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Septic shock: Targeting evaluation and treatment

Halting the progression to multiple organ failure

KHALDOUN FARIS, MD

ABSTRACT: Shock may be defined in physiologic terms as a state in which the circulatory system is unable to meet the cellular needs for perfusion to maintain tissue homeostasis. Septic shock is defined as a state of tissue hypoperfusion arising from a documented infection or the infection-induced release of inflammatory mediators. Successful resuscitation depends on careful patient assessment to determine the causal organisms of infection and appropriate antibiotic therapy targeting the key pathogens. In many cases, where high cardiac output is opposed by reduced left ventricular filling pressure despite fluid loading, administration of inotropic agents may be warranted to alleviate myocardial dysfunction. Septic shock requires rapid intervention to stop the downward spiral to multiple organ failure and death. (*J Crit Illness*. 2002;17(9):357-363)

The pathophysiology of septic shock focuses on infection as the primary event, stimulating a cascade of mediators that leads to uncontrolled systemic inflammation, microvascular coagulopathy, deregulated apoptosis, and tissue hypoxia.¹ The overall mortality rate from septic shock is about 40%, and elderly patients or those with immune dysfunction such as that caused by diabetes, burns, malignancy, or cirrhosis may have an even greater likelihood of death. Septic shock complicated by multiple organ dysfunction is the most common cause of death in the ICU, and its incidence has approximately doubled since 1979 to over 400,000 cases annually in the United States.² This increased incidence probably reflects more aggressive support of seriously ill patients, a growing percentage of whom are elderly, and increased use of invasive devices, such as bladder and intravascular catheters.³

In this review, I describe the common manifestations of sepsis, ini-

tial assessment and diagnostic strategies that may help define the causative organism(s), and my approach to monitoring and treating patients with this challenging disease.

CLINICAL MANIFESTATIONS

Hemodynamic criteria for shock include a mean arterial pressure less than 60 mm Hg or a decrease in the systolic blood pressure of more than 40 mm Hg from baseline. The hypotension usually presents with high cardiac output such that the patient has warm extremities with a rapid capillary refill, as opposed to cardiogenic or hemorrhagic shock, in which the extremities are cool and the capillary refill is delayed.

Patients with septic shock generally are in a hyperdynamic state characterized by high cardiac output and low systemic vascular resistance.⁴ Despite the high cardiac output, significant myocardial dysfunction with reduced left ventricular ejection fraction is frequently observed in this pa-

tient population.⁵ Cellular dysfunction ensues—brought about by the hypotension, insufficient blood flow to various tissue beds, or the infection-induced release of inflammatory mediators.

In addition to the hemodynamic aberrations, other clinical manifestations of sepsis include fever, hypothermia, tachycardia, tachypnea or hyperventilation, oliguria, and altered sensorium (Table 1).⁶ In more advanced stages, the condition may progress to profound hypoxemia refractory to supplemental oxygen (acute respiratory distress syndrome), acute renal failure, or disseminated intravascular coagulation.

Laboratory abnormalities such as leukocytosis (white blood cell [WBC] count greater than 12,000/ μ L) or leukopenia (WBC count less than 4000/ μ L) with an increase in “immature band forms,” evidence of poor oxygenation on arterial blood gas analysis, and metabolic acidosis with an increased serum lactate level

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Table 1 – Definitions

Infection

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

Bacteremia

The presence of viable bacteria in the blood.

Systemic inflammatory response syndrome

The systemic inflammatory response to a variety of severe clinical insults. The response is manifested by 2 or more of the following:

- Temperature > 38°C (100.4°F) or < 36°C (96.8°F)
- Heart rate > 90 beats/min
- Respiratory rate > 20 breaths/min or PaCO₂ < 32 mm Hg
- WBC count > 12,000/μL, < 4000/μL, or > 10% immature (band) forms

Sepsis

The systemic response to infection. This systemic response is manifested by 2 or more of the following conditions as a result of infection:

- Temperature > 38°C (100°F) or < 36°C (96.8°F)
- Heart rate > 90 beats/min
- Respiratory rate > 20 breaths/min or PaCO₂ < 32 mm Hg
- WBC count > 12,000/μL, < 4000/μL, or 10% immature (band) forms

Severe sepsis

Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.

Septic shock

Sepsis with hypotension, despite adequate fluid resuscitation, along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time perfusion abnormalities are measured.

Hypotension

A systolic BP of < 90 mm Hg or a reduction of > 40 mm Hg from baseline in the absence of other causes of hypotension.

Multiple organ dysfunction syndrome

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

WBC, white blood cell; BP, blood pressure.

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may be apparent also. Other associated abnormalities may include thrombocytopenia, prolonged prothrombin/partial thromboplastin time, or elevated levels of blood urea nitrogen and creatinine.

INITIAL ASSESSMENT

The first objective in the evaluation of a patient in whom sepsis is suspected

is careful assessment of the adequacy of the patient's airway, breathing, and circulation. Only after this is done is a more detailed history taken and physical examination performed. A patient's mental status should be assessed as well as his or her degree of respiratory distress and hemodynamic instability.

The patient who is obtunded or

comatose cannot protect his airway, and this is as compelling an indication for endotracheal intubation as severe respiratory fatigue or impending respiratory failure. Patients with profound hypotension and those who remain refractory to initial resuscitative efforts also should be intubated, since metabolic acidosis often induces respiratory muscle fatigue.

The respiratory status of a patient with sepsis can be evaluated rapidly by making a few simple observations. The respiratory rate and the difficulty of the patient's respiratory effort are helpful in assessing respiratory distress, as are intercostal, suprasternal, or supraclavicular retractions. Anxiety, accessory muscle use, or diaphoresis may signal impending respiratory failure. Even if the patient does not have obvious respiratory distress, supplemental oxygen by face mask should be administered if sepsis is suspected.

On evaluation of the circulation, rapid vascular access with a large-bore peripheral venous catheter should be established. Unless there is evidence of fluid overload, an initial fluid bolus of 1 L of crystalloid (either normal saline or lactated Ringer solution) should be administered rapidly (over 10 to 20 minutes) and the patient's response to the fluid challenge observed. If there is no improvement in the patient's pulse or blood pressure after the initial volume infusion, subsequent fluid boluses may be administered. No improvement after several fluid boluses may indicate the need for inotropic support and invasive monitoring in the ICU.

During initial resuscitation, the patient should be rapidly examined to determine the source of infection. In the examination, the CNS (meningitis), the lungs (pneumonia), the abdomen (ruptured appendix or perforated viscus), and the urinary system (urosepsis from an indwelling Foley

catheter), as well as sites of intravascular catheter insertion, are of particular interest. Often the source of infection is not apparent, requiring further evaluation and diagnostic studies.

While initiating resuscitative efforts, blood, urine, and sputum samples should be collected for culture. A minimum of 20 mL and ideally 30 mL of blood should be drawn from 2 separate peripheral venipuncture sites if possible.⁷ Patients also should be examined for cellulitis at either a peripheral or central venous insertion site. Patients who are granulocytopenic or who have received corticosteroids in large doses for prolonged periods may not demonstrate signs of inflammation, such as erythema, warmth, and swelling at the infection site.⁸

Antibiotic therapy should be initiated as rapidly as possible after the appropriate cultures have been ordered and after the patient has been examined for an obvious source of infection. The choice of empiric antibiotic therapy should be based on the suspected site of infection, the organisms likely to be responsible, and the sensitivities of organisms frequently isolated from the local microbiology laboratory documented in the "antimicrobial sensitivity report."

Patients need to be assessed frequently for a clinical response while taking antibiotics—especially if there are signs of deterioration—and until a surgically correctable source of infection can be identified (for example, an abscess or perforated viscus). The most recent results of the pertinent microbiologic studies need to be reviewed.⁹ Likely causes of an infection's failure to respond to therapy include a resistant or unidentified organism or an undrained septic focus.¹⁰

Patients in whom septic shock is suspected should be transferred to an ICU, and appropriate hemody-

namic monitoring should be initiated. Patients who have significant myocardial disease, those in whom initial resuscitative efforts failed, and those with significant oxygenation difficulties requiring high levels of positive end-expiratory pressure (PEEP) will probably need a pulmonary artery catheter.^{11,12} After providing hemodynamic support and identifying the source of infection, the third therapeutic goal involves modifying the inflammatory cascade to prevent further tissue injury (Figure).¹³⁻¹⁵

HEMODYNAMIC SUPPORT

The objective is to restore effective perfusion to the vital organs. To assess the adequacy of hemodynamic support, one must be able to evaluate indices of global as well as regional perfusion (Table 2). Clinical parameters used to assess global perfusion include mental status, capillary refill, urinary output, heart rate, and blood pressure, as well as cardiac output and serum lactate level.

Mixed venous oxygen saturation concentrations frequently are elevated in septic shock because of compromised blood flow and the inability of the tissues to participate in aerobic metabolism; therefore, its use as an indicator of global perfusion is limited. Assessment of splanchnic circulation using gastric tonometry represents an index of regional perfusion. Gastric tonometry has been used to measure gastric intramucosal PCO_2 and to subsequently determine the intramucosal pH by assuming that the gastric bicarbonate level equals the serum bicarbonate level.¹⁶ The arterial-gastric PCO_2 difference is considered representative of gastric mucosal oxygenation.¹⁷

Fluids

Hypovolemia is present in the initial phase of septic shock and remains until adequate fluid resuscitation is

achieved—when a hyperdynamic profile becomes manifest.¹⁸ Effective fluid resuscitation has been shown to improve cardiac output, tissue perfusion, oxygen delivery, and survivability in patients with septic shock.^{19,20} Crystalloid (normal saline or lactated Ringer solution) initially should be given in boluses to achieve clinical end goals such as adequate urinary output (greater than 0.5 mL/kg/h), normal blood pressure (or one approximating a hypertensive patient's baseline blood pressure), and a normal heart rate (or a diminution in tachycardia). Failure to achieve these goals may indicate the need for a pulmonary artery catheter to assess volume status and changes in cardiac output or stroke volume in response to fluid boluses.

The target for the filling pressures may be a pulmonary capillary wedge pressure of 12 to 15 mm Hg, which is consistent with an optimal cardiac output in many patients.^{13,21} Since crystalloid solutions, such as 0.9% sodium chloride (normal saline) and lactated Ringer solution, are distributed in the extracellular space, roughly 25% or less of the infused volume will remain in the intravascular space. Isotonic crystalloid infusions of 1 L have been demonstrated to increase the intravascular volume by only 100 to 200 mL.²²

The most commonly used colloid solutions in resuscitating patients are albumin and hydroxyethyl starch, known as hetastarch. Unlike crystalloids, colloids have the advantage of raising the colloid oncotic pressure and do not migrate as readily from the intravascular to the interstitial space. The result is that smaller volumes of colloid are required to expand intravascular volume. For example, 1 L of a 5% albumin solution may increase the intravascular volume by 500 to 1000 mL.²² Hetastarch, a synthetic colloid available in a 6% solu-

Table 2 – Indices of perfusion

Global	Regional
Mental status	CNS: decreased sensorium
Capillary refill	Heart: ECG changes of ischemia
Urinary output	Renal: elevated blood urea nitrogen and creatinine levels; decreased creatinine clearance
Mean arterial pressure and heart rate	Hepatic: elevated transaminase and bilirubin levels; prolonged prothrombin time
Serum lactate level	GI tract: stress ulceration; ileus; malabsorption; decreased intestinal pH via gastric tonometry

tion, may cause a decrease in factor VIII activity when administered in large volumes, which may prolong the partial thromboplastin time. Heta-starch may cause an increase in circulating plasma volume similar to the increase in intravascular volume caused by 5% albumin.

Vasopressors

If a patient remains refractory to aggressive fluid therapy, a vasopressor, such as dopamine, epinephrine, or norepinephrine, may be used to increase mean arterial pressure. The goal of therapy with these agents is to

restore effective perfusion pressure without compromising stroke volume, renal perfusion, or splanchnic perfusion (Table 3).

Dopamine affects α , β , and dopaminergic receptors depending on the dosage used. At low doses (2 to 5 $\mu\text{g}/\text{kg}/\text{min}$), the drug activates predominantly dopaminergic receptors, causing renal and splanchnic vasodilation. At intermediate doses (5 to 10 $\mu\text{g}/\text{kg}/\text{min}$), the drug has an inotropic effect by virtue of its activity on β_1 (cardiac) receptors. At still higher doses (greater than 10 $\mu\text{g}/\text{kg}/\text{min}$), the α receptors are stimulated and a

vasopressor response is produced.

Dopamine's effect at higher doses may be diminished by its tendency to produce tachycardia and reduce stroke volume by limiting ventricular filling time. In contrast to dopamine, norepinephrine has more potent α -adrenergic effects and less pronounced β effects such that it may be used to augment mean arterial pressure in volume-loaded patients with sepsis whose hemodynamics remain refractory to dopamine infusion.²³ Norepinephrine may be infused starting at doses as low as 0.01 $\mu\text{g}/\text{kg}/\text{min}$ up to a maximum of 3 $\mu\text{g}/\text{kg}/\text{min}$.

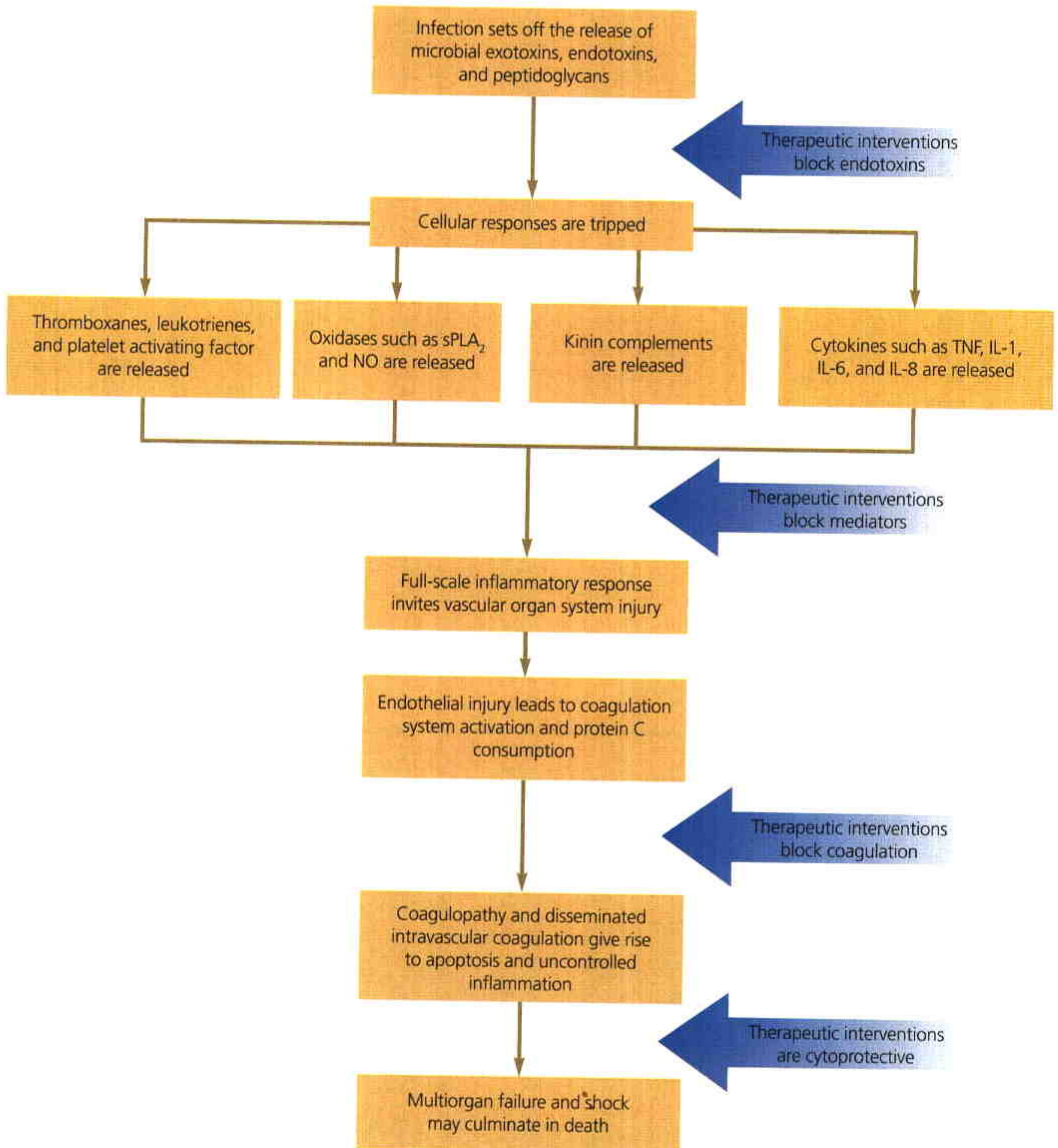
Epinephrine has been shown to decrease splanchnic perfusion, increase hepatic venous lactate concentrations, and decrease gastric mucosal pH, although only transiently. In addition, it increases myocardial oxygen consumption. It should be reserved for occasions when other sympathomimetic agents fail to restore mean arterial pressure.²⁴ Phenylephrine, a pure α_1 -agonist, is used rarely and only for patients—such as those with myocardial ischemia or severe aortic stenosis—in whom tachy-

Table 3 – Receptor activity of vasopressors/inotropic agents

Agent	α Effect	β_1 Effect	β_2 Effect	Dopaminergic effect
Norepinephrine	++++	++++	+ / ++	None
Epinephrine	+++	++++	+++	None
Dopamine	++ / +++	++++	++	++++
Dobutamine	+	++++	++	None
Phenylephrine	++++	None	None	None
Amrinone	None	None	None	None
Milrinone	None	None	None	None
Glucagon	None	None	None	None

+ , intensity of effect.

Figure – Customizing sepsis therapy to points in pathogenesis



sPLA₂, secretory phospholipase A₂; NO, nitric oxide; TNF, tumor necrosis factor; IL, interleukin.

dysrhythmias from other agents would be poorly tolerated.

Inotropic agents

Many patients with septic shock who have been adequately resuscitated with fluid may still need inotropic support to optimize regional perfusion indices when ventricular ejection fraction remains reduced despite high cardiac output.

Dobutamine is a racemic mixture of L and D forms, which when administered together possess a predominantly β_1 effect that has been shown to improve splanchnic blood flow compared with other catecholamines.²⁵ Dobutamine has a variable effect on mean arterial pressure ranging from no change to hypotension requiring α -agonists. Dobutamine's efficacy may be limited because it induces significant tachycardia, which may be unacceptable in certain groups of patients (such as those with coronary artery disease or atrial fibrillation). Phosphodiesterase inhibitors such as amrinone and milrinone also are known for their inotropic effects; however, their routine use in

patients with sepsis is not recommended because of their vasodilatory effects.

A recent, prospective, randomized trial has shown a significant decrease in the severity of organ dysfunction and in-hospital mortality in patients with severe sepsis and septic shock who received early goal-directed therapy. This aggressive therapy included fluid resuscitation to maintain central venous pressure higher than 8 mm Hg, vasoactive agents to maintain mean blood pressure between 65 and 90 mm Hg, and blood transfusion in addition to inotropic agents to maintain mixed venous oxygen saturation concentrations higher than 70%.²⁶

Immune response modulators

New modalities for treatment of septic shock modify the response of the immune system. Theoretically, interrupting the septic cascade would prevent multiple organ failure and the corresponding mortality. Endotoxin inactivation and inhibition of the tumor necrosis factor as well as various receptors are examples of im-

mune response modulation areas under study.

The role of corticosteroids in sepsis and septic shock has been extensively studied. Despite earlier disappointing results, new trials have been very encouraging. A stress dose of hydrocortisone (100 mg followed by 0.18 mg/kg/h infusion) in septic shock patients was found to reduce the time to cessation of vasopressor therapy.²⁷ Also, in pressor-dependent septic shock patients, hydrocortisone, 100 mg IV 3 times a day, has been shown to improve hemodynamics and survival.²⁸

Activated protein C is an endogenous protein with anti-inflammatory, antithrombotic, and profibrinolytic properties that may play a major role in modulating inflammation and coagulation in sepsis and septic shock.

The safety of activated protein C and its efficacy in reducing D dimer (marker of coagulopathy) and interleukin-6 (marker of inflammation) levels as well as mortality in severe sepsis has been proved in 2 randomized, double-blind, placebo-controlled, multicenter trials.^{29,30} An infusion of drotrecogin alfa (recombinant human activated protein C) for 96 hours in patients with severe sepsis was shown to reduce mortality significantly (30.8%, vs 24.7% for placebo).

A recombinant tissue factor pathway inhibitor also has been evaluated in severe sepsis. Its safety and efficacy in reducing levels of thrombin-antithrombin complexes (markers of coagulopathy) and interleukin-6 have been proved in a prospective, randomized, single-blind, placebo-controlled, multicenter trial.³¹

SUMMARY

In conclusion, septic shock is a clinical entity with a myriad of possible presentations as precipitated by a common sequence of events: an infectious agent instigates circulatory

CLINICAL CONCLUSIONS:

Successful resuscitation for septic shock is all-encompassing

- 1 Septic shock—and its frequent corollary multiple organ failure—is the most common cause of death in the ICU and is increasing in frequency as the nation's proportion of elderly persons grows.
- 2 Take pains to properly identify the source, the site, and the sensitivities of the infectious agents suspected to be causal in septic shock.
- 3 Inotropic support may be necessary for a significant number of patients who have myocardial dysfunction as evidenced by decreased ventricular ejection fraction despite volume loading.
- 4 Human recombinant activated protein C has been shown to be effective in calming the pathogenic inflammatory response.
- 5 Other promising treatment strategies under study include the use of corticosteroids and monoclonal antibodies.

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failure that leads to tissue hypoxia—and ultimately, multiple organ dysfunction and death. Management of septic shock patients involves rapid assessment of the most likely causes and organisms, acquisition of ade-

quate samples for culture, and resuscitation. Resuscitation includes selecting antibiotics targeting the most likely pathogens, volume loading to prevent or reverse hypovolemia, and administering inotropic agents to aug-

ment mean arterial pressure, cardiac output, and oxygen delivery. Promising new options in the area of immune response modulation are being researched to better meet the needs of patients with sepsis in the future.

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