

# 11 Managing Septic Shock in ICU

**Abstract:** Numerous mechanisms are involved in the pathophysiology of sepsis and septic shock. These include the release of numerous cytokines, with the activation of neutrophils, monocytes, and microvascular endothelium, along with the activation of neuroendocrine system. The complement system, intrinsic and extrinsic pathways of coagulation, and the fibrinolytic system. Gastrointestinal tract epithelium dysfunction plays a major role in the pathogenesis of septic shock. There is extensive complementary and synergistic interaction of the different components in this cascade, and this phenomenon explains the difficulty in altering the progression of sepsis and septic shock to MODS. From a clinical point of view, early recognition of sepsis is of paramount importance in order to start early appropriate therapy and prevent the development of septic shock.

Appropriate, aggressive resuscitation to preserve organ function remains an essential code in the care of septic patients. The precise care is directed at identifying and treating the basic illness. The physician should investigate meticulously for the existence of active infection using modern imaging methods and other diagnostic studies to narrow down the site of infection and to obtain appropriate culture specimens from likely infective sources. Early and proper administration of effective antibiotic therapy is imperative in the management of sepsis. Source control should be performed without any delay by draining infected fluid collections and debridement of infected tissue. Adequate nutritional support should be considered in the management of all septic patients. A number of adjuvant therapies should or may be considered in these very sick patients to improve the final outcome.

## INTRODUCTION

Sepsis is an infection-induced syndrome characterized by a widespread inflammatory state. The septic reaction is an enormously multifaceted cascade of events, including pro-inflammatory, anti-inflammatory, humoral, cellular, and circulatory involvement. The standard reaction to infection engages a chain of compound immunologic processes. An effective, complex immunologic cascade guarantees a timely defensive response to microbial invasion. Although initiation of the immune system during microbial invasion is usually protective, septic shock develops in some of the patients as a result of unwarranted or poorly synchronized immune response to the offending organism (bacteria, fungi, viruses, or microbial toxins). This deranged reaction may harm the host through an unsuitable release of endogenously produced inflammatory mediators. Several mechanisms are implicated in the pathogenesis of septic shock, which involve the release of cytokines, the activation of neutrophils, monocytes, and microvascular endothelial cells, also the initiation of neuroendocrine reflexes and plasma protein cascade systems, such as the complement system, the intrinsic and extrinsic pathways of coagulation, and the fibrinolytic system. In critically ill patients, the gastrointestinal tract plays a crucial role in the pathogenesis of septic shock. The mutual reaction of the different mechanism in this cascade points to the problem one comes across in trying to distinguish methods of changing the evolution of sepsis and septic shock to multiple organ dysfunction syndrome (MODS).

Precise definitions are necessary to improve the ability to accurately diagnose,<sup>1-3</sup> monitor, and treat septic patients. The physician should be familiar with the following entities (Fig. 1):

- **Infection** is defined as the pathological process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic microorganisms.
- **SIRS** (Systemic Inflammatory Response Syndrome) is diagnosed when patients have more than one of the clinical findings reported in Table 1. It should be emphasized that signs of systemic inflammation can be observed in the absence of an infectious cause of the syndrome.
- **Sepsis** is defined as the clinical syndrome characterized by the presence of both infection and a systemic inflammatory response (as a response to infection). The clinical manifestations would include  $\geq 2$  of the following conditions as a result of a documented infection:
  - i. Body temperature higher than 38°C or lower than 36°C,
  - ii. Heart rate higher than 90/min,
  - iii. Hyperventilation evidenced by respiratory rate higher than 20/min or PaCO<sub>2</sub> lower than 32 mmHg.
  - iv. White blood cell count higher than 12,000 cells/ $\mu$ l, lower than 4,000/ $\mu$ l, or >10% immature (band) forms.
- **Severe sepsis** is sepsis complicated by organ dysfunction, tissue/organ hypoperfusion, or hypotension.
- **Septic shock** is the syndrome characterized by a persistent arterial hypotension in a septic patient. Hypotension is defined by a systolic arterial pressure <90 mmHg, a MAP <60, or a reduction in systolic blood pressure of >40 mmHg from baseline, despite adequate volume resuscitation, in the absence of other causes for hypotension.
- **Refractory septic shock** is the need for dopamine >15 mcg/kg/min noradrenaline or adrenaline >0.25 mcg/kg/min to maintain mean blood pressure above 60 mm Hg (80 mm Hg if previous hypertension).

### Pathophysiology of Sepsis

When the body is challenged by foreign microbial agents, homeostatic mechanisms come into play that attempt to rid the body of the foreign agent without damaging the host. This involves the activation of pro- and anti-inflammatory pathways, which are tightly controlled and regulated.<sup>4</sup> In most individuals, the body is able to achieve a balance between pro-inflammatory and anti-inflammatory mediators and homeostasis is restored. In some patients, however, this balance is upset with an excessive pro-inflammatory response resulting in SIRS, MODS, septic shock and, ultimately, death<sup>5</sup> (Fig. 2).

The evidence that sepsis results from an exaggerated systemic inflammatory response induced by infecting organisms is compelling; inflammatory mediators are the key players in the pathogenesis. The gram-positive and gram-negative bacteria induce a variety of pro-inflammatory mediators, including cytokines. Such cytokines play a pivotal role in initiating sepsis and shock. The bacterial cell wall components are known to release the cytokines. Several of the harmful effects of bacteria are mediated by pro-inflammatory cytokines.<sup>5</sup> The complement system is activated and helps to clear the infecting microorganisms but probably also enhances the tissue damage.<sup>6</sup> Hypotension, the cardinal manifestation of sepsis, occurs via induction of nitric oxide.<sup>7</sup> Nitric oxide plays a major role in hemodynamic alteration of septic shock.<sup>8,9</sup> A dual role exists for neutrophils; they are necessary for defense against microorganisms but also may become toxic inflammatory mediators contributing to tissue damage and organ dysfunction.<sup>10</sup> Tissue hypoxia is understood to be an important factor leading to multi-organ failure and death. Thus, early aggressive resuscitation of the septic patient may limit or reverse tissue hypoxia and the progression to organ failure. This transition to organ failure occurs during the critical “golden hours,” when time is survival and “tissue”, and the definitive recognition and treatment of sepsis provides maximal benefit in terms of outcome.

### Mechanisms of Organ Dysfunction

The conduit leading to organ failures all through sepsis can involve stepping up of the inflammatory responses and neuroendocrine systems. Timely recovery from organ failures in survivors and the normal anatomy of the failed organs indicate that ischaemic and hemorrhagic injury are an unusual means. Then again, mediators such as TNF, interleukin-1a and NO might slow down the mitochondrial respiratory chain, inducing cellular hypoxia with lower energy production, an effect aggravated by hormonal deficiencies.<sup>4,6</sup> Finally, too much expression of tissue factor, decreased concentrations and activity of coagulation inhibitors (antithrombin III, activated protein C, and tissue factor pathway inhibitor),<sup>11</sup> and deficient fibrinolytic activity resulting in increased coagulation that can interact with inflammatory mediators, leading microthrombi in the microcirculation and eventually to organ failure.<sup>12</sup>

## Diagnosis

A definite diagnosis of septic shock can be made when there is a clinically apparent and microbiologically documented infection and no other acute illness.<sup>3</sup> Septic shock is likely when clinically apparent infection is present without microbial documentation and without any other acute illness. Septic shock is unlikely when the diagnosis of infection is in doubt, no microbiological documentation is present, and another illness could explain the organ dysfunction. There may be a clinically obvious infection, such as purpura fulminans, cellulitis, toxic shock syndrome, community-acquired pneumonia in a previously healthy individual, or a purulent discharge from a wound or normally sterile cavity (e.g., bladder, peritoneal or pleural cavity, or cerebrospinal fluid). Otherwise, diagnosis of infection relies mainly on recovery of pathogens from blood or tissue cultures. However, cultures take 6–48 h and are negative in 30% of cases; furthermore, sepsis might be related to toxic agents produced by pathogens rather than to the pathogens themselves. Indeed, endotoxaemia is present in 30–40% of patients with gram-negative sepsis; it can also be detected in gram-positive bacteremia. Although need for vasopressors to maintain arterial pressure is widely used as the criterion for shock, low central venous oxygen saturation (<70%), direct noninvasive visualization of altered microcirculation, or impaired cardiovascular variability could provide earlier diagnosis.<sup>13</sup>

Establishing a causal link between infection and organ dysfunction is difficult. The likelihood of infection and the presence of another acute illness such as trauma, burns, pancreatitis, cardiac disease, or poisoning should be taken into account. Tools such as procalcitonin (PCT)<sup>14,15</sup> may be useful and have been shown to be superior to other inflammatory markers such as TNF, IL-6, IL-1, and C-reactive protein (CRP)<sup>15</sup> in outcome prediction among critically ill patients. The triggering receptor expressed on myeloid cells (TREM-1) is strongly and specifically expressed by neutrophils and macrophages from tissues infected by bacteria or fungi. Concentrations of soluble TREM-1 in bronchoalveolar lavage fluid of 5 ng/L or more can indicate ventilator associated pneumonia.<sup>16,17</sup> High concentrations of procalcitonin or TREM-1 in tissue can assist in the diagnosis of culture-negative septic shock, and concentrations of procalcitonin in serum lower than 0.25mg/L can further rule out infection when septic shock is unlikely.<sup>14</sup>

Numerous studies have evaluated the use of lactate as a diagnostic, therapeutic, and prognostic marker of global tissue hypoxia in patients with circulatory shock. An elevated serum lactate concentration, although lacking in precision, may identify tissue hypoperfusion in non-hypotensive patients. Lactate concentrations > 4 mmol/L in the presence of the systemic inflammatory response syndrome (SIRS) have been shown to significantly increase intensive care unit (ICU) admission rates and mortality rate in normotensive patients.<sup>18</sup> Although the sensitivity and specificity of single lactate concentrations as markers of tissue hypoperfusion have been debated, serial measurements or lactate clearance over time have been shown to be better prognosticators of organ failure and mortality. Persistent elevations in lactate > 24 h are associated with a mortality rate as high as 89%.<sup>18</sup>

The evaluation of severity of illness in the critically ill patient is made through the use of severity scores and prognostic models. Several scoring systems have been developed and one of the most used in ICUs worldwide is the Acute Physiology and Chronic Health Evaluation (APACHE) II score.<sup>19</sup> The APACHE II is a good severity score for the generic critically ill patient and it is able to predict outcome, but it poorly correlates to organ dysfunction, which is the main characteristic of patients with severe sepsis. Sepsis-related Organ Failure Assessment score, which does not predict an outcome but rather describes organ dysfunction, expressing the level of morbidity rather than the mortality index. It studies six organs with a scale for each from 0 (normal) to 4 (worse situation) For Respiratory system PaO<sub>2</sub>/FiO<sub>2</sub> ratio, for Coagulation-Platelet count, for Liver-bilirubin, for Cardiovascular system hypotension, for Central Nervous System-Glasgow Coma Scale and for Renal system S. Creatinine or urine output<sup>20</sup> (Table 2).

## **SOURCE CONTROL**

When the systemic inflammatory response is recognised and an infection is suspected, the first step to undertake is to document and treat it as soon as possible. The evaluation and discovery of a patient with sepsis of unknown origin represents a true clinical challenge for the critical care physician. In this clinical setting radiologic imaging is necessary to localize or rule out a focus as a source of sepsis. Ultrasonography is the initial diagnostic procedure in patients with suspected intra-abdominal abscesses. CT is not only a diagnostic tool, because CT-guided percutaneous drainage can be used as the definite therapy for abscesses.<sup>21</sup>

### *Suggestions*

Source control consists of drainage of infected fluid collection, debridement of infected solid tissue and the removal of devices or foreign bodies.

## **Early Goal-directed Therapy**

A single center study showed that early goal-directed hemodynamic optimization starting in the emergency department for severe sepsis and septic shock patients significantly decreases morbidity and mortality. Early aggressive therapy that optimized cardiac preload, afterload, and contractility in patients with severe sepsis and septic shock improved survival. Fluid infusions of colloid or crystalloid, vasoactive agents, and transfusions of red blood cells to increase oxygen delivery. Resuscitation endpoints chosen for assessment of the adequacy of oxygen delivery were the normalization of values for mixed venous oxygen saturation (ScVO<sub>2</sub>), lactate concentration, base deficit, and pH. Patients in the group that received early goal directed therapy received more fluid, inotropic support, and blood transfusions during the first 6 hrs than did control patients, who received “standard” resuscitation therapy. The patients in the treatment group showed a statistically significant mortality reduction of 16.5%.<sup>22</sup>

### *Suggestions*

1. Maintain central venous pressure (CVP) between 8-12 mmHg and 12-15 mmHg in patients who are mechanically ventilated.
2. Maintain mean arterial pressure (MAP)  $\geq$  70 mm Hg.
3. Maintain a urine output  $\geq$  0.5 ml/Kg/h.
4. To maintain central venous oxygen saturation (ScVO<sub>2</sub>)  $\geq$  70%.

These targets have to be achieved with fluid therapy (colloids or crystalloids) initially. Vasopressors can be used in those patients not responding to fluid resuscitation (To start with dopamine or noradrenaline has to be used, continuous venous infusion of vasopressin, 0.01 to 0.04 units/min, may be tried in patients not responding to noradrenaline). If central or mixed

venous oxygen saturation remains below 70% after correcting CVP to 8-12 mmHg, a transfusion of packed red blood cells to achieve a hematocrit of  $\geq 30\%$  or dobutamine up to a maximum of 20 mcg/Kg/min should be administered to achieve this goal.<sup>22</sup>

### **Newer Approach for Managing Severe Sepsis and Septic Shock**

The use of protective lung strategy for septic patients has established that mechanical ventilation with high tidal volumes could stretch lung tissue to cause volume trauma exacerbating the inflammatory response and inducing acute lung injury or ARDS.<sup>23</sup> The protective lung strategy consists of ventilating patients with low tidal volumes, trying to keep the airway plateau pressure below 30 cm H<sub>2</sub>O, even allowing a moderate grade of hypercarbia to reach this goal. A multicenter randomized controlled trial demonstrated an absolute reduction in mortality of 9.9% in septic patients with acute lung injury and ARDS ventilated with this particular ventilation strategy. Because sepsis is the most common cause of ARDS, it is sensible to establish ventilation with low tidal volumes when lung injury or ARDS is present.

Activated protein C (rhAPC) is a protein with anticoagulant, fibrinolytic, and anti-inflammatory properties; its mechanism of action is to improve microcirculation, oxygen delivery, limiting the coagulation and the endothelial inflammation induced by the septic process. Activated protein C (rhAPC) showed a reduction in mortality rate (from 30.7–24.7%) in a large multicenter randomized controlled study.<sup>24</sup> Results coming out from a recent study, which has shown no mortality benefit of the administration of rhAPC to patients with low risk of death (APACHE II <25 and single-organ failure).<sup>25</sup> Its elevated cost, and anticoagulant properties, the use of this molecule is limited to patients with high risk of death and no risk of bleeding.

Corticosteroids were regarded to be useful in sepsis because of their anti-inflammatory effect and their ability to prevent inflammatory cascade activation by the complement, prevention of prostaglandin production. The use of high-dose corticosteroids in septic shock has not improved overall survival and has even increased the risk of secondary infections.<sup>26</sup> The use of low-dose corticosteroid in severe sepsis and septic shock has its rationale, that in the neurohormonal response to septic shock, many patients have an insufficient adrenal reserve, because of a reduced release of adrenocorticotrophic hormone and a peripheral steroid resistance at the receptor level. The administration of low-dose hydrocortisone and fludrocortisone in patients with relative adrenal insufficiency has shown a 10% reduction in absolute mortality at 28 days in one multicenter randomized controlled trial.<sup>27</sup>

Following initial resuscitation of patients with severe sepsis, blood glucose should be maintained <150 mg/dl. A large single-center trial of postoperative surgical patients showed significant improvement in survival when continuous infusion insulin was used to maintain glucose between 80 and 110 mg/dl. Exogenous glucose was given simultaneously with insulin along with frequent monitoring of glucose (every 1 h). Hypoglycemia may occur. Best results were obtained when glucose was maintained between 80 and 110 mg/dl, achieving a goal of less than 150 mg/dl also improved outcome when compared to higher levels.<sup>28</sup>

This goal will likely reduce the risk of hypoglycemia. The control of the blood glucose concentration appears to be more important than the amount of insulin infused.

### **Guidelines of Managing Patients with Septic Shock (based on *Surviving Sepsis Guidelines*):<sup>29</sup> (Fig. 3)**

#### *Initial Resuscitation*

The initial resuscitation of patients with septic shock or elevated serum lactate must be rapid, or mortality can increase by 30%. The following should be achieved within 6 hours of the onset of septic shock:

*Fluid resuscitation* is initiated to achieve a CVP of 8 to 12 mmHg

*Vasoactive drugs:* are then used to achieve a mean arterial pressure of 65 to 70 mmHg.

*Inotropic agents:* are used to achieve ScVO<sub>2</sub> of at least 70%.

*Urine output:* should be at least 0.5 and preferably at least 1 ml/kg/hr.

*Fluid Therapy:* Fluid challenges in patients with perfusion deficits are given rapidly (1000 ml over 30 min for crystalloid, or 500 ml over 30 min for colloid). Fluid input-output balance is of no value in assessing fluid requirements during first 24 h because of capillary leak.

### *Antibiotic Therapy*

Antibiotics are initiated within 1 hour of recognition of severe sepsis.<sup>39</sup> Monotherapy with carbapenems is usually sufficient in non-neutropenic patients, with consideration for vancomycin for resistant gram-positive organisms. Neutropenic patients should receive combination therapy. Antibiotic therapy should consider the incidence and susceptibility patterns within the hospital.<sup>31</sup> Antibiotic therapy is reassessed upon culture results and sensitivities within 48 to 72 hours, stop antimicrobials within 72 hours if no infectious source is found.

### *Source Control*

Evaluate the patient for an identifiable focus of infection, and initiate source control as soon as identified. Abscess drainage can be performed percutaneously in most instances. Devitalized tissue should be debrided. Sepsis associated with vascular devices requires removal of that device, and replacement at a separate site. Tunneled devices without external drainage may receive consideration for sterilization via antibiotic therapy.

### *Vasopressor Therapy*

Vasopressor therapy is indicated when the following conditions are met: Hypotension (MAP < 60-65) adequate completed fluid resuscitation (target CVP reached), lack of peripheral vasoconstriction on physical examination. Do not use vasopressors in vasoconstrictive or low cardiac output states or in volume depleted patients. The vasopressor of choice are dopamine and noradrenaline.<sup>32</sup> The initial dose of noradrenaline is 0.1-0.2 mcg/kg/min, up to 1 mcg/kg/min. Do not exceed 5 mcg/kg/min. Dopamine dose varies from 6-20 mcg/kg/min, low-dose dopamine for renal perfusion is not used in critically ill patients.<sup>33</sup>

### *Inotropic Therapy*

Dobutamine is used for patients with low cardiac index (or a decrease in cardiac index with vasopressors) following targeted fluid resuscitation. Dobutamine is titrated to achieve a normal to physiologic cardiac output (up to 1.5 times normal, e.g. 4.5 L/min). Do not titrate to supraphysiologic cardiac index.<sup>34,35</sup>

### *Endocrinologic Therapy*

Administer hydrocortisone 50 mg Q6H for 7 to 10 days in patients with vasopressor dependence regardless of adequate fluid resuscitation. If shock resolves more rapidly, the dose may be discontinued sooner.

Patients with low-dose vasopressor requirements may undergo an ACTH stimulation test, and steroids withheld if an adequate response is noted.

Administer vasopressin 0.0005 to 0.001 U/kg/min to patients with vasopressor dependence as a physiologic replacement for vasopressin deficiency in severe sepsis.<sup>36</sup> Do not titrate to blood pressure.

### *Recombinant Activated Protein C (rhAPC)*

Patients with septic shock requiring vasopressors or patients with sepsis-related organ failures should receive rhAPC if no absolute contraindications exist.<sup>24</sup> Patients with relative contraindications should have risk/benefit evaluated before proceeding. Limiting factor for this therapy is the prohibitive cost and bleeding diathesis, which is frequently encountered in septic patients.

### *Extracorporeal Support*

The systems currently in use are continuous renal replacement therapies (CRRT). Continuous renal replacement therapy is used when one or more of the following are present: in acute renal failure of sepsis, the inability to achieve an appropriate circulating volume status, using diuretics or fluid restriction.<sup>37</sup> Therapy is started before excess fluid accumulation occurs. In acute renal failure, continuous veno-venous hemofiltration or intermittent hemodialysis are considered equivalent. Continuous hemofiltration offers easier management of fluid balance in hemodynamically unstable septic patients.

*Red blood cells:* are limited to the following circumstances: Volume- and vasopressor/inotrope-resuscitated patients with an SvO<sub>2</sub> < 65% (to achieve a target SvO<sub>2</sub> > 70%).<sup>22</sup> In the absence of these measurements, evaluate for excessive cardiovascular work and the presence of lactic acidosis).

Coronary artery disease with recent angina or coronary syndromes (to achieve a target hemoglobin of 12g/dl). Acute hemorrhage in the face of anemia (Hb < 9).

*Fresh frozen plasma:* Is administered for clinical bleeding or the need to undergo an invasive procedure in the presence of coagulopathy due to deficiency in coagulation factors.

*Platelets transfusion:* for counts < 10,000, or < 30,000 and there is risk of bleeding. For invasive procedures (surgery or access of a non-compressible vessel), a platelet count > 50,000 is usually desirable.

*Metabolic and Nutritional Therapy:* Maintain blood glucose through the use of appropriate caloric support and insulin infusion following initial stabilization.

Do not administer sodium bicarbonate for metabolic (anion- gap) acidosis, such as lactic acidosis if the pH is > 7.15. For a lower pH, consider a trial of 50 to 100 mEq NaHCO<sub>3</sub> by slow infusion, with evaluation for improvement in hemodynamics. For non-anion gap acidosis (hyperchloremic), consider correction with sodium bicarbonate to achieve a base excess > -5 mEq/L, and avoidance of hyperchloremic intravenous solutions.

Initiate enteral nutrition following stabilization. If gastric tonometry is used, delay nutritional support. Continuous gastric or post-pyloric feeding is preferred, with appropriate precautions for over distension, including the use of promotility agents if needed. Parenteral nutrition should be avoided unless there is an absolute contraindication to enteral feeding (e.g. mechanical obstruction).

*Sedation:* Target sedation to predetermined sedation score. Use minimal sedation necessary. Combination regimens may be better. Benzodiazepines in moderate dose either continuously or intermittently is useful. Low-dose narcotics are also helpful. Agitation will require treatment with antipsychotic agents like haloperidol. Titration to higher doses of benzodiazepines or narcotics is not recommended, and can compound the agitation/delirium.

In long-term sedation, transition to shorter acting agents is recommended prior to attempts at extubation.

*Stress Ulcer Prophylaxis:* Provide stress ulcer prophylaxis in all patients. H<sub>2</sub> antagonists are preferred to Sucralfate.

*Deep Venous Thrombosis Prophylaxis:* Provide DVT prophylaxis with low-molecular weight heparin or low-dose unfractionated heparin in the absence of significant bleeding risk. Use mechanical intermittent compression in patients with bleeding disorders.

## SUMMARY

The incidence of severe sepsis and septic shock still remains quite high, as does its mortality, which has decreased very little over the past decades. Optimal management depends on rapid recognition, aggressive restoration of circulating volume with fluid boluses, initiation of appropriate antibiotic therapy, implementation of adequate monitoring, and meticulous attention to the details of care. Mean arterial pressure should be increased to between 65 and 75 mm Hg as soon as possible to reduce the likelihood of multiorgan dysfunction. Despite these therapeutic maneuvers, however, mortality rates are likely to remain high until the development of therapies that better target the underlying mechanisms of sepsis. Regardless of the advances in the knowledge of sepsis and septic shock there is no “magic bullet” to treat this syndrome.

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**Continuous veno-venous hemofiltration improves hemodynamics in septic shock with acute renal failure without modifying TNFalpha and IL6 plasma concentrations. *J Nephrol* 2002;15(2):150-7.**



## Multiple Choice Questions

- 1. Which of the following is not a characteristic feature of sepsis?**
  - A. Temperature  $> 38^{\circ}\text{C}$  or  $< 36^{\circ}\text{C}$
  - B. Heart rate  $> 90/\text{min}$
  - C. WBC count  $> 12,000/\text{mm}^3$
  - D. Respiratory rate 14-18/min
- 2. Which of the following parameters is not used as a resuscitation end point to assess adequacy of oxygen delivery?**
  - A.  $\text{ScVO}_2$
  - B. Lactate concentration
  - C. Base deficit
  - D. All of the above
- 3. All the following are mechanism by which activated protein C acts in sepsis?**
  - A. Improve microcirculation
  - B. Improve oxygen delivery
  - C. Promotes coagulation
  - D. Limits endothelial inflammation
- 4. Which of the following are targets to be achieved in the first six hours of onset of septic shock?**
  - A. CVP of 8-12 mm Hg
  - B. Mean arterial pressure 65-70 mm Hg
  - C.  $\text{ScVO}_2 \geq 70\%$
  - D. All of the above
- 5. Which of the following is not preferred mode of renal replacement therapy in septic shock?**
  - A. Hemodialysis
  - B. Intermittents peritoneal dialysis
  - C. Continuous veno-venous hemofiltration
  - D. Continuous arteriovenous hemofiltration

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1. D 2. D 3. C 4. D 5. A