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## EDITORIAL COMMENTS

*Septic shock is a common clinical problem encountered in day to day clinical practice. The mortality from this condition is very high unless managed properly. Sepsis involves many organ system of the body, but cardiovascular complications are the most important and are the immediate cause of death. The recognition of these complications and their proper management will improve survival.*

## CARDIOVASCULAR MANAGEMENT OF SEPTIC SHOCK

Sepsis, septic shock, and multiple organ failure (MOF) are very common, afflicting 750,000 people and resulting in 215,000 deaths annually in the United States alone. Sepsis mortality, estimated at 9.3% of all deaths in the United States, is numerically equivalent to mortality from acute myocardial infarction and far exceeds mortality related to either AIDS or breast cancer. The average length of hospital stay and the cost per case were 19.6 days and \$22,100, with an annual cost estimated at \$16.7 billion in the US. Despite, significant advances in our knowledge of the pathophysiologic processes involved in sepsis and septic shock incidence of sepsis and the associated mortality has steadily increased over the past several decades.

### Definition of Septic Shock

In 1992, the ACCP/SCCM Consensus Conference Committee defined septic shock as follows: ". . .sepsis-induced hypotension (systolic blood pressure < 90 mm Hg or a reduction of  $\geq 40$  mm Hg from baseline or a MAP < 60 mm Hg) despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, lactic acidosis, oliguria, or an acute alteration in mental status.

### Pathophysiology and Associated Clinical Considerations

The hemodynamic profile of septic shock is influenced by multiple sepsis induced physiologic changes and characterized by components of

hypovolemic, obstructive, cardiogenic, distributive, and cytotoxic shock (Table1). This hemodynamic profile is modified by fluid resuscitation. After adequate restoration of left ventricular filling, the presence and severity of hypotension are directly dependent on impairment of contractility (both sepsis-induced and baseline) and the degree of systemic vascular resistance lowering. Persistent hypotension, despite adequate fluid resuscitation, mandates the use of vasopressors and is the hallmark of septic shock. Even when cardiac output in septic shock has been normalized or is supranormal, hypoperfusion abnormalities (lactic acidosis, decreased urine output, or altered mental status) may persist. This "distributive shock" may be related to a maldistribution of blood flow at the organ level (decreased blood flow to the stomach, pancreas, and small bowel) or microvascular level (shunting).

**Table 1:** Septic shock-A melting pot of shock etiologies

- *Hypovolemic* (loss of cardiac filling)  
Capillary leak (absolute hypovolemia)  
Venodilation (relative hypovolemia)
- *Cardiogenic*  
Decrease in contractility
- *Obstructive*  
Rise in pulmonary vascular resistance
- *Distributive* (hypoperfusion, despite normal/increased cardiac output)
  - Macrovascular*  
Decreased splanchnic blood flow
  - Microvascular*  
Shunting
- *Cytotoxic*  
Cellular inability to utilize oxygen, despite adequate supply

### Diagnosis

Septic shock is diagnosed when there is clinical evidence of infection, persistent sepsis-induced hypotension, despite volume resuscitation (or requirement for vasopressors), and evidence of sepsis-related organ hypoperfusion (lactic acidosis, decreased urine output, or altered mental status).

### Invasive Monitoring

Because of the rapid changes in blood pressure that may occur in the presence of septic shock, arterial cannulation for continual monitoring of blood pressure is recommended. In addition, central venous catheters are needed to infuse vasopressors. The role of central hemodynamic monitoring is less clear. Although one retrospective analysis using paired cohorts suggested harm with pulmonary artery catheterization, randomized, prospective trials in patients with septic shock are lacking. A study using historical controls demonstrated improved survival when on-site intensivists were involved in the care of septic shock patients. Pulmonary artery catheters were used more frequently during the intensivist involvement period. It is now well established that use of the pulmonary artery catheter (PAC) is frequently associated with inaccurate measurements. Further more, even when measurements are accurate, benefit could only be gained when appropriate decisions are made based on these measurements. It is likely that only a randomized, prospective trial in which both education on proper measurements and consensus treatment protocols are used will answer the question of whether the PAC offers potential benefit for patients with septic shock.

### FLUID RESUSCITATION IN SEPSIS

#### Goals and Monitoring of Fluid Resuscitation

An important factor contributing to the impairment in tissue perfusion is hypovolemia. Large fluid deficits exist in patients with septic shock. Up to 6-10 L of crystalloid solutions or 2 to 4 L of colloid solutions may be required for initial resuscitation in the first 24 hrs. Despite sepsis-induced myocardial depression, cardiac index will usually improve by 25-40% during fluid resuscitation. In approximately 50% of septic patients who initially present with hypotension, fluids alone will reverse hypotension and restore hemodynamic stability. Intravascular volume can be repleted through the use of packed red cells, crystalloid solutions, and colloid solutions.

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The goal of fluid resuscitation in septic shock is restoration of tissue perfusion and normalization of oxidative metabolism.

Increasing cardiac output and oxygen delivery is dependent on expansion of blood and plasma volume.

Fluid infusion is best initiated with predetermined boluses (250-500 mL every 15 mins) titrated to clinical end points of heart rate, urine output, and blood pressure. Patients who do not respond rapidly to initial fluid boluses or those with poor physiologic reserve should be considered for invasive hemodynamic monitoring. Filling pressures should be increased to a level associated with maximal increases in cardiac output. In most patients with septic shock, cardiac output will be optimized at pulmonary artery occlusion pressures between 12 and 15 mm Hg. If only central venous pressure is available, levels of 8-12 mm Hg should be targeted. Resuscitation should be titrated to end points of oxygen metabolism and organ function. Associations have been observed between improved survival and increased levels of central venous oxygen saturation, systemic oxygen delivery, reversal of lactic acidosis, and increases in gastric intramucosal pH. However, the specific choice of end points remains controversial.

## **Fluid Resuscitation Therapies**

### ***Crystalloids***

The crystalloid solutions used most commonly for resuscitation are 0.9% sodium chloride (normal saline) and lactated Ringer's solution. The lactate content of Ringer's solution is rapidly metabolized during resuscitation and does not significantly affect the use of arterial lactate concentration as a marker of tissue hypoperfusion. The volume of distribution of normal saline and Ringer's lactate is the extracellular compartment. Under ideal conditions, approximately 25% of the infused amount will remain intravascular while the rest is distributed to the extravascular space. Clinically, 100-200 mL of intravascular volume expansion can be expected after the infusion of 1 L

of isotonic crystalloids. Resuscitation from septic shock frequently requires crystalloid volumes ranging from 6 to 10 L during the initial 24-hr period. Hypertonic saline solutions have a sodium content ranging from 400 to 2400 mOsm/L. Hypertonic solutions have potentially advantageous physiologic effects including improved cardiac contractility and precapillary vasodilatation. The primary risk when using these fluids is iatrogenically induced hypertonic states due to sodium load. Experience with hypertonic solutions in septic shock is limited.

### ***Colloids***

Many different colloidal solutions are available, including plasma protein fraction, albumin, gelatins, dextrans, and hydroxyethyl starch. The principal solutions used in clinical resuscitation are albumin and hydroxyethyl starch. Human serum albumin is available in the 5%, 20% and 25% solutions. The 5% solution should be used for initial resuscitation. After 1 L of 5% albumin, plasma volume expansion ranges from 500 to 1000 mL. Mobilization of extravascular volume is required for effective increases in intravascular volume when using 25% albumin. If fluid is successfully mobilized from the interstitial space, a 100-mL aliquot can produce increases of 400-500 mL in the intravascular volume 1 hr after infusion. In the setting of increased vascular permeability such as septic shock, significantly smaller amounts of fluid may be mobilized.

The recently completed Saline versus Albumin Fluid Evaluation (SAFE) trial randomized 6,997 critically ill patients to resuscitation with albumin or saline. There was no difference in 28-day mortality rate (20.9% with albumin vs. 21.1% with saline).

Hydroxyethyl starch is a synthetic colloid formed from hydroxyethyl-substituted branched-chain amylopectin. It is available as 6% solution of normal saline with a colloid osmotic pressure of approximately 300 mOsm/L. One liter of hydroxyethyl starch solution expands plasma volume by 700 mL to 1 L with as much as 40% of maximum volume expansion persisting for 24 hr. Hydroxyethyl starch

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molecules may adversely affect renal function by causing tubular injury. In patients with sepsis, resuscitation with hydroxyethyl starch solution, as compared with gelatin, resulted in significantly higher serum creatinine concentrations without associated differences in the need for renal replacement. Hydroxyethyl starch can cause dose dependent decreases in factor VIII activity and prolongation of partial thromboplastin time. Although these changes appear to be primarily dilutional, there have been reports of increased bleeding, primarily in patients undergoing cardiac surgery. However, only minor clotting abnormalities and no increased incidence of bleeding have been noted in patients with hypovolemic and septic shock.

### **Efficacy**

Patients with septic shock can be successfully resuscitated with either crystalloid or colloids. Increases in cardiac output and systemic oxygen delivery are proportional to the expansion of intravascular volume achieved. When crystalloids and colloids are titrated to the same level of filling pressure, they are equally effective in restoring tissue perfusion. Resuscitation with crystalloid solutions will require two to four times more volume than colloids and may require slightly longer periods to achieve desired hemodynamic end points. Colloid solutions are much more expensive than crystalloid solutions.

### **Complications**

The major complications of fluid resuscitation are pulmonary and systemic edema. Tissue edema may reduce tissue oxygen tensions by increasing the distance for diffusion of oxygen into cells. These complications are related to three principal factors: a) increases in hydrostatic pressures; b) decreases in colloid osmotic pressure; and c) increases in microvascular permeability associated with septic shock. The controversy concerning crystalloid and colloid resuscitation revolves around the importance of maintaining plasma colloid osmotic pressure.

whereas plasma colloid osmotic pressure is maintained with colloid infusion. In experimental studies, decreases in plasma colloid osmotic pressure increase extravascular fluid flux in the lungs and lower the level of hydrostatic pressure associated with lung water accumulation. Some, but not all, clinical reports have observed a correlation between decreases in the colloid osmotic pressure-pulmonary artery occlusion pressure gradient and the presence of pulmonary edema. Several clinical studies have randomized subjects to crystalloid or colloid infusion and examined the development of pulmonary edema with mixed results, demonstrating either no differences between solutions or an increased incidence of pulmonary edema with crystalloids. Experimental reports in septic models demonstrate no increase in extravascular lung water when hydrostatic pressures are maintained at low levels, indicating that in sepsis the primary determinant of extravascular fluid flux appears to be microvascular pressure rather than colloid osmotic pressure. Together, these data suggest that when lower filling pressures are maintained there is no significant difference in the development of pulmonary edema with crystalloids or colloids. However, if higher filling pressures are required to optimize cardiac performance in patients with ventricular dysfunction, colloids may mitigate against extravascular fluid flux. The acute respiratory distress syndrome occurs in 30-60% of patients with septic shock. Of concern has been the possibility that in the setting of increased microvascular permeability, colloid particles could migrate into the interstitium where they would favor fluid retention in the lung and worsen pulmonary edema. A number clinical studies in patients with septic shock and the acute respiratory distress syndrome, have not found evidence of increased lung water or compromised lung function with colloids. Multiple meta-analyses of the clinical studies comparing crystalloids with colloids, evaluating the effect of resuscitation with these solutions on mortality rate have shown no differences.

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## Transfusion Therapy

The optimal hemoglobin and hematocrit for patients with septic shock is uncertain. Hemoglobin concentrations usually range between 8 and 10 g/dL in patients with septic shock. The decrease in hemoglobin is related to several factors including ineffective erythropoiesis and hemodilution. This degree of anemia is well tolerated because the associated decrease in blood viscosity decreases afterload and increases venous return thereby increasing stroke volume and cardiac output. The decrease in blood viscosity may also compensate for other rheologic changes that occur in patients with septic shock and may enhance microvascular blood flow. To date, studies examining the effects of transfusing critically ill patients with hemoglobin concentrations in the range of 8-10 g/dL have not demonstrated any consistent benefit in tissue perfusion. . Indeed, the transfusion of aged, more rigid, red cells has been associated with decreased gastric intramucosal pH and may accentuate the rheologic abnormalities seen in sepsis. Blood transfusion may also have immunosuppressive effects. Most patients will tolerate hemoglobin concentrations in the range of 8-10 g/dL. Some, may have clinical variables, that suggest a need for increased oxygen delivery, including excessive tachycardia, cardiac dysfunction, significant underlying cardiac or pulmonary disease, severe mixed venous oxygen desaturation, or failure to clear lactic acidosis. Most experts recommend maintenance of hemoglobin concentrations in the 8-10 g/dL range in patients with sepsis and hemodynamic instability.

## Vasopressor Therapy

### ***Goals and Monitoring of Vasopressor Therapy.***

When fluid administration fails to restore an adequate arterial pressure and organ perfusion, therapy with vasopressor agents should be initiated. Vasopressor therapy may also be required transiently to maintain perfusion in the face of life-threatening hypotension, even when adequate cardiac filling pressures have not yet been attained.

Potential agents include dopamine, norepinephrine, phenylephrine, epinephrine, and vasopressin. Maintenance of a mean arterial pressure of 60 mm Hg is usually required to maintain and optimize flow. However loss of autoregulation can occur at different levels of mean arterial pressure in different organs, and thus some patients may require higher blood pressures to maintain adequate perfusion. It is important to supplement end points such as blood pressure with assessment of regional and global perfusion. If vasopressor infusion impairs stroke volume, addition of an inotropic agent such as dobutamine should be considered.

## Individual Vasopressor Agents

### ***Dopamine***

Dopamine is the natural precursor of norepinephrine and epinephrine. Dopamine possesses several distinct dose-dependent pharmacologic effects. At doses <5 µg/kg/min the predominant effect of dopamine is to stimulate dopaminergic DA1 and DA2 receptors to cause vasodilatation in the renal, mesenteric, and coronary beds. At doses of 5-10 µg/kg/min β1-adrenergic effects predominate, increasing cardiac contractility and heart rate. At doses 10 µg/kg/min, α1-adrenergic effects predominates, leading to arterial vasoconstriction and an increase in blood pressure. However, there is a great deal of overlap in these effects, particularly in critically ill patients. Dopamine produces a median increase in mean arterial pressure of 24% in patients who remained hypotensive after optimal fluid resuscitation. Dopamine increases mean arterial pressure and cardiac output, primarily due to an increase in stroke volume, and to a lesser extent to an increase in heart rate. Central venous, pulmonary artery, and pulmonary occlusion pressures, systemic vascular resistance index, and pulmonary artery resistance index are unchanged. In patients with elevated pulmonary artery occlusion pressures, dopamine may further increase occlusion pressure by increasing venous return. Dopamine has been shown to improve right ventricular contractility in patients

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with underlying right ventricular failure. Dopamine increases pulmonary shunt fraction, decreases anterior-venous oxygen difference and mixed venous oxygen saturation, however, PaO<sub>2</sub> remains relatively constant. Dopamine has been shown to increase oxygen delivery, but its effects on calculated or measured oxygen consumption have been mixed. Oxygen extraction ratio typically decreases, suggesting no improvement in tissue oxygenation. Dopamine increase splanchnic blood flow but this increased flow has not always been associated with increases in splanchnic oxygen consumption or gastric intramucosal pH. Dopamine may cause splanchnic oxygen utilization without increase oxygen delivery, resulting in oxygen debt. Dopamine may redistribute blood flow within gut, reducing mucosal blood flow and increasing oxygen debt. In healthy volunteers, low doses of dopamine increase renal blood flow and glomerular filtration rate and inhibit proximal tubular resorption of sodium, which result in natriuresis. With this physiologic rationale, low-dose dopamine is commonly administered to critically ill patients in the belief that it reduces the risk of renal failure by increasing renal blood flow. This issue has now been addressed by an adequately powered randomized clinical trial, which enrolled 328 critically ill patients with early renal dysfunction (urine output <0.5 mL/kg/hr over 4 hrs, creatine >150mol/L or an increase of >80 mol/L over 24 hrs). Patients were randomized to low ("renal") dose dopamine (2 µg/kg/min) or placebo, and the primary end point was peak serum creatinine. No difference was found in either the primary outcome (peak serum creatinine 245 vs. 249 mol/L, p=.92), other renal outcomes (increase in creatinine, need for renal replacement), urine output, time to recovery of normal renal function, or secondary outcomes. Thus, the available data do not support administration of low doses of dopamine solely to maintain renal function. The major undesirable effects of dopamine are tachycardia and arrhythmogenesis, both of which are more prominent than with other vasopressor agents. Other side effects include increased pulmonary artery occlusion pressure, increased pulmonary

shunt, and the potential for decreased prolactin release and consequent immunosuppression.

### ***Norepinephrine***

Norepinephrine is a potent α-adrenergic agonist with less pronounced β-adrenergic agonist effects. Norepinephrine causes a significant increase in mean arterial pressure attributable to its vasoconstrictive effects, with little change in heart rate or cardiac output. Norepinephrine increase cardiac output by 10-20% and increases stroke volume by 10-15%. There is either no change or modest increases (1-3 mm Hg) in pulmonary artery occlusion pressure. Mean pulmonary arterial pressure is either unchanged or increased slightly. The combination of norepinephrine with dobutamine may be attractive in the setting of sepsis. Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in septic shock patients.

In patients with hypovolemia and hypotension, the vasoconstrictive effects of norepinephrine can have detrimental effects on renal hemodynamics, with the potential for renal ischemia but not in hyperdynamic septic shock. Norepinephrine has a greater effect on efferent than afferent renal arteriolar resistance. It increases the filtration fraction, urine output, creatinine clearance, and osmolar clearance in patients with septic shock. Use of norepinephrine does not worsen but can even improve tissue oxygenation in patients with septic shock. Results of studies of the effects of norepinephrine on splanchnic blood flow in patients with septic shock have been mixed, however, splanchnic oxygen consumption remained unchanged.

In a recent multivariate analysis including 97 septic shock patients, mortality rate was favorably influenced by the use of norepinephrine as part of the hemodynamic management; use of high-dose dopamine, epinephrine, or dobutamine had no significant effect. When the use of norepinephrine is contemplated, it should be used early and not withheld as a last resort.

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## **Phenylephrine**

Its rapid onset, short duration, and primary vascular effects make it an attractive agent in the management of hypotension associated with sepsis. However, it can reduce cardiac output and lower heart rate in septic shock patients. Guidelines on its clinical use are limited. Phenylephrine results in an increase in mean arterial pressure, systemic vascular resistance, cardiac index, and stroke index. There is no change in heart rate, a significant increase in urine output without a change in serum creatinine. In addition, phenylephrine therapy does not impair cardiac or renal function. Phenylephrine may be a good choice when tachyarrhythmias limit therapy with other vasopressors. An increase in oxygen consumption and delivery may occur during therapy.

## **Epinephrine**

In patients unresponsive to volume expansion or other catecholamine infusions, epinephrine can increase mean arterial pressure, primarily by increasing cardiac index and stroke volume with more modest increases in systemic vascular resistance and heart rate. In patients with right ventricular failure, epinephrine increases right ventricular function by improving contractility. Epinephrine can increase oxygen delivery, but oxygen consumption may be increased as well. Epinephrine decreases splanchnic blood flow, with transient increases in arterial, splanchnic, and hepatic venous lactate concentrations, decreases in pH<sub>i</sub>, and increases in PCO<sub>2</sub> gap. These effects may be due to a reduction in splanchnic oxygen delivery to a level that impairs nutrient blood flow and results in a reduction in global tissue oxygenation. Alternatively, CO<sub>2</sub> production secondary to the thermogenic effect of epinephrine. Epinephrine administration has been associated with increases in systemic and regional lactate concentrations. Other adverse effects of epinephrine include increases in heart rate, but electrocardiographic changes indicating ischemia or arrhythmias have not been reported in septic patients. Epinephrine has minimal effects on pulmonary artery pressures and

pulmonary vascular resistance in sepsis. Because of its effects on gastric blood flow and its propensity to increase lactate concentrations, its use should be limited to patients who fail to respond to traditional therapies for increasing or maintaining blood pressure.

## **Corticosteroids**

Corticosteroids may up-regulate the sympathetic nervous system and the renin-angiotensin system and also enhance vascular responses to norepinephrine and angiotensin II, possibly through stimulation of the phosphoinositide signaling system in smooth muscle cells. Glucocorticoids also inhibit nitric oxide production by inducible nitric oxide synthase. Corticosteroids may potentiate catecholamine activity by several mechanisms: (1) increasing phenylethanolamine N-methyltransferase activity and epinephrine synthesis (2) inhibiting catecholamine reuptake in neuromuscular junctions and decreasing their metabolism (3) increasing binding capacity and affinity of  $\beta$ -adrenergic receptors in arterial smooth muscle cells (4) and potentiating receptor G coupling and catecholamine induced cyclic adenosine monophosphate synthesis. Corticosteroids also increase angiotensin II type I receptor expression in vascular smooth muscles and significantly enhance pressor effects of exogenous angiotensin II.

The favorable effect of corticosteroids on vascular responsiveness to vasopressor agents is manifested at the bedside by a shortening of the time on vasoconstrictor drugs. High doses of corticosteroids (i.e., 30 mg/kg of methylprednisolone or equivalent) once to four times had no effect on survival in severe sepsis or septic shock. By contrast, in septic shock, low doses ranging from 200 to 300 mg daily of corticosteroids given for a prolonged period of time (>5 days) have been shown to improve outcome in several controlled clinical trials. A phase III, multiple-center, placebo-controlled, randomized, double-blind study evaluated the efficacy and safety of a combination of hydrocortisone (50-mg intravenous bolus four times per day) and

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fludrocortisone (50 µg orally once a day) given for 7 days in 300 patients with septic shock. In this trial, nonresponders to ACTH were more likely to benefit from cortisol replacement, with 30-day survival rates 47% vs. 37%. Patients who responded normally to ACTH (cortisol increment of >9 µg/dL [250 nmol/L] after 250µg of corticotropin) had no benefit from corticosteroid therapy.

### ***Vasopressin***

Vasopressin is a peptide hormone synthesized in the hypothalamus and then transported to and stored in the pituitary gland. Vasopressin is released in response to decreases in blood volume, decreased intravascular volume, and increased plasma osmolality. Vasopressin constricts vascular smooth muscle directly via V1 receptors and also increases responsiveness of the vasculature to catecholamines. Vasopressin may also increase blood pressure by inhibition of vascular smooth muscle NO production and K<sup>+</sup>-ATP channels. Normal concentrations of vasopressin have little effect on blood pressure in physiologic conditions, but vasopressin helps maintain blood pressure during hypovolemia, and seems to restore impaired hemodynamic mechanisms and also inhibit pathologic vascular responses in shock. Increased concentrations of vasopressin have been documented in several types of shock, but a growing body of evidence indicates that this response is abnormal or blunted in septic shock. One potential mechanism for this relative vasopressin deficiency would be depletion of pituitary stores, possibly in conjunction with impaired synthesis.

In septic shock, a relative deficiency of vasopressin may contribute to persistent hypotension. Current evidence demonstrates that in catecholamine-resistant septic shock, the addition of low-dose vasopressin (0.01-0.04 units/min) to catecholamines can be used to increase blood pressure and decrease catecholamine doses. There is concern, however, that vasopressin infusion in septic patients may either decrease splanchnic perfusion or redistribute blood flow away from the splanchnic mucosa.

### **Complications of Vasopressor Therapy**

- 1) Tachycardia, Tachyarrhythmias
- 2) Myocardial ischemia and infarction in patients with significant coronary atherosclerosis
- 3) Limb ischemia and necrosis.
- 4) Impair blood flow to the splanchnic system (stress ulceration, ileus, malabsorption, and even bowel infarction)

### **INOTROPIC THERAPY IN SEPSIS**

Sepsis is characterized by a hyperdynamic state with normal to low blood pressure, normal to high cardiac index, and a low systemic vascular resistance.

#### ***Cardiac dysfunction***

Although cardiac output is usually maintained in the volume-resuscitated septic patient, a number of investigations have demonstrated that cardiac function is impaired. This myocardial dysfunction is characterized by a decreased ejection fraction, ventricular dilation, impaired contractile response to volume loading, and a low peak systolic pressure/end-systolic volume ratio. The mechanism of this cardiac dysfunction is complex. Myocardial edema, alterations in sarcolemmal or intracellular calcium homeostasis, and uncoupling or disruption of β-adrenergic signal transduction may contribute to the cardiac contractile dysfunction. A variety of inflammatory mediators, including prostanoids, platelet-activating factor, tumor necrosis factor-α, interleukin-1 and interleukin-2, and nitric oxide have been shown to cause myocardial depression.

#### **Goals**

Inotropic therapy in septic shock is complex, because different approaches endeavor to achieve different goals. In patients with decreased cardiac output, the goals of therapy are straightforward. An inotropic agent should be considered to maintain an adequate cardiac index, mean arterial pressure, SvO<sub>2</sub>, and urine output. Because of the complexity of assessment of clinical variables in septic patients, measurement of cardiac output is advisable and

**Summary of cardiac effects of inotropes used in sepsis and shock. Physiologic values are reported as percent change from baseline.**

Drug	Dose Range (µg/kg/m)	HR	Cardiac Index	Stroke volume index	SVRI	LVSWI
Isoproterenol	1.5 to 18	11 to 20	47 to 119	22 to 89	-24 to -44	74 to 157
Dopamine	2 to 55	1 to 23	4 to 44	7 to 32	-6 to 18	5 to 91
Epinephrine	0.06 to 0.47	-6 to 27	24 to 54	12	-7 to 34	32 to 95
Norepinephrine	0.03 to 3.3	-6 to 8	-3 to 21	5 to 15	13 to 111	42 to 142
Dobutamine	2 to 28	9 to 23	12 to 61	15	-6 to -21	23 to 28
Dopexamine	2 to 6	6 to 17	17 to 20	14	-15 to -27	6
Milrinone	0.5	1	49	47	-30	56

**HR : heart rate; SVRI : systemic vascular resistance index; LVSWI : left ventricular stroke work index**

need to be interpreted in the clinical context. Cardiac output can be measured using a pulmonary artery catheter, by echocardiography with an esophageal Doppler probe, or by pulse contour analysis. Regardless of the measurement method chosen, clinicians should define specific goals and desired end points of inotropic therapy in septic patients and titrate therapy to those end points. These goals and end points should be refined at frequent intervals as patients' clinical status changes.

***Hyper resuscitation ?***

Some critically ill septic patients are hypermetabolic and may require high levels of oxygen delivery to maintain oxidative metabolism. Data from the 1980s and early 1990s suggested that a linear relationship between oxygen delivery and oxygen consumption ("pathologic supply dependency") exists in patients with septic shock. These observations led to the hypothesis that resuscitation to predetermined elevated end points of cardiac index and oxygen delivery and consumption (cardiac index of >4.5 L/min/m<sup>2</sup>, oxygen delivery of >600 mL/min/m<sup>2</sup>, and oxygen consumption of >170 mL/min/m<sup>2</sup>) ("hyper resuscitation") might improve patient outcome. Although cardiac index and oxygen delivery have correlated with outcome, it is unclear if increases in these variables are the cause of increased survival or represent the underlying physiologic reserve of the patient. A strategy of

routinely increasing oxygen delivery to predetermined elevated end points of cardiac index and oxygen delivery cannot be recommended on the basis of current data.

**Individual Inotropic Agents**

***Isoproterenol***

Isoproterenol is a β<sub>1</sub>- and β<sub>2</sub>-adrenergic agonist. In septic shock patients with a low cardiac index (mean <2.0 L/min/m<sup>2</sup>), isoproterenol (2 to 8 µg/ min) significantly increases cardiac index without decreasing blood pressure but at the expense of increasing heart rate. In patients with a normal cardiac index, however, isoproterenol can decrease blood pressure through its β<sub>2</sub>- adrenergic effects. In addition, the chronotropic effects of β<sub>1</sub>-adrenergic stimulation can precipitate myocardial ischemia.

***Dopamine***

Dopamine is an adrenergic agonist with predominant dopaminergic properties at doses <5 µg/kg/min and increased β and α activity at doses > 5 µg/kg/min. However, even at low doses, significant α and β agonism may occur since the pharmacokinetics of dopamine in critically ill patients is highly variable. In patients with severe sepsis and/or septic shock, dopamine increase cardiac index with a range from 4% to 44%, left ventricular stroke work index by 5-91%, and right ventricular stroke work index by a modest 5-10%. These

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improvements in cardiac performance come at the expense of an increase in the heart rate of approximately 15% (range up to 23%). The greatest increase in these variables occurs at doses ranging from 3 to 12  $\mu\text{g}/\text{kg}/\text{min}$ . At higher doses, the rate of improvement in cardiac function decreases.

### ***Dobutamine***

Dobutamine is a racemic mixture of two isomers, a D isomer with  $\beta_1$ - and  $\beta_2$ -adrenergic effects, and an L isomer with  $\beta_1$ - and  $\alpha_1$ -adrenergic effects; its predominant effect is inotropic via stimulation of  $\beta_1$  receptors, with a variable effect on blood pressure. Dobutamine increases cardiac index (range 12% to 61%.) and, heart rate (range 9-23%). Although dobutamine does not influence the distribution of blood flow, therapy is often aimed at increasing blood flow to organs such as the gut or the kidneys.

### ***Epinephrine***

Epinephrine stimulates both  $\alpha$  and  $\beta$  receptors. At low doses, the  $\beta$ -adrenergic effects predominate. The increase in cardiac index varies from 24% to 54%, and the heart rate response is variable and increases in left ventricular stroke work index as high as 95%. Some studies indicated that lactic acidosis is increased and perfusion to the gut is altered with the use of epinephrine.

### ***Norepinephrine***

Norepinephrine stimulates both  $\alpha$  and  $\beta$  receptors; however, the  $\alpha$ -adrenergic response is the predominant effect. The effect of norepinephrine on cardiac index is modest, with no change or increases of up to 21% while heart rate is unaffected or even decreases by up to 8%. However, several studies have shown a marked increase in left and right ventricular stroke work index due to increased blood pressure.

### ***Phosphodiesterase Inhibitors.***

Phosphodiesterase inhibitors are vasodilators with long half-lives, raising the potential for prolonged decreases in blood pressure when used in septic

patients. There are few small studies of these agents in patients with sepsis, but meaningful conclusions cannot be made because of the size of the studies and the concomitant use of disparate adrenergic agents.

### **Complications**

In the septic patient who has been inadequately volume resuscitated, all the inotropic agents can cause significant tachycardia and other cardiac arrhythmias. In patients with coexisting coronary disease, the change in myocardial oxygen consumption may precipitate myocardial ischemia and infarction. Excessive doses of catecholamines can also result in myocardial band necrosis independent of the presence of coronary disease. Sole use of inotropic agents that also have vasodilatory activity (e.g., isoproterenol, milrinone) is likely to reduce blood pressure. These reductions can be longlasting with agents that have long half-lives. Administration of inotropic agents that have pressor activity may impair blood flow to other organ beds, such as the splanchnic circulation. Efforts to ensure adequate volume resuscitation and to assess end-organ function must be made.

## **RECOMMENDATIONS FOR HEMODYNAMIC SUPPORT OF SEPTIC PATIENTS (Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update)**

### **Basic Principles**

1. Resuscitation of patients with sepsis should be initiated expeditiously and pursued vigorously. Measures to improve tissue and organ perfusion are most effective when applied early.
2. Patients with septic shock should be treated in an intensive care unit, with continuous electrocardiographic monitoring and monitoring of arterial oxygenation.
3. Arterial cannulation should be performed in patients with shock to provide a more accurate measurement of intra-arterial pressure and to allow beat-to-beat analysis so that decisions

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regarding therapy can be based on immediate and reproducible blood pressure information.

4. Resuscitation should be titrated to clinical end points of arterial pressure, heart rate, urine output, skin perfusion, and mental status, and indexes of tissue perfusion such as blood lactate concentrations and mixed venous oxygen saturation.
5. Assessment of cardiac filling pressures may require central venous or pulmonary artery catheterization. Pulmonary artery catheterization also allows for assessment of pulmonary artery pressures, cardiac output measurement, and measurement of mixed venous oxygen saturation. Echocardiography may also be useful to assess ventricular volumes and cardiac performance.

### **Fluid Resuscitation**

*Recommendation 1-Level B.* Fluid infusion should be the initial step in hemodynamic support of patients with septic shock. Initial fluid resuscitation should be titrated to clinical end points.

*Recommendation 2-Level B.* Isotonic crystalloids or iso-oncotic colloids are equally effective when titrated to the same hemodynamic end points.

*Recommendation 3-Level D.* Invasive hemodynamic monitoring should be considered in those patients not responding promptly to initial resuscitative efforts. Pulmonary edema may occur as a complication of fluid resuscitation and necessitates monitoring of arterial oxygenation. Fluid infusion should be titrated to a level of filling pressure associated with the greatest increase in cardiac output and stroke volume. For most patients, this will be a pulmonary artery occlusion pressure in the range of 12-15 mm Hg. An increase in the variation of arterial pressure with respiration may also be used to identify patients likely to respond to additional fluid administration.

*Recommendation 4-Level C.* Hemoglobin concentrations should be maintained between 8 and 10 gm/dL. In patients with low cardiac output, mixed

venous oxygen desaturation, lactic acidosis, widened gastric-arterial PCO<sub>2</sub> gradients, or significant cardiac or pulmonary disease, transfusion to a higher concentration of hemoglobin may be desirable.

### **Vasopressor Therapy**

*Recommendation 1-Level C.* Dopamine and norepinephrine are both effective for increasing arterial blood pressure. It is imperative to ensure that patients are adequately fluid resuscitated. Dopamine raises cardiac output more than norepinephrine, but its use may be limited by tachycardia. Norepinephrine may be a more effective vasopressor in some patients.

*Recommendation 2-Level D.* Phenylephrine is an alternative to increase blood pressure, especially in the setting of tachyarrhythmias. Epinephrine can be considered for refractory hypotension, although adverse effects are common, and epinephrine may potentially decrease mesenteric perfusion.

*Recommendation 3-Level B.* Administration of low doses of dopamine to maintain renal function is not recommended.

*Recommendation 4 -Level C.* Patients with hypotension refractory to catecholamine vasopressors may benefit from addition of replacement dose steroids.

*Recommendation 5-Level D.* Low doses of vasopressin given after 24 hrs as hormone replacement may be effective in raising blood pressure in patients refractory to other vasopressors, although no conclusive data are yet available regarding outcome.

### **Inotropic Therapy**

*Recommendation 1-Level C.* Dobutamine is the first choice for patients with low cardiac index and/or low mixed venous oxygen saturation and an adequate mean arterial pressure following fluid resuscitation. Dobutamine may cause hypotension and/or tachycardia in some patients, especially those with decreased filling pressures.

*Recommendation 2-Level B.* In patients with evidence of tissue hypoperfusion, addition of dobutamine may be helpful to increase cardiac output and improve organ perfusion. A strategy of routinely increasing cardiac index to predefined "supranormal" levels (>4.5 L/min/m<sup>2</sup>) has not been shown to improve outcome.

*Recommendation 3-Level C.* A vasopressor such as norepinephrine and an inotrope such as dobutamine can be titrated separately to maintain both mean arterial pressure and cardiac output.

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