Journal of Respiratory Diseases and Medicine

Review Article ISSN: 2633-1063

Sepsis

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Abstract

Sepsis is defined as a systemic inflammatory response to infection. TNF activates adhesion molecules on the leukocyte surface, causing neutrophils to attach to endothelial cells. Proteases and toxic oxygen radicals released as a result of degranulation of activated neutrophils facilitate damage to the endothelial cell. Excessive inflammatory response occurring in epsis is tried to be balanced and regulated with molecules, mediators and cytokines that have opposite effects. IL-10 is a prototype of anti-inflammatory cytokines .An important reason for the suppression of immunity in septic patients is lymphocyte apoptosis. Fibrin thrombi are formed in the microvascular bed and contribute to organ failure. Consumption of coagulation proteins causes bleeding, both bleeding and thrombus development are observed in patients. On the other hand, fibrin breaks down by plasmin, causing fibrinolysis. This table, which is defined as disseminated intravascular coagulation (DIC), is one of the most important causes of poor prognosis in sepsis. Severe sepsis is the onset of acute end organ dysfunction, which is not related to the primary infection focus in SIRS and the primary infection focus within the last 72 hours and is not related to any underlying chronic disease, which is not related to the primary infection focus within the last 24 hours. It should be the first step and the target points should be determined. Dobutamine is the first choice in cases with low cardiac index and low mixed venous oxygen saturation and adequate mean arterial pressure after fluid treatment. It increases systemic vascular resistance and minimally affects heart rate and cardiac output.

Sepsis

It is defined as a systemic inflammatory response to infection. Some antigenic structures and toxins of microorganisms initiate inflammation. While cytokines are useful in defeating local infection, their synthesis in large quantities and mixing into the circulation results in widespread endothelial cell damage. TNF activates adhesion molecules on the leukocyte surface, causing neutrophils to attach to endothelial cells. Proteases and toxic oxygen radicals released as a result of degranulation of activated neutrophils facilitate damage to the endothelial cell. It also activates the endotoxin complement system. It stimulates the exposed C3a and C5a basophil and mast cells, causing the release of some vasoactive mediators, most of which cause hypotension, especially histamine. C5a provides activation of neutrophils and adhesion to endothelial cells. Nitric oxide secreted by the endothelial cell is responsible for widespread vasodilation in sepsis.

The release of arachidonic acid metabolites such as thromboxane, prostoglandin and leukotrienes, with the direct effect of endotoxin or stimulation of cytokines, causes an increase in capillary permeability. Endothelial damage, increased capillary permeability, depletion of blood in microcirculation, decreased circulating blood volume results in shock and organ failure. One of the systems activated by the endotoxin effect is the coagulation system. Most of the cytokines released from the cells in sepsis stimulate thrombin production, the intrinsic coagulation system is activated initially by the extrinsic pathway and then by factor XII activation. Fibrin thrombi are formed in the microvascular bed and contribute to organ failure. Consumption of coagulation proteins causes bleeding, both bleeding and thrombus development are observed in patients. On the other hand, fibrin breaks down by plasmin, causing fibrinolysis. This table, which is defined as disseminated intravascular coagulation (DIC), is one of the most important causes of poor prognosis in sepsis. [1]

In 1996, Bone [2] described the concept of "innate or natural anti-inflammatory activity" from Sir Isaac Newton's law of "opposite reactions for all reactions". This concept allowed us to better understand different patient responses in sepsis. According to this concept, the causative agent triggers local proinflammatory and anti-inflammatory response, then this response is poured into the circulation and initiates a systemic reaction.

In this answer, if;

1. If the proinflammatory response (SIRS) is predominant, cardiovascular depression and shock are evident and apoptosis and organ dysfunctions develop.
2. If the opposite anti-inflammatory response (CARS: Counter antiinflammatory response syndrome) is predominant, immune suppression develops.
3. This response develops as a mixture of SIRS and CARS (MARS: mixed antiinflammatory response syndrome) and in the balance, homeostasis develops. If homeostasis cannot be achieved, multiple organ failure develops.

The extreme inflammatory response occurring in sepsis is tried to be balanced and regulated by molecules, mediators and cytokines that have opposite effects. IL-10 is a prototype of anti-inflammatory cytokines An important reason for immune suppression in septic patients is lymphocyte apoptosis. Septic patients are usually

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Key words: *sepsis, noradrenaline, steroid*

Received: June 23, 2020; **Accepted:** July 06, 2020; **Published:** July 13, 2020

lymphopenic. In addition, these patients also experience a decrease in B and CD4 lymphocyte subgroups. A decrease in T-cell response and anergy, seen in a significant proportion of septic patients, is an extreme counter-response to offset the pro-inflammatory response that first appeared. This can also lead to the development of organ failure, which may occur later.

Incidence and mortality

When a total of 10,319,418 sepsis cases observed in the USA between 1979 and 2001 are examined, an average of 660.000 sepsis episodes are detected annually [3].

ICD-9 discharge coding data in the USA [4]:

- Over 750,000 serious cases of sepsis per year

- Mortality 28.6%

- The number of cases increases by 1.5% each year

Infection

Inflammatory response induced by pathogenic microorganisms or invasion of normally sterile tissues with microbial pathogens.

Systemic inflammatory response syndrome (SIRS): there are two or more of the following data;

1. Body temperature: <36°C or >38°C
2. Tachycardia: >90 beats / min (if β is not receiving blockers)
3. Follow-up: respiratory rate >20 / min or PaCO2< 32 mmHg (in spontaneous breathing) or mechanical ventilation requirement
4. Leukocyte count: >12000 / μL or 4000 / μL or 10 10% immature band form presence

Sepsis

Systemic inflammatory response triggered by infection.

Serious sepsis

Suspicion of clinical infection requiring initiation or replacement of systemic antimicrobial therapy in the last 72 hours and the onset of acute end organ dysfunction not related to SIRS and the primary focus of infection in the past 24 hours and not explained by any underlying chronic disease. Organ dysfunction, hypoperfusion, or sepsis accompanied by hypotension.

Septic shock

Presence of tissue hypoperfusion findings accompanying arterial hypotension with sepsis (blood lactate > 2 mmol / lt, oliguria, impaired mental state etc.)

1. Systolic arterial blood pressure <90 mm Hg or
2. Average arterial blood pressure < 60 mm Hg or
3. Systolic arterial blood pressure drop more than 40 mm Hg compared to the baseline value in the absence of other causes of hypotension.

Refractory septic shock

Septic shock that continues for more than 1 hour and does not respond to intravenous fluid administration and pharmacological (vasopressors) treatments.

Diagnostic criteria of 2001 sepsis [5]

- Infection, document or prescribed and some of the following;

General

- Hyperthermia (> 38.3 ° C)

- Hypothermia (<36 ° C)

- Heart rate> 90 / min or> 2 SD above its normal value based on age

- Tachypnea

Affected mental state

- Significant edema or positive fluid balance (> 20 ml / kg at 24 hours)

- Hyperglycaemia (plasma glucose> 120 mg / dl) without diabetes inflammatory

- Leukocytosis> 12000 / μl

- Leukopenia <4000 / μl

- Normal leukocyte count +> 10% immature forms

- Plasma C-reactive protein> 2 SD above its normal value

- Plasma procalcitonin> 2 SD above its normal value

Hemodynamic

- Arterial hypotension (SBP <90 mmHg, MAP <70 or more than> 40 mmHg decrease in SBP compared to baseline in adult, or 2 SD below normal value of SBP)

Organ dysfunction

- Arterial hypoxemia (PaO2 / FiO2 <300)

- Acute oliguria (<0.5 ml / kg / hour, at least 2 hours despite adequate fluid resuscitation)

Increased serum creatinine (> 0.5 mg / dl)

- Coagulation abnormality (INR> 1.5 or aPTT> 60 sec)

- Ileus (absence of bowel sounds)

- Thrombocytopenia (<100000 /)l)

- Hyperbilirubinemia (plasma total> 4 mg / dl)

Tissue hypoperfusion

- Hyperlactatemia (> 1 mmol / L)

- Capillary refill slows down

Note: Since the normal value of SvO2 in the child is 75-80% and the normal value of the cardiac index is 3.5-5.5, these two parameters are not used in the diagnosis of sepsis in the child.

Severe sepsis

Tissue hypoperfusion or organ dysfunction due to sepsis (considering that any of the following is due to infection)

1. Hypotension due to sepsis
2. Lactate values exceeding normal laboratory values
3. Urine flow <0.5 ml / hour (at least 2 hours despite adequate fluid resuscitation)

4. Acute lung injury (PaO2 / FiO2 <250 when the source of infection is not the lung)
5. Acute lung injury (PaO2 / FiO2 <200 when infection source is lung)
6. Serum creatinine> 2 mg / dl
7. Bilirubin> 2 mg / dl
8. Platelet count <100.000 µl
9. Coagulopathy (INR> 1.5)
10. In the physical examination of sepsis cases, it is essential to determine the focus of infection, major morbid organ dysfunctions and shock status.
11. Some findings warn the clinician about the presence of sepsis [6]

Clinical findings

1. Fever, hypothermia
2. Unexplained tachycardia
3. Unexplained follow-up
4. Peripheral vasodilation findings
5. Unexplained shock
6. Mental disorder

Laboratory and monitoring findings

1. Low systemic vascular resistance and high cardiac output
2. Leukocytosis, leukopenia
3. Unexplained lactic acidosis
4. Unexplained renal-hepatic dysfunction
5. Thrombocytopenia, diffuse intravascular coagulation
6. Increased serum procalcitonin level
7. Increased serum cytokine and CRP level

Sepsis is a hypermetabolic and hyperdynamic process. Hypodynamia is observed with a decrease in cardiac output in the preterminal period.

If early fluid adequate resuscitation has been performed, hyperdynamics are observed:

1. Cardiac output increased
2. Systemic vascular resistance is low
3. Oxygen delivery to the periphery is normal or increased
4. Peripheral oxygen use decreased

Late period (hypodynamia):

1. Cardiac output decreased
2. Systemic vascular resistance is low
3. Peripheral oxygen delivery decreased
4. Peripheral oxygen use decreased

Oxygen supply (SO2) or oxygen delivery (DO2) is the total amount of oxygen distributed to the tissues per minute (N: 1000 ml / min).

Factors determining DO2:

1. Cardiac output (CO)
2. Hemoglobin oxygen saturation of arterial blood
3. Partial oxygen pressure in arterial blood
4. Hemoglobin concentration of arterial blood

Normal tissues increase in metabolism, oxygen requirement increases, blood oxygen extraction rate increases. However, the oxygen extraction rate (OER) of tissues in sepsis decreases to 30-40% of normal. Oxygen requirement of tissues also increases to 2-3 times normal due to hypermetabolism.

The normal value of DO2 in patients with sepsis does not guarantee adequate tissue oxygen use:

1. Increased oxygen demand of tissues
2. Inability of tissues to extract oxygen from the blood

Normal tissues do not increase oxygen extraction rates despite increased oxygen presentation, unless their metabolism increases. In other words, oxygen use of tissue is normally independent of oxygen delivery. If oxygen extraction increases with increasing oxygen supply to the tissue, this suggests that the current oxygen supply to that tissue is not yet sufficient. As the tissues 'oxygen extraction ability decreases (sepsis), the amount of oxygen delivery to the tissues becomes the primary determinant of the tissues' use of oxygen. Hemoglobin oxygen saturation (SvO2) of mixed venous blood is a good indicator of systemic oxygen use (N: 70-75%). SvO2 value increases due to insufficient use of peripheral oxygen in sepsis. The difference in arteriovenous oxygen content in sepsis is typically below 3 ml / dl (N: 5 ml / dl).

Management-treatment

1. Mortality can be reduced by early diagnosis and early treatment. Treatment of sepsis begins with the correction of oxygenation: It is aimed that PaO2 is above 60-65 mmHg.
2. Oxygenation (PaO2> 60 mmHg)
3. Low tidal volume protective lung ventilation (peak respiratory pressure <30 cmH2O)
4. Rapid (within 1 hour) appropriate antibiotherapy
5. Early targeted treatment
6. Glycemia control (110-180 mg / dl)
7. Nutrition (positive nitrogen balance)

They will be completed in 3 hours

1. Measure the lactate level
2. Take a blood culture before giving antibiotics
3. Start broad-spectrum antibiotics
4. If hypotension or blood lactate≥4 mmol / L, give 30 ml / kg of crystalloid fluid

To be completed in 6 hours

1. If MAP does not reach> 65 mmHg despite initial fluid therapy, give a vasopressor to achieve this goal.
2. If there is ongoing hypotension (septic shock) or initial blood

lactate≥4 mmol / L despite volume resuscitation; Measure central venous pressure and central venous oxygen saturation (ScvO2).

3. Goals of resuscitation: CVP≥8 mmHg, ScvO2≥ 70%, urine flow> 0.5 ml / kg / h, MAP> 65 mmHg, normalization of blood lactate

If the initial blood lactate is mmol4 mmol / L, repeat the lactate measurements

It was found that mortality was decreased in those who applied protective ventilation strategy with low tidal volume.

1. Tidal volume≤ 6 ml / kg
2. Plateau pressure ≤ 30 cmH2O
3. Respiratory rate / intended pH…. 6-36 / min / 7.35-7.45
4. I / E …… ..1: 1, 1: 3
5. Targeted oxygenation… ..PaO2: 55-80 mmHg, SpO2: 88-95%
6. FiO2 / PEEP .... 0.3-0.4 / 5, 0.4-0.5 / 8, 0.5-0.7 / 10, 0.7 / 12-14, 0.8-0.9 / 14, 0.9 / 16-18, 1 / 18-24 weaning: FiO2 / PEEP ≤ 0.4 / 8

At least 2 sets of culture should be taken before antibiotic treatment is started. Two blood cultures should be taken from at least one from the peripheral vein and the other from the venous catheter (if the catheter is not newly inserted; <48 hours). 1,3 beta-D-glucan, mannan and anti-mannan antibody test should be requested. Imaging methods should be used for the source of the infection. In septic shock and severe sepsis, empirical treatment should be started, which includes possible factors (bacteria, fungus, virus) within the first 1 hour and can penetrate the predicted focus of infection. The antibiotic regimen should be reviewed daily for antibiotic restriction (deescalation). Combined empirical antibiotics should be used in severe sepsis, in cases of difficulty in treatment, and in multiple-resistant bacterial growth, such as acinetobacter and pseudomonas. In severe infection with septic shock and respiratory failure, broad spectrum beta lactam antibiotics for P. Aeruginosa should be combined with aminoglycoside or fluoroquinolone. It should be combined with beta lactam antibiotic macrolide in septic shock due to bacteremic Streptococcus pneumoniae. Empirical combined therapy should not be applied for more than 3-5 days. Antibiotic restriction should be applied according to the clinical situation and reproductive results.

The duration of antibiotic therapy is typically 7-10 days, excluding:

1. Slow clinical response
2. Infection focus that cannot be resisted
3. S. Aureus bacteremia
4. Fungal and viral infections in immune deficit (neutropenia) cases regional perfusion needs to be evaluated once and for all

The infection focus should be determined within 12 hours and an evaluation should be made for the control of the focus. Abscess drains should be done by methods that affect the physiological condition least (eg percutaneous drainage rather than surgical drainage of abscess). Vascular catheters that are considered to be focused should be removed quickly.

Hemodynamic support in septic shock

Septic shock despite normal or high cardiac output, it is a type of distribution shock characterized by inappropriate peripheral vasodilation and infective tissue oxygen distribution and extraction.

Due to the inflammatory response to infection in septic shock;

1. Pathological vasodilation
2. Relative or absolute hypovolemia
3. Myocardial depression
4. A complex process involving disturbed blood flow distribution continues

Despite the restoration of intravascular volume, there are microvascular abnormalities caused by maldistribution of cardiac output [7].

Clinical picture after fluid treatment

1. High preload
2. Significantly increased cardiac output despite myocardial depression:

a. Stroke volume is normal or high due to increased ventricular end-diastolic and end-systolic volume despite low ventricular ejection fraction

d. Stroke volume increase provides normal or increased cardiac output with tachycardia

e. The dilatation function of the left ventricle is an adaptive mechanism in septic shock. The inadequacy of this function is associated with poor prognosis.

f. Adaptive mechanisms (left ventricular dilation, end-diastolic and end-systolic volume increase) provide adequate systemic arterial blood pressure with 50% of the patients with adequate fluid resuscitation (4 lt colloid or 10 lt crystalloid) despite ongoing vasodilation.

Inotropic and vasopressor treatment indications arise in cases that do not respond to aggressive fluid therapy.

The purpose of hemodynamic support in septic shock is to normalize cellular metabolism by providing effective tissue perfusion. Despite the increased oxygen supply in sepsis, adequate tissue oxygen use cannot be guaranteed, because oxygen delivered to the tissues is bypassed by the tissues for the following reasons:

1. Anatomic microcirculatory shunts from arterioles to venous capillaries
2. fast capillary transition time

Structural microvascular heterogeneity causing the stealing phenomenon

Even if a high level of oxygen is created in the cellular level in sepsis, due to the insufficient use of oxygen in the cellular level, the necessary energy cannot be generated for the cells. The causes of tissue hypoperfusion in septic shock may be hypotension and increased or normal cardiac output is abnormally blackened in the tissues.

Global perfusion indices

1. **Average arterial pressure (MAP):** MAP shows better parallelism with the autoregulatory limits of organ blood flow compared to systolic arterial pressure. MAP value should not be below 60-70 mmHg
2. **Decreased perfusion findings:** Oliguria, closed sensoryum, slowing of capillary refill, cold skin

3. **Lactate:** It was found that increasing global [8] or regional [9] blood flow in sepsis does not decrease high lactate levels. Therefore, it is thought that high lactate levels in sepsis are caused by cellular metabolic disorder rather than global hypoperfusion [10]. Increased prudent production due to glycolysis in sepsis and decreased clearance of lactate from the liver also contributes to the increase in blood lactate level [11]. The trend of lactate concentration rather than a single lactate value in septic shock should be used to monitor anaerobic metabolism

4. **Mix venous oxygen saturation (SvO2)**: SvO2 reflects the balance between oxygen delivery and oxygen utilization of tissues. SvO2 value increases due to the decrease in blood flow maldistribution and peripheral oxygen use in sepsis. If the SvO2 value remains low despite resuscitation, this indicates that the oxygen extraction of the tissues is still high and that the resuscitation has not yet achieved its purpose.

Indices of regional perfusion

Clinical evaluation:

1. Myocardial ischemia findings
2. Decreased urine flow
3. Increased serum nitrogen and creatine value
4. Closed sensoryum
5. Elevation of serum transaminase values
6. Elevation of serum lactate dehydrogenase value
7. Elevation of serum bilirubin values
8. Prolongation of coagulation tests may indicate regional perfusion disorders.

Hepatosplanknik current: Desaturation in hepatic vein suggests that hepatosplanknic oxygen delivery is insufficient, even if adequate global perfusion is achieved in septic patients.

Intestinal microcirculation: Countercurrent flow in the intestinal microcirculation increases the risk of mucosal hypoxia. Therefore, intestines have a higher critical oxygen delivery threshold than other organs and intestinal ischemia increases intestinal permeability [12]. Gastric tonometry can be used to evaluate regional perfusion in the gut [13,14]. Since gastric mucosal PCO2 is directly affected by systemic arterial PCO2, the use of the gastric-arterial PCO2 difference is more appropriate. Sublingual capnography is a simpler method and correlates well with gastric tonometry [15]. In fluid treatment, the targeted heart rate, urinary flow and blood pressure are tried to be reached with predetermined fluid boluses (250-500ml / 15min). In most cases, when PCWP is 12-15 mmHg, cardiac output is optimized. Continuing fluid loading after this limit does not significantly increase end-diastolic and stroke volumes, but increases the likelihood of developing pulmonary edema. If CVP is used for monitoring, a pressure of 8-12 mmHg should be targeted [16].

In fluid resuscitation, oxygen metabolism and organ functions should be determined as target points.

After fluid treatment:

1. Increased mix venous oxygen saturation and systemic oxygen delivery
2. The beginning of recovery of lactic acidosis
3. Increased gastric intramucosal pH improves survival [17]

Increased vascular permeability is typical in sepsis. The Starling Equation determines the kinetics of the fluid passing through the capillary endothelium:

$$\mathbf{Jv} \propto [(\mathbf{Pe}\text{-}\mathbf{Pi}) - \sigma\,(\pi\mathbf{e}\text{-}\pi\mathbf{i})]$$

Jv: transcapillary fluid flow

Pe: capillary hydrostatic pressure

Pi: interstitial hydrostatic pressure

E: intravascular oncotic pressure

I: interstitial oncotic pressure

σ: reflection coefficient

σ = 0; free pass, water

σ = 1; impermeablit to

Colloids

Colloid molecules escape from the intravascular space to the extravascular space. With this escape, the plasma volume expansion effects of colloids in sepsis decrease, and tissue edema increases as a result of increasing interstitial oncotic pressure.

Crystalloids

1. The most commonly used isotonic saline and lactated ringer's solutions
2. The distribution volume of isotonic saline and ringer solutions is extracellular compartment.
3. While 25% of these solutions remain in the vascular bed, the rest is distributed over the extravascular area. Clinically, 1 L crystalloid solution produces 100-200 ml of intravascular volume expansion [18].
4. In the initial period of septic shock, 6-10 L crystalloid solution is required in the first 24 hours, one of the results of this fluid resuscitation is the pronounced hemodilution of plasma proteins and lowering of colloid osmotic pressure.

The major complication of fluid resuscitation is systemic and pulmonary edema.

This complication is associated with three main factors:

1. Increase in capillary hydrostatic pressure
2. Capillary colloid osmotic pressure drop
3. increased microvascular permeability in septic shock

In studies comparing crystalloids and colloids, it has been found that crystalloids do not increase the risk of pulmonary edema [19] Fluid escape into the extravascular area in sepsis depends on microvascular pressure rather than colloid osmotic pressure [20].

1. Unless high ventricular filling pressures are reached, there is no difference between the crystalloid and colloids in terms of pulmonary edema development.
2. 30-60% ARDS develops in septic shock.

3. Colloids can aggravate pulmonary edema by switching to interstitium and increasing fluid retention in the lungs due to increased microvascular permeability in sepsis.

It should be noted:

1. Despite high volume resuscitation, organ dysfunctions continue as the underlying inflammatory process continues.
2. Adequate circulating volume is required to provide adequate tissue perfusion, but adequate tissue perfusion may not be sufficient to correct microvascular flow abnormalities in sepsis.
3. The first goal in fluid therapy is to correct life-threatening hypotension.

Vasopressor treatment

1. As autoregulation of organs is impaired in sepsis, blood flow of organs becomes directly dependent on perfusion pressure.
2. Therefore, while vasopressors provide adequate mean arterial pressure, stroke should be titrated in a way that does not reduce volume.
3. Vasopressor therapy is aimed at ensuring proper blood pressure.
4. However, blood pressure does not always show equality in blood flow and the appropriate blood pressure targeted for each patient is not the same.
5. To optimize blood flow, it is usually necessary to keep the average arterial pressure above 60 mmHg [21]
6. Vasopressors should be titrated according to their minimum dose, which optimizes urine flow, and this goal is achieved with an average arterial pressure of 60 mmHg in most cases
7. Bowel perfusion plays a key role in sepsis-induced multiple organ failure
8. Therefore, in the selection of vasopressor agents, the effects of the agent on bowel perfusion should be considered.
9. Positive inotropic agents such as dobutamine may be used when vasopressor agents reduce stroke volume [22].

Dopamine

1. It is the natural precursor of epinephrine and norepinephrine
2. At doses below 5 μg/kg/DK, it activates the DA1 and DA2 receptors, creating vasodilation in the renal, mesenteric, and coronary bed
3. At doses between 5-10 μg/kg/min, the adrenergic effect of β1 is predominant and increases cardiac output and heart rate
4. At doses above 10 μg/kg/DK, the adrenergic effect of α1 is predominate, resulting in arterial vasoconstriction.
5. Dopamine increases mean arterial pressure and cardiac output mainly by increasing stroke volume [23].
6. The average dose of dopamine required to restore blood pressure is 15 μg/kg/DK.
7. In patients with high PCWP, dopamine may further increase PCWP by increasing venous return.
8. Dopamine increases the rate of pulmonary shunt as it increases blood flow to poorly ventilated areas of the lung by increasing cardiac output [24].
9. Dopamine increases peripheral oxygen delivery while reducing peripheral oxygen extraction rate [25].
10. This finding suggests that dopamine does not correct tissue oxygenation as it does not increase microcirculatory blood flow in vital organs [26].
11. One study found that although dopamine increases systemic oxygen delivery and use, it reduces mucosal blood flow and decreases gastric intramucosal pH by causing redistribution of blood flow in the intestine [27].
12. Low dose dopamine increases renal blood flow and glomerular filtration rate and inhibits renal tubular sodium reabsorption, causing natriuresis [28].
13. The major undesirable effect of dopamine is its arrhythmogenic effect, which is more pronounced than other vasopressor agents
14. Another undesirable effect is that it increases PCWP and pulmonary shunt rate, as well as inhibits prolactin release and creates immunosuppression [29]

Norepinephrine

1. It is a Potent α-adrenergic agonist. β-adrenergic effect is minimal
2. Increases systemic vascular resistance while minimally affecting heart rate and cardiac output
3. It either does not change PCWP at all or causes a moderate increase (1-3 mmHg) [30].
4. Norepinephrine is more potent than dopamine.
5. The mean arterial pressure increases in patients who do not respond to dopamine and liquid therapy [31].
6. Reported doses of norepinephrine range from 0.01-3.3 μg / kg / min
7. Due to α-receptor down-regulation in sepsis, some patients may require higher doses [32].

Norepinephrine increases renal filtration fraction as it creates greater resistance increases in the efferent renal arterioles than in the afferent renal arterioles. Studies in septic shock cases showed that urine flow, creatinine clearance and osmolar clearance increased [33]. These results suggest that norepinephrine may optimize renal blood flow and renal vascular drainage in septic shock cases that do not respond to fluid. Norepinephrine does not disrupt tissue oxygenation, but it has been found to lower lactate level in septic shock [34]. Norepinephrine increases blood pressure without worsening cardiac index and organ function. If the use of norepinephrine is considered, it should be started early and not considered as the last option.

Epinephrine

In patients who do not respond to fluid therapy, it increases mean arterial pressure by increasing cardiac index and stroke volume, by increasing systemic vascular resistance and heart rate to a moderate extent [35].

1. Epinephrine reduces splanchnic blood flow
2. Splanchnic blood flow reduction that will affect nutrition presentation can be corrected with dobutamine
3. Epinephrine increases carbon dioxide production due to thermogenesis.

4. Epinephrine increases systemic and regional lactate concentration
5. Short-term follow-up has been done in studies on this subject, so it is not clear whether epinephrine-induced lactate increase is temporary
6. One study found that epinephrine-induced lactate increase returned to normal within 24 hours
7. Epinephrine has been found to be minimally effective on pulmonary arteries and pulmonary vascular pressure in sepsis
8. The effect of increasing blood pressure is evident
9. Reducing gastric blood flow and increasing lactate concentration restricts its use

Corticosteroids

1. They up-regulate the sympathetic nervous system and the renin-angiotensin system [36]
2. They strengthen the vascular response to norepinephrine and angiotensin II by stimulating the phosphoinositide signaling system in smooth muscle [37]
3. They inhibit nitric oxide synthesis
4. They increase catecholamine activity:

   a. They increase phentolamine N-transferase activity and epinephrine synthesis [38]

   b. They inhibit the reuptake of catecholamines in the neuromuscular compound

   c. They increase the binding capacity and affinity of β-adrenergic receptors in arterial smooth muscle [39]

   d. They increase the synthesis of cyclic adenosine monophosphate induced by catecholamines [40]

5. They increase angiotensin type I receptor expression in vascular smooth muscle [41]
6. In the 1990s, it was reported that corticosteroids in 2 metanalysis had no place in the treatment of sepsis as anti-inflammatory, and that short-term high-dose steroid administration increased nosocomial infections and mortality [42]
7. Some septic patients have a relative adrenal cortical insufficiency and no response to ACTH stimulation can be obtained in these cases [43]
8. Adequate cortisol production is essential for survival in septic shock (44) and lack of adrenocortical response is indicative of poor prognosis in septic shock [44]
9. In recent years, it has been reported that corticosteroids may be used as long-term replacement therapy in low-to medium doses, but not as anti-inflammatory drugs in sepsis. [45]
10. Adrenal insufficiency should be considered especially in patients who do not respond to high dose catecholamines
11. Low dose and continuous long-term corticosteroid therapy has been shown to reduce the need for catecholamine in septic shock [46]

50-75% of resistant septic shock cases have relative adrenal insufficiency [47]

Possible mechanisms of relative adrenal insufficiency in septic shock may be:

1. Peripheral tissue resistance to corticosteroids [48]
2. Decreased cortisol binding [49]
3. Decreased number and binding capacities of glycocorticoid receptors [47]
4. The results of 4 randomized controlled trials of 300 mg/day hydrocortisone administered to catecholamine-dependent septic shock patients for ≥3 days were analyzed [50]
5. Systemic vascular resistance and mean arterial pressure were found to increase without any change in cardiac output
6. Annane and arkd 300 septic shock and severe sepsis patients with a period of 7 days 4x50 mg hydrocortisone and 50 g fludrocortisone effects were examined. adrenal failure (pegged 75 index of cases) (250 g ACTH stimulation cortisol level compared to the baseline values after 9 dg/dL rising to more than cases) mortality is high in patients with these patients, steroid displacement mortality of 10% has shown a decrease.
7. It has been reported that random cortisol levels should be higher than 25 g/dl for adequate adrenal function in intensive care patients [51]
8. Since rebound is more frequent in continuous applications, series bolus applications should be preferred.

Vasopressin

1. Is a peptide hormone synthesized in the hypothalamus and stored in the pituitary gland
2. It is released in response to decreased blood volume and intravascular volume and increased plasma osmolality
3. With the onset of septic shock, its stores empty [52]
4. Plasma vasopressin levels have been shown to decrease more in septic shock than in cardiogenic shock [53]
5. Vasopressin produces its effects through receptors V1 in smooth muscle and V2 in renal collector tubules
6. Muscle contraction through V1 receptors
7. Improves vascular bed's response to catecholamines
8. Vascular smooth muscle raises blood pressure by inhibiting nitric oxide synthesis and K-ATP channels [54]
9. The use of vasopressin (0.04 U/Min) at physiological doses has been shown to reduce the number of vasopressors required to keep the average arterial blood pressure above 65 mmHg in septic shock [55]
10. When a total of 75 patients were examined in 4 case series, low dose vasopressin used in hypotension with catecholamine resistance was found to increase mean arterial pressure, systemic vascular resistance, and urine flow [56]
11. In 2 randomized controlled trials, vasopressin significantly reduced vasopressor requirement and significantly increased urinary flow rate [57].

    a. Administration of low-dose continuous vasopressin (0.01-0.04 U / Min) to catecholamines in resistant septic shock can be used to optimize blood pressure

b. Vasopressin may reduce splanchnic blood flow or cause redistribution of blood flow from splanchnic mucosa [58]

Inotropic treatment

Myocardial dysfunction in sepsis:

1. Decreased ejection fraction,
2. Ventricular dilation,
3. Not enough contractile response to volume load
4. Low peak systolic pressure / end-diastolic volume ratio characterized by [59]

The mechanism of cardiac dysfunction that occurs is complex:

1. Myocardial edema [60]
2. Sarcolemma or intracellular calcium homeostasis [61]
3. Interruption of β-adrenergic signal transduction [62]
4. Prostanoids [63], Platelet-activating factor, TNF-α, IL1, IL2 and nitric oxide were found to cause myocardial depression [64].
5. Although the cause of lactate formation in sepsis is complex, the decrease in lactate value along with increased cardiac flow is a good prognostic indicator.

In studies that increase peripheral oxygen delivery to pre-determined high values, improvement in survival:

1. Is it due to increased cardiac output and oxygen delivery or
2. It is not clear whether these increased values actually reflect the physiological reserves that the patient had previously, which supported his survival [65]

Therefore, it is not recommended to increase cardiac index and oxygen delivery to high values [66]

1. It is clear that the decrease in oxygen delivery causes lactic acidosis, but it is not true that the increase in oxygen delivery always corrects lactic acidosis
2. High lactate levels in sepsis cases do not always reflect a lack of oxygen delivery [67]
3. In cases of adequately resuscitated sepsis, mixed venous oxygen saturation is usually normal or high, but these high values of mixed venous oxygen saturation do not correlate well with cardiac flow.
4. Therefore, it is controversial to take mixed venous oxygen saturation as a target point in inotropic therapy [25]
5. Inotropic treatment should be considered to achieve adequate cardiac index, mean arterial pressure, mixed venous oxygen saturation and urine flow
6. The clinician should set a target point for inotropic treatment and titrate the drugs according to this goal. These target points should be revisited as the patient's clinic changes and frequently.

Dopamine

1. In sepsis cases, dopamine increased cardiac index by 4-44%, Lvswi by 5-91% and rvswi by 5-10% [68]
2. The maximum increase in these parameters was at a dose of 12 μg/kg/min. At higher doses, the rate of improvement in cardiac performance decreased.
3. Dopamine may increase mesenteric blood flow but may reduce the use of mesenteric oxygen [35]
4. the superiority of dopamine as an inotropic agent over other agents have not been determined

Dobutamine

1. Dobutamine is a racemic mixture of two isomers: The D isomer β1 and β2, while the L isomer β1 and α1 are adrenergically effective
2. Predominant effect is positive inotropy via β1 receptors
3. In sepsis cases, a dose of 2-28 μg/kg/min was tested. It was found to increase cardiac index by 12-61% in studies. [69]
4. Dobutamine can be used to increase blood flow to organs such as the bowel and kidney, as it does not affect blood flow distribution

Epinephrine

1. α and β are adrenergically effective
2. At low doses the β-agonist effect is predominant
3. Doses of 0.1-0.5 μg / kg / min were used in the studies and it was found to increase cardiac index by 24-54% [70].
4. its use should be restricted because it increases lactic acidosis and impairs bowel perfusion [71]

Norepinephrin

The α-adrenergic effect is predominant. The effect of cardiac index is moderate.

In trials [72 ,64]:

1. It did not affect the cardiac index or increase it by up to 21 %
2. It did not affect the heart rate or increase it by up to 8 %
3. Blood pressure increases significantly with LVSWI and Rvswi due to increased blood pressure
4. Dobutamine + norepinephrine: this combination was found to be effective in increasing blood pressure and mesenteric perfusion [73].

Blood transfusion in sepsis

1. There is no optimum hemoglobin and hematocrit value yet determined for septic shock cases
2. The clinical practice in this subject is to maintain the hemoglobin value between 8-10 gr/dl
3. Decline in Hemoglobin value may be associated with ineffective erythropoiesis and hemodilution
4. A decrease of 1-3 g/dL is predictable during initiation fluid resuscitation in septic shock cases [74].
5. In most cases, this level of anemia is well tolerated because the decrease in blood viscosity reduces the afterload and increases venous return, thus increasing stroke volume and cardiac flow.
6. Decrease in blood viscosity can compensate for rheological changes in septic shock and increase microvascular blood flow

Factors affecting patient's tolerance of anemia should be considered

1. Increased cardiac flow due to decreased blood viscosity may not be tolerated due to cardiac dysfunction and ultimately systemic oxygen delivery may remain insufficient

2. Increased cardiac flow due to decreased blood viscosity alone may not provide adequate oxygen delivery necessary for increased metabolism in hypermetabolic situations

In cases where peripheral oxygen extraction is reduced, such as Sepsis, oxidative metabolism becomes largely dependent on arterial oxygen content [75].

1. Blood transfusion has immunosuppressive effects [76].
2. No clinically significant difference was detected in a study aiming to have Hemoglobin levels of 7 and 10 gr/dl [77].

Higher hemoglobin values may be targeted to increase oxygen delivery

1. Severe tachycardia
2. Cardiac dysfunction
3. Underlying severe pulmonary or cardiac disease
4. Severe mixed venous oxygen desaturation
5. Lack of improvement in lactic acidosis

Summary: fluid resuscitation

1. Fluid therapy should be the first stage in hemodynamic support and target points should be determined
2. In achieving hemodynamic goals, crystalloids and colloids have equal effectivity
3. Liquid infusion should be titrated to reach the filling pressures that provide the highest cardiac flow and stroke volume. This goal is usually achieved in Pcwps of 12-15 mmHg
4. Hemoglobin concentration should be kept between 8-10 gr/dl. This level can be increased in the following cases:

a. Low cardiac flow

b. Low mixed venous oxygen saturation

c. Lactic acidosis

d. Increase in gastric-arterial pCO2 gradient

e. Apparent cardiac or pulmonary disease

Summary: vasopressors

1. Dopamine increases cardiac output more than norepinephrine, but its tachycardia-inducing effect restricts its use. The most effective agent as a vasopressor is norepinephrine.
2. Phenylephrine may be a good alternative to raising blood pressure in cases of tachyarrhythmia
3. Epinephrine may be used in refractory hypotension, but it should be noted that it reduces mesenteric perfusion
4. Use of dopamine to correct Renal function is not recommended
5. Steroid replacement is suggested in catecholamines-resistant hypotension
6. 24 in refractory hypotension to vasopressors. low-dose vasopressin treatment after hours may be effective in raising blood pressure

Summary: inotropic treatment

1. Dobutamine is the first option in patients with low cardiac index and low mixed venous oxygen saturation and adequate mean arterial pressure after fluid therapy.
2. In patients with tissue hypoperfusion, the addition of dobutamine can help increase cardiac output and improve organ perfusion. Continuous increase of cardiac index to pre-determined supranormal levels (>4 l/min/m2) did not increase survival.
3. Titration of norepinephrine as a vasopressor and dobutamine as an inotropic is recommended to ensure adequate mean arterial pressure and cardiac output

Antibiotic therapy

1. Early and effective application of antibiotics and control of the source of infection are cornerstones in the treatment of sepsis
2. Empirical treatment should be started as early as possible (within 1 hour as soon as diagnosis is made) and culture should be directed according to the results of the antibiotic) [78].
3. Debridement of infected tissues and discharge of abscesses is essential because antibiotics are effective in such tissues and inflammation cannot be expected to recede unless such tissues are removed
4. Intensive care cases are rapidly colonized with gram-negative bacilli, gram-positive cocci, and Candida species (within 24-48 hours))
5. The prevalence of this colonization cannot be reduced by broad spectrum empirical antibiotic therapy
6. On the contrary, unnecessary use of broad-spectrum antibiotics leads to infection with resistant microorganisms
7. Long-term use of broad-spectrum beta lactam antibiotics parallels increased enterococcal infections
8. One of the most important factors leading to sepsis is the patient's prior use of broad-spectrum antibiotics.

Glucose control

1. Hyperglycemia is common in intensive care patients due to insulin drencin
2. Blood sugar 110-180 mg / dl with insulin therapy
3. Critical illness polyneuropathy, bacteremia and inflammation were reported significantly lower in patients with strict glucose control.

Steroids

1. Patients with septic shock who need vasopressor should be given 200-300 mg/day hydrocortisone at 3-4 times or as continuous Perfusion for 7 days
2. In order to correct septic shock, it is necessary not to exceed 300 mg of hydrocortisone per day.
3. Cortisone use not recommended except for septic shock-Grade E

Blood products

1. After initial resuscitation, erythrocyte suspension should be given only if Hb falls below 7 g/dL, except for coronary artery disease, acute hemorrhage, and lactic acidosis

2. TDP is not recommended for correction of clotting parameters other than bleeding or planned invasive procedures

3. Transfusion is recommended if the platelet count is < 5000/mm3. 5000-30000 is recommended if there is a risk of serious bleeding. Over 50000 are recommended only if surgical intervention or invasive intervention is planned

Bicarbonate

In the treatment of lactic acidosis due to hypoperfusion, it is not recommended to use it to correct hemodynamic parameters or to reduce the need for vasopressors unless the blood pH is below 7.15.

DVT prophylaxis

If there is no contraindication, Heparin or DMAH is recommended. Intermittent compression devices or socks should be used in patients with contraindications. Both should be used in patients with high risk of DVT

Stress Ulcer Prophylaxis

It should be given to all patients with severe sepsis. H2-receptor inhibitors are more effective than sucralfate. Proton pump inhibitors have not been directly compared and their relative efficacy is unknown.

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