatic hemorrhagic shock, however, shock is now considered a life-threatening condition that occurs due to a mismatch in supply and consumption of oxygen, given that this is a main characteristic of all types of shock. Later, it was determined that various etiopathogenetic factors can progress to this condition. These factors, as well as different therapeutic measures, have led to a new classification of shock that contains four main categories:

- hypovolemic,
- distributive,
- cardiogenic,
- obstructive (3).

EPIDEMIOLOGY OF SHOCK

The three most common types of shock are, in order of frequency, distributive, hypovolemic, and cardiogenic shock. The fourth, the obstructive type, is somewhat rare. Septic shock, a type of distributive shock, is the most common type of all shocks, and carries a mortality rate between 40% and 50% (4). This is shown in Table 1.

Table 1. *Relative frequency of different types of shock*

Shock type	Relative incidence
Hypovolemic	16%
Distributive/Septic	64%/55%
Cardiogenic	15%
Obstructive	2%

ETIOLOGY OF SHOCK

Shock represents one of the most difficult clinical syndromes with a complex list of causes and is potentially fatal without adequate diagnosis and treatment. Numerous etiological factors can contribute to each of the four categories of shock.

Hypovolemic shock is divided in two broad subtypes: hemorrhagic and non-hemorrhagic.

Causes of hemorrhagic shock include:

- traumas and polytraumas (external and internal bleeding due to tissue, organ or blood vessel injuries);
- gastrointestinal bleeding (variceal bleeding, portal hypertensive bleeding, peptic ulcer, diverticulosis and many others);
- vascular etiology (aortoenteric fistula, abdominal aortic aneurysm rupture, tumor eroding into the main blood vessel, etc.);
- bleeding due to inadequate use of drugs (anticoagulants).

Causes of non-hemorrhagic shock include:

- gastrointestinal—vomiting, diarrhea;
- loss of the third space—pancreatitis, cirrhosis, intestinal obstruction;
- renal—endocrine disorders (hypoaldosteronism, diabetes), drug-induced diuresis;
- skin—Stevens-Johnson syndrome, burns, heat stroke, pyrexia (1, 5).

Distributive shock is divided into: septic, systemic inflammatory response syndrome (SIRS), anaphylactic, neurogenic, and endocrine (3).

The 2009 European Prevalence of Infections in Intensive Care Study (EPIC II study) found that Gram-negative bacterial infections (62%), followed by Gram-positive infections (47%), far exceeded other pathogens as the primary cause of sepsis syndrome. The increased prevalence of Gram-positive infections can be attributed to the increased frequency of invasive procedures and hospital-acquired infections. Among the most frequent pathogens are *E. coli, K. pneumoniae, Haemophillus spp, S. pneumoniae, S. pyogenes, S. aureus, N. meningitidis, Pseudomonas spp*, anaerobes (6).

Risk factors for developing sepsis are: malignancy, prolonged hospitalization, liver cirrhosis, immunosuppressive conditions, diabetes, major operations, burns, use of corticosteroids, trauma, the presence of permanent catheters, age, and hemodialysis.

SIRS is a condition of an excessive inflammatory reaction that can be triggered by bacteria, fungi, viruses, parasites, burns, pancreatitis, fat or air embolism, etc (7).

Anaphylactic shock is a condition characterized by a hypersensitivity response which is interfered by immunoglobulin E (IgE). Bronchospasm and cardiovascular collapse are the most severe con-

sequences. Allergens that can cause this are food, drugs (e.g., antibiotics, and NSAIDs), insect stings, etc. (8).

Neurogenic shock occurs in case of trauma to the spinal cord or brain. It includes damage to the autonomic nervous system and vagal tone (9).

Endocrine shock can be present in adrenal insufficiency and myxedema.

Cardiogenic shock occurs due to inadequate functioning of the heart. It leads to reduced cardiac output and hypoperfusion. Various causes contribute to this shock such as:

- cardiomyopathies—fulminant dilated cardiomyopathy, acute myocardial infarction, cardiac arrest, myocarditis;
- mechanical—mitral insufficiency, aortic insufficiency, rupture of papillary muscles, chordae tendineae or aneurysm of the ventricle;
- arrhythmias—tachy- and brady-arrhythmias (10, 11).

Obstructive shock mainly occurs due to extracardiac causes that leads to inadequate minute volume:

- pulmonary vascular—pulmonary hypertension, pulmonary embolism,
- mechanical—pericardial tamponade, tension pneumothorax, restrictive cardiomyopathy (12, 13).

PATHOGENESIS OF SHOCK

The main reason for the occurrence of this condition is hypoxia in the cells, which switches from aerobic to anaerobic metabolism, creating an increase in lactate in the blood. This leads to increased acidosis that reduces organ perfusion, which further leads to tissue hypoxia causing cell death and MODS (14).

Hypovolemic shock is a state where the loss of intravascular lumen causes inadequate organ perfusion. Cardiogenic shock is characterized by a reduction in the pumping capacity of the heart leading to reduced ejection or aggravated filling of the ventricles with blood (15). Obstructive shock appears when there is an obstruction of large blood vessels or the heart itself, which results in an increase in right ventricular afterload and a decrease in left ventricular preload. In these three types of shock, there is a decrease in cardiac output that prevents adequate oxygen transport. In distributive shock, there is decreased peripheral vascular resistance due to immune response and bacterial toxins, which leads to inadequate oxygen extraction.

Generally speaking, shock has the following three phases:

- pre-shock or compensated shock is reflected in the response to hypoxia causing peripheral vasoconstriction, tachycardia and changes in systemic blood pressure;
- shock-the most typical symptoms of shock are caused by early organ dysfunction, which is the result of the progression of the previous phase, as compensation mechanisms prove to be insufficient;
- irreversible organ dysfunction—the final phase that leads to multiorgan failure and death (16).

Compensated phase. Initially, when oxygen supply and arterial pressure are reduced, an adrenergic response is triggered by sympathetic vasoconstriction of most blood vessels, but primarily of the precapillary sphincter, excluding a large part of tissue from the supply. At first, blood flow is being diverted to the heart and brain and perfusion of less important organs is reduced. Beta-adrenergic amines increase cardiac contractility and initiate the release of corticosteroids, renin, and glucose. Increased glucose due to lack of oxygen in the cells causes further production of lactate, while renin-angiotensin-aldosterone system and antidiuretic hormone are the cause of fluid conservation (17).

Cellular distress phase. It is characterized by the formation of lactate in the cells due to the lack of oxygen, which results in the loss of ATP and countering the effects of catecholamines by creating vasodilation. Constriction of the postcapillary sphincter and inclusion of AV shunts occurs. A decrease in cardiac output causes compensatory tachycardia, however, when energy reserves are used up, heart failure occurs with an additional decrease in cardiac output and stroke volume (18).

Decompensation phase. At the level of microcirculation, leukocytes and endothelium interact and destroy proteoglycans and glycosaminoglycans attached to the endothelial membrane, causing microvascular dysfunction with capillary leakage syndrome and vasodilatation of the precapillary sphincter (19). At the cellular level, mitochondrial damage occurs with consequences on blood vessels (20). Neurohumoral mediators are consumed, and hypoxic tissues hardly create new mediators, while adrenergic receptors become insensitive due to down-regulation (21).

A combination of all the listed factors can lead to progressive dysfunction of two or more organs or life-threatening damage called multiorgan dysfunction syndrome (MODS). MODS is characteristic of every shock in later stages, but it is most likely in septic shock (22).

During septic shock, inflammatory and coagulation cascades are activated in areas of hypoperfusion. These areas activate the immune system and release harmful substances (reactive oxygen, proteolytic enzymes), as inflammatory mediators (cytokines, leukotrienes, tumor necrosis factor). All this triggers a cascade reaction that results in the production of a strong vasodilatator agent (nitric oxide) (23).

In septic shock, vasodilation of blood vessels leads to hypotension. Despite normal blood pressure and cardiac function, localized vasodilation can cause focal cellular hypoxia. In addition, excess nitric oxide is converted to free radicals, such as peroxynitrite. These free radicals can damage mitochondria and reduce ATP (adenosine triphosphate) production. All this can significantly increase microvascular permeability, allowing fluid and sometimes plasma proteins to end up in the interstitial space. In the gastrointestinal tract, this can translocate enteric bacteria, which can lead to metastatic infections (23).

The main process is endothelial dysfunction that can cause vasodilation and disturbance in the macro- and microcirculation, leading to an increase in vascular permeability (24).

Bacterial toxins lead to hemolysis of erythrocytes and accumulation of hemoglobin, which, along with damaged tubular epithelium, leads to acute renal failure. Alveocapillary membrane damage and non-cardiogenic pulmonary edema also occur. All the mentioned mechanisms lead to MODS.

Lungs are mostly highly affected, where elevated membrane permeability causes alveolar infiltration and inflammation. Due to the progression of hypoxia, acute lung injury (ALI) can occur, and if the progression continues, it can lead to acute respiratory distress syndrome (ARDS). Renal hypoperfusion may lead to acute tubular necrosis. Typical signs of renal failure are oliguria, anuria, and an increase in nitrogenous products (23).

Coronary hypoperfusion together with mediators (tumor necrosis factor and interleukin-1) can decrease contractility, which reduces cardiac output, further worsening of myocardial perfusion and arrhythmias can occur, causing a vicious cycle that often culminates in death (15). Due to hypoperfusion in the gastrointestinal tract, ileus and bleeding may be manifested. Hepatocellular necrosis can be developed along with elevation of transaminases and decreased production of coagulation factors (25). All this can lead to disseminated intravascular coagulopathy (DIC) (26).

CLINICAL PRESENTATION OF SHOCK

Clinical presentation may be various depending on the severity of the disease. Changes that occur during this syndrome are at the level of hemodynamics, so the most common clinical signs indicating shock are hypotension, tachycardia, tachypnea, disturbed mental status, cold extremities, changes in the skin color, anuria, acidosis, and elevated lactate level (27, 28). Table 2 shows hemodynamic changes in different types of shock.

Table 2. *Hemodynamic changes in different types of shocks*

Type of shock	Hemodynamic changes
Hypovolemic	↓ preload ↑ SVR ↓ CO
Distributive	↓ preload ↓ SVR ↓ / ↑ CO
Cardiogenic	↑ preload ↑ SVR ↓ CO
Obstructive	↓ preload ↑ SVR ↓ CO

*SVR- systemic vascular resistance; CO- cardiac output

All the abovementioned may be present in hypovolemic shock, as well as orthostatic hypotension, pallor, flattened jugular veins, and bleeding (29).

The septic shock is usually associated with a various clinical picture, but the initial sings are:

- fever;
- temperature > 38 °C or < 6 °C;
- tachycardia with a heart rate > 90 beats per minute in adult patients or less than two standard deviations for age in pediatric patients;

• tachypnea with respiratory rate > 20 breaths per minute in adult patients or more than two standard deviations for age in pediatric patients (30).

Severe sepsis involves multiple organ dysfunction and includes the following signs and symptoms:

• cardiovascular system—hypotension, cyanosis, chest pain, suffocation, Beck's triad (pericarditis with tamponade), petechiae;

• respiratory system—cough, dyspnea, tachypnea, chest pain;

• gastrointestinal system—vomiting, diarrhea, blood in the stool, purulent stool, abdominal pain, ileus, stress ulcers;

• urinary system—oliguria, anuria, hematuria, pyuria;

• nervous system—disorders of consciousness, meningeal signs, headache, photophobia, stiff neck (28, 31).

Septic shock is diagnosed as a clinical condition associated with infection and vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and a serum lactate level greater than 2 mmol/L (> 18 mg/dl) in the absence of hypovolemia (32).

It is characterized by two phases:

• compensated hyperdynamic (warm) phase, and,

• decompensated hypodynamic (cold) phase.

In the compensated phase of shock, blood pressure is maintained due to peripheral vasodilation and cardiac output is preserved with tachycardia, but other signs may be present (rapid capillary refill, warm extremities, strong pulse). If fluid resuscitation and vasoactive support are properly managed, healing can occur (31).

As shock goes into the decompensated phase, hypotension and a drop in cardiac output occur, so patients have cold extremities, delayed capillary refill (longer than three seconds). Following the worsening of condition, shock can become irreversible, which can result in multiorgan dysfunction syndrome and death (30). Table 3 shows the diagnostic criteria for SIRS.

Table 3. *Systemic inflammatory response syndrome (SIRS)*

Temperature > 38 °C or < 36 °C	1
Heart rate > 90/min	1
Respiratory rate > 20/min or $PaCO_2$ < 32 mm Hg	1
Leukocyte number > 12 000/mm^3 or < 4000/mm^3 or > 10% immature forms	1

The clinical picture of anaphylactic shock varies significantly from patient to patient depending on the dose, the site of antigen entry and the degree of sensitization of the individual. Hypotension, flushing, urticaria, tachypnea, hoarseness, macroglossia, edema of the face and oral mucosa, inspiratory stridor may develop in patients with a positive history of exposure to a known allergen (medications, food, stings). The fatal outcome occurs most often due to thromboembolic complications, ventricular dysfunction or heart rhythm disorders (33).

Cardiogenic shock should be suspected if the patient has chest pain, convergent arterial blood pressure, late inspiratory cracks or the presence of arrhythmias with the presence of cold extremities, agitation, disturbances of consciousness and oliguria (15).

Clinical picture of obstructive shock is nonspecific (tachycardia, tachypnea, oliguria and disturbances of the state of consciousness). Patients with subcutaneous emphysema, auscultatory silent breathing, deviation of the trachea to the healthy side on X-ray, enlarged jugular veins, as well as information about trauma, mechanical ventilation or cystic lung disease may have tension pneumothorax. Aortic dissection is characterized by chest or abdominal pain, while pericardial effusion includes dyspnea, Beck's triad, and pulse paradox (12).

SHOCK DIAGNOSIS

The diagnosis of shock is based on history, physical examination, clinical presentation, vital parameters, biochemical analyses, SOFA criteria (sequential organ failure assessment score), SIRS criteria, acid-base status, blood count, hemodynamic monitoring, diuresis measurement, chest X-ray, blood culture, and other samples depending on the need (urine, bronchoalveolar lavage, stool, manure, etc.) (34). Diagnostic criteria are complex and consist of several general clinical and laboratory parameters. Table 4 provides a more detailed explanation of MODS diagnostic criteria and Table 5 shows the criteria for quick evaluation of the SOFA score.

All patients should continuously have cardiopulmonary monitoring in intensive care units. It is

necessary to evaluate the function of all organs, through various tests and examinations. These include the mental status assessment with Glasgow Coma Scale (GCS), lung function via arterial blood gasses (ABG), heart function with invasive hemodynamic monitoring, renal function via diuresis measurement and metabolism with lactate measurement. In addition, a complete blood count with leukocyte formula analysis is needed, as well as complete biochemical tests of liver, kidney, cardiac biomarkers, a panel for disseminated intravascular coagulopathy (coagulation screening and d-dimer) and acid-base status (30).

Determining the level of CD14 or presepsin can help in the diagnosis of sepsis, considering that it is significantly related to the severity of the clinical presentation and the prognosis of the disease. Presepsin is generated as the body's response to bacterial infection, although it is not entirely clear how presepsin is produced in the body. Research shows that presepsin could be a diagnostic biomarker for sepsis with high sensitivity and specificity. Interleukin-6 (IL-6) is a molecule that helps cells communicate during the body's response to infection. It has been suggested that measurement of IL-6 levels during sepsis can be helpful in identification of patients with sepsis and initiation of adequate treatment (35).

Determination of C-reactive protein and procalcitonin can help in differentiating between viral and bacterial sepsis, as bacterial sepsis shows a higher trend of these proteins. Compared to CRP, procalcitonin has a higher diagnostic value. Namely, the levels of procalcitonin correlate well with the severity of the clinical picture in sepsis, while on the other hand, the decrease in the level of this biomarker indicates an effective therapeutic course and adequately implemented antibiotic therapy.

Table 4. *Multiorgan dysfunction syndrome (MODS) diagnostic criteria*

General indicators: • Temperature (> 38.3 °C); • Hypothermia (basal temperature < 36 °C); • Heart rate > 90/min; • Tachypnea; • Altered mental state; • Significant edema or positive fluid balance (> 20 ml/kg during 24 h); • Hyperglycemia (plasma glucose> 140 mg/dl or 7.7 mmol/l) in the absence of diabetes.
Inflammatory indicators: • Leukocytosis (leukocyte number > 12,000 μl^{-1}); • Leukopenia (leukocyte number < 4000 μl^{-1}); • Normal number of leukocytes with more than 10% immature forms; • C-reactive plasma protein with more than two standard deviations (SD) above the normal value; • Plasma procalcitonin with more than two SD above normal value:
Hemodynamic variables • Arterial hypotension (systolic pressure < 90 mmHg, mean arterial pressure < 70 mmHg, or reduction in systolic pressure > 40 mmHg in adults).
Indicators of organ failure: • Arterial hypoxemia (PaO2/FiO2 < 300); • Acute oliguria (urine output < 0.5 ml/kg/h for at least 2 hours despite adequate fluid replacement); • Creatinine increase > 0.5 mg/dl or 44.2 μmol/l; • Coagulation disorders (INR > 1.5 or aPTT > 60 s); • Ileus (absent sounds of peristalsis); • Thrombocytopenia (platelet count < 100,000 μl); • Hyperbilirubinemia (total bilirubin in plasma > 4 mg/dl or 70 μmol/l).
Indicators of tissue perfusion: • Hyperlactatemia (> 2 mmol/l), • Reduced capillary refill.

Table 5. SOFA *score of organ failure assessment*

Respiratory rate ≥ 22/min	1
Change in mental status	1
Systolic blood pressure ≤ 100 mmHg	1

Disruption of antithrombin III can indicate a septic condition in the body up to 72 hours before the clinical manifestation of the disease, while a decrease in fibronectin indicates the existence of sepsis and is a bad prognostic sign (26, 35).

An X-ray of the chest can be used to reveal pneumonia, acute respiratory distress syndrome (ARDS), or tension pneumothorax. Cardiac ultrasound can be useful in the differential diagnosis of shock and resuscitation of hypotensive patients (36). MSCT of the pulmonary arteries is the gold standard for the detection of thromboembolic events (37). CT scanning can be used to detect abdominal abscess, intestinal perforation, ischemia, or aortic dissection.

CONCLUSION

In summary, a comprehensive understanding of the etiopathogenesis of shock is crucial for effective diagnosis and management. Accurate diagnosis hinges on a thorough clinical assessment, integration of patient history, and the utilization of advanced diagnostic tools. Recognizing the early signs and symptoms of shock allows for timely interventions that can significantly improve patient outcomes. As medical science continues to evolve, ongoing research into the pathophysiological processes of shock at the molecular level will enhance our diagnostic capabilities and treatment strategies, ultimately leading to improved recovery rates.

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Savremeni koncept etiopatogeneze i dijagnostike šoka

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SAŽETAK

Uvod. Šok predstavlja stanje koje ugrožava život, a nastaje usled neusklađenosti ponude i potrošnje kiseonika; to dovodi do hipoksije ćelija i tkiva, koja uzrokuje smrt ćelija i disfunkciju vitalnih organa. Premda su efekti šoka u ranim fazama reverzibilni, odlaganje dijagnoze i započinjanja lečenja može dovesti do nepovratnih promena, uključujući multiorgansku insuficijenciju (MODS) i smrt. Postoje četiri glavne kategorije šoka: hipovolemijski, distributivni, kardiogeni i opstruktivni. Cilj ovog rada bio je da predstavi novu percepciju sagledavanja etiopatogeneze i efikasno postavljanje dijagnoze šoka.

Etiologija. Uzroci nastanka hipovolemijskog šoka mogu biti hemoragijski i nehemoragijski. Distributivni šok se deli na septički šok, sindrom sistemskog inflamatornog odgovora (SIRS), anafilaktički, neurogeni i endokrini šok usled razlika u njihovoj etiopatogenezi. Do kardiogenog šoka dovode intrakardijalni uzroci, dok se opstruktivni šok javlja usled ekstrakardijalnih faktora.

Patogeneza. Patogeneza svakog podtipa šoka je različita i zavisi od načina njegovog nastanka. Uopšteno govoreći, šok ima tri faze: kompenzovanu fazu, fazu celularnog distresa i dekompenzovanu fazu. Kada šok pređe u ireverzibilnu fazu, dolazi do multiorganskog oštećenja i smrti.

Klinička slika. Simptomi mogu varirati u zavisnosti od vrste i stadijuma šoka. Najvažnije promene koje se dešavaju u ovom sindromu tiču se hemodinamike. Naime, najčešći klinički znaci koji upućuju na šok jesu: hipotenzija, tahikardija, tahipneja, poremećen mentalni status, hladni ekstremiteti, modra koža i oligurija.

Dijagnoza. Dijagnoza šoka se zasniva na anamnezi, kliničkoj slici, fizikalnom pregledu, vitalnim parametrima i biohemijskim analizama. Važnu ulogu u postavljanju dijagnoze imaju i skor procene sekvencijalnog otkazivanja organa (engl. *sequential organ failure assessment score* – SOFA *score*), acido-bazni status, krvna slika, hemodinamski monitoring, merenje diureze, hemokultura i dr.

Zaključak. Razumevanje etiopatogeneze šoka i njegovo rano prepoznavanje omogućavaju pravovremenu terapiju i poboljšavaju ishod bolesti.

Ključne reči: **šok, hemodinamski poremećaji, sepsa, etiopatogeneza**