Practice Parameters for Hemodynamic Support of Sepsis in Adult Patients

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American College of Critical Care Medicine
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Objective: *To present guidelnes for hemodynamic support of adult patients with sepsis.*
Participants*: An international task force of nine experts in disciplines related to critical care medicine was convened from the membership of the Society of Critical Care Medicine.*
Evidence: *Review of published literature and expertise and personal experience of task force. The strength of evidence of human studies was classified according to study design and scientific value.*
Consensus Process: *The task force met several times in person and communicated by electronic mail to identify the pertinent literature and arrive at consensus recommendations. Consideration was given to the relationship between the weight of scientific evidence and the experts' opinions. Draft documents were composed and debated by the task force until consensus was reached. The strength of recommendations was graded according to evidence-based guidelines.*
Conclusions: *The panel formulated an underlying approach to the hemodynamic support of sepsis. Hemodynamic therapies should be titrated to specific and definable end points. The effects of therapy should be assessed by monitoring a combination of parameters of global and regional perfusion. Using this approach, the panel made specific recommendations for fluid resuscitation, vasopressor therapy, and inotropic therapy of septic patients.*

Shock occurs when the circulatory system fails to maintain adequate cellular perfusion. Shock is a syndrome which may arise from any of several initiating causes. As this syndrome progresses, a common pattern resulting from the consequences of inadequate tissue perfusion emerges. If shock is not reversed, irreversible cellular damage will ensue.

Septic shock results when infectious agents or infection-induced mediators in the bloodstream produce cardiovascular decompensation. Septic shock is primarily a form of distributive shock and is usually characterized by a high cardiac output and a low systemic vascular resistance.[1] In septic shock, patients can have both hypotension, resulting from decreased systemic vascular resistance, and maldistribution of blood flow in the microcirculation with compromised tissue perfusion. About half of the patients who succumb to septic shock die of multiple organ system failure.[1] Most of the rest have progressive hypotension with low systemic vascular resistance refractory to vasopressor agents.[1] Although myocardial dysfunction is not uncommon, death from myocardial failure is rare.[1]

Cellular dysfunction in sepsis is the final outcome of a process with multiple stimuli. Prominent mechanisms include cellular ischemia, disruption of cellular metabolism by the effects of inflammatory mediators, and the toxic effects of free radicals.[2] Activation of caspases and induction of heat-shock proteins may lead to apoptotic cell death. In early shock, compensatory mechanisms are activated in an attempt to restore pressure and flow to vital organs. When these compensatory mechanisms begin to fail, damage to cellular membranes, leakage of lysosomal enzymes, and reductions in cellular energy stores occur and may result in cell death.[2] Once enough cells from vital organs have reached this stage, shock can become irreversible, and death can occur despite eradication of the underlying septic focus.

Therapy of septic shock may be viewed as having three main components. The initial priority in managing septic shock is to maintain a reasonable mean arterial pressure (MAP) to keep the patient alive. Then the nidus of infection must be identified and eliminated, using surgical drainage, antimicrobial therapy, or both. The third therapeutic goal is to interrupt the pathogenic sequence leading to septic shock. While these goals are being pursued, adequate organ system perfusion and function must be maintained, guided by cardiovascular monitoring. The purpose of this practice parameter is to provide guidance for hemodynamic support in sepsis to maintain adequate organ system and cellular perfusion.

General Outline of Septic Shock Therapy

Patients with septic shock should be treated in an intensive care unit. Continuous electrocardiographic monitoring should be performed for detection of rhythm disturbances, and pulse oximetry is useful to detect fluctuations in arterial oxygenation. Laboratory measurements, such as arterial blood gases, serum electrolytes, complete blood counts, coagulation parameters, and lactate concentrations should be done early and repeated as indicated. In shock states, estimation of blood pressure using a cuff is commonly inaccurate, and use of an arterial cannula provides a more appropriate and reproducible measurement of arterial pressure.[1] Such monitoring facilitates the administration of large quantities of fluids and potent vasopressor and inotropic agents to critically ill patients.

Although patients with shock and mild hypovolemia may be treated successfully with rapid fluid replacement, right-side heart catheterization is usually necessary to provide a diagnostic hemodynamic assessment in patients with moderate or severe shock. In addition, because hemodynamics can change rapidly in sepsis, and because noninvasive evaluation is frequently incorrect in estimating filling pressures and cardiac output, pulmonary artery catheterization is often useful for monitoring the response to therapy. Therapeutic modalities for the hemodynamic support of sepsis can be broken down into three main categories: volume infusion; vasopressor therapy; and inotropic therapy.

Fluid Therapy

Because septic shock is accompanied by fever, venodilation, and diffuse capillary leakage, most septic patients present with inadequate preload.[3] Thus, fluid resuscitation represents the best initial therapy for treatment of hypotension in sepsis. Patients with clinically important anemia may require blood transfusion to increase oxygen delivery.

Vasopressor Therapy

If fluid therapy alone fails to restore adequate arterial pressure and organ perfusion, therapy with vasopressor agents should be initiated. Potential vasopressor agents include dopamine, norepinephrine, epinephrine, or phenylephrine.

Inotropic Therapy

When adequately fluid resuscitated, most septic patients are hyperdynamic, but myocardial contractility, as assessed by ejection fraction, is impaired.[4] Some patients, especially those with preexisting cardiac dysfunction, may have decreased cardiac output and may require inotropic agents such as dobutamine, dopamine, and epinephrine.

Septic patients are hypermetabolic and may need higher levels of oxygen delivery to maintain oxidative metabolism.[3, 5] Some patients with evidence of tissue hypoperfusion may benefit from inotropic therapy to increase cardiac output. Nonetheless, routine administration of inotropes to achieve predefined end points has not been shown to be effective.

Purpose and Structure of Practice Parameters for Hemodynamic Support in Sepsis

These practice parameters were developed by a panel convened by the American College of Critical Care Medicine of the Society of Critical Care Medicine to assist healthcare providers in the management of hemodynamic support for patients with sepsis and septic shock. These guidelines are intended for adult patients and do not cover all conceivable clinical scenarios. Nonetheless, they do represent an attempt to review the state of knowledge concerning hemodynamic therapy of sepsis and to supplement specific therapeutic recommendations with guidelines about how to optimize therapy and how to evaluate the results of therapeutic interventions. The information and recommendations are predicated on an expert-based review of the available scientific data, clinical

investigations, and outcomes research. Where such data are unavailable or limited in scope, consensus was attained by considering published expert opinion and debate among a wide range of experts. The citations of human studies have been annotated into levels of scientific support as modified from the guidelines of Evidence-Based Medicine Table 1.[6] Each reference was graded by all of the conference participants, and discrepancies resolved by group consensus. The strength of the recommendations has been graded according to a modification of evidence-based guidelines.[6]

Some comments about the use of evidence-based medicine in this context may be useful. An evidence-based approach puts appropriate emphasis on the structured, critical examination of the clinical literature. Such an approach, however, places a very heavy reliance on randomized, double-blind clinical trials, which may be extremely difficult to conduct in some clinical settings. One such setting is septic shock. Septic patients requiring hemodynamic support are, by definition, unstable to some degree. In addition, they have a broad range and severity of underlying diseases. Conducting a trial with a well-defined population of these patients can be challenging at best and unworkable at worst. Not surprisingly, few of the trials of hemodynamic therapy in sepsis conducted to date are large, randomized trials. Nonetheless, the purpose of this document is to formulate guidelines for practitioners to use in hemodynamic support of sepsis based on currently available information, even in areas in which randomized clinical trials may be limited. We have found the evidence-based framework to be useful when a certain degree of skepticism is applied; definitive evidence may be lacking on some issues, and obtaining such evidence may be impractical.

After the consideration of volume infusion, vasopressor therapy, and inotropic therapy, experimental therapies are discussed for the hemodynamic support of patients with sepsis.

GOALS AND END POINTS OF HEMODYNAMIC SUPPORT IN SEPTIC PATIENTS

Overview

Shock represents the failure of the circulatory system to maintain adequate delivery of oxygen and other nutrients to tissues, causing cellular and then organ dysfunction. Thus, the ultimate goals of hemodynamic therapy in shock are to restore effective tissue perfusion and to normalize cellular metabolism.

In hypovolemic, cardiogenic, and extracardiac obstructive shock, hypotension results from a decrease in cardiac output, with consequent anaerobic tissue metabolism. Septic shock, the prototypical form of distributive shock, is different and more complicated. In septic patients, tissue hypoperfusion results not only from decreased perfusion pressure attributable to hypotension but also from abnormal shunting of a normal or increased cardiac output.[2] Hemodynamic support of sepsis thus requires consideration of both global and regional perfusion.

The practical import of the complexity of hemodynamics in sepsis is that the goals of therapy are much more difficult to define with certainty than in other forms of shock in which global hypoperfusion is the predominant pathology. In cardiogenic shock, for example, the goal of therapy is to increase cardiac output, although different organs may be hypoperfused to variable degrees. Indices of regional perfusion usually correlate well with indices of global perfusion, and both can be used to monitor the effects of therapy. In sepsis, maldistribution of a normal cardiac output can impair organ perfusion; within an organ, maldistribution of blood flow due to perturbation of resistance vessel tone or patency of nutritive microvessels can exacerbate organ dysfunction. To add to the complexity, mediators of sepsis can perturb cellular metabolism, leading to inadequate utilization of oxygen and other nutrients, despite adequate perfusion. One would not expect such abnormalities to be corrected by hemodynamic therapy.

The complexity of the pathophysiology of sepsis has led to some confusion and much controversy. Nonetheless, it is possible to formulate an underlying approach to the hemodynamic support of sepsis, with the understanding that the basic principles of the approach are more important than the specific recommendations, which will certainly change as our understanding of sepsis improves. For example, although which parameters most accurately reflect the effects of therapy in septic patients may be contested, it should be apparent that those effects should be assessed by monitoring a combination of parameters. Similarly, although specific end points may be arguable, the principle that clinicians should define the goals and desired end points of their therapy and evaluate the results of their

interventions on an ongoing basis is not. Despite the fact that therapies for sepsis will continue to evolve as our understanding of the pathogenesis of sepsis increases, the notion that such therapies should be titrated to specific and definable end points remains a fundamental principle.

Indices of Global Perfusion

Bedside clinical assessment provides a good indication of global perfusion. Septic shock is by definition characterized by hypotension, which in adults generally refers to an MAP of <60 mm Hg. MAP is preferable to systolic pressure because it is a better reflection of organ perfusion pressure. In interpreting any given level of arterial pressure, however, the chronic level of pressure must be considered; patients with severe chronic hypertension may be relatively hypotensive when their MAP decreases by 40 mm Hg, even if it still exceeds 60 mm Hg. Hypotension is usually accompanied by tachycardia.

Indications of decreased perfusion include oliguria, clouded sensorium, delayed capillary refill, and cool skin. Some caution is necessary in interpreting these signs in septic patients, however, since organ dysfunction can occur in the absence of global hypoperfusion.

In most forms of shock, increased blood lactate concentrations reflect anaerobic metabolism due to hypoperfusion, but the interpretation of blood lactate concentrations in septic patients is not always straightforward. Some studies in animal models of sepsis have found normal high-energy phosphate concentrations[7] but others have not.[5] The differences may relate to the severity of the septic model, with more severe sepsis being associated with depletion of ATP (adenosine triphosphate), despite maintenance of systemic oxygen delivery and tissue oxygenation. A number of studies have indicated that increasing either global[8] or regional oxygen delivery[9] fails to alter increased lactate concentration in patients with sepsis. Measurements of tissue P_{O_2} in septic patients have failed to demonstrate tissue hypoxia in the presence of lactic acidosis[10], and a number of studies[11,12] have suggested that increased lactate concentrations may result from cellular metabolic alterations rather than from global hypoperfusion in sepsis. Accelerated glycolysis, high pyruvate production[13], and decreased clearance by the liver may contribute to increased lactate concentrations. Nonetheless, although lactate concentrations should not be considered to represent tissue hypoxia in the strict sense, the prognostic value of increases of blood lactate concentrations has been well established in septic shock patients.[14-16] The trend of lactate concentrations is a better indicators than a single value.[14, 15] Also, blood lactate concentrations are a better prognostic indicator than oxygen-derived variables.[17]

Mixed venous oxyhemoglobin levels have been suggested as an indicator of the balance between oxygen delivery and consumption. Mixed venous oxygen saturation can be measured by withdrawing a blood sample from the pulmonary artery in patients with a right heart catheter in place; continuous measurement of mixed venous oxygen saturation can be achieved using an oximetric right heart catheter. Mixed venous oxygen saturation is dependent on cardiac output, oxygen consumption, hemoglobin concentration, and arterial oxygen saturation. In patient with a stable oxygen demand, in the absence of hypoxemia and anemia, mixed venous desaturation can reflect decreased cardiac output. Normal mixed venous oxygen saturation is 70% in critically ill patients. However, in septic patients, mixed venous oxygen saturation can be elevated due to maldistribution of blood flow. The utility of using mixed venous oxygen saturation as an index of global perfusion to guide therapy in patients with septic shock has not been demonstrated conclusively, although saturations <65% usually indicate decreased perfusion.

Indices of Regional Perfusion

Adequacy of regional perfusion is usually assessed clinically by evaluating indices of organ function. These indices include evidence of myocardial ischemia, renal dysfunction as reflected by decreased urine output and increased blood urea nitrogen and creatinine, and central nervous system dysfunction as indicated by an abnormal sensorium. Hepatic parenchymal injury can be manifested by increased serum concentrations of transaminases, lactic dehydrogenase, and bilirubin; decreased concentrations of albumin and clotting factors indicate decreased synthetic capability. Splanchnic hypoperfusion can be manifested by stress ulceration, ileus, and malabsorption. In sepsis,

however, organ dysfunction can result from the effects of toxic mediators, as well as from perfusion failure.[2]

Interest has thus focused on methods of measuring regional perfusion more directly. The splanchnic circulation has been the focus of these investigations for several reasons: a) the countercurrent flow in the gut microcirculation increases the risk of mucosal hypoxia; b) the gut may have a higher critical oxygen delivery threshold than other organs;[18] and c) gut ischemia increases intestinal permeability. Measurements of oxygen saturation in the hepatic vein have revealed oxygen desaturation in a subset of septic patients, suggesting that hepatosplanchnic oxygen supply may be inadequate in these patients, even when more global parameters appear adequate.[19]

Gastric tonometry has been proposed as a simple method to assess regional perfusion in the gut by employing a balloon in the stomach to measure intramucosal P_{CO_2}. From this P_{CO_2} measurement and the arterial bicarbonate concentration, one can then calculate gastric mucosal pH (pHi) using the Henderson-Hasselbalch equation, assuming that bicarbonate concentration in the gastric mucosal tissue is in equilibrium with systemic arterial bicarbonate.[20] Because this may not be true in shock[21], and because remote systemic metabolic acidosis and alkalosis change systemic bicarbonate, gastric mucosal P_{CO_2}, which is not confounded by arterial bicarbonate, may be more accurate than pHi. Gastric mucosal P_{CO_2} is influenced directly by systemic arterial P_{CO_2}, however, and so use of the gastric-arterial P_{CO_2} difference has been proposed as the primary tonometric variable of interest, although even this measure is not a simple measure of gastric mucosal hypoxia.[21]

Despite this complexity, gastric tonometry is a good predictor for the ultimate outcome of critically-ill patients.[22-25] Its utility to guide therapy in patients with sepsis and septic shock, however, has not been proven. One study[24] has shown decreased mortality with pHi-directed care in critically ill patients admitted to an intensive care unit with initially normal pHi. Interpretation of this study is complicated by the fact that mortality in the control group was high, and that therapy based on pHi was heterogeneous because changes in treatment were made at the discretion of the clinicians and not by protocol. In addition, the degree to which the results of this trial are applicable to patients with septic shock is unclear. Gastric tonometry may prove to be a useful measure of regional perfusion in the splanchnic circulation. However, further randomized, controlled trials, with clear, reproducible treatment algorithms, will be necessary to establish the utility of gastrc tonometry in the management of patients with septic shock.

Goals and Monitoring of Fluid Resuscitation

The goal of fluid resuscitation in septic shock is restoration of tissue perfusion and normalization of oxidative metabolism. Increases in cardiac output and oxygen delivery are dependent on expansion of blood and plasma volume.

Fluid infusion is best initiated with predetermined boluses titrated to clinical end points, such as heart rate (HR), urine output, and blood pressure. Invasive hemodynamic monitoring should be considered for those patients who do not respond rapidly to initial fluid boluses or those with insufficient physiologic reserve. Fluids should be titrated to maximize cardiac output; in most patients, this will occur at filling presures between 12 and 15 mm Hg.[26]

Fluid resuscitation, along with ineffective erythropoises, usually causes anemia with hemoglobin concentrations in the range of 8 to 10 g/dL, but this degree of anemia is usually well tolerated. In some patients, however, clinical parameters, such as cardiac dysfunction, underlying coronary artery disease, failure to clear lactic acidosis, or severe mixed venous oxygen desaturation, may suggest a need for increased oxygen delivery. These patients may benefit from blood transfusion, but transfusing to a predefined threshold to increase oxygen delivery cannot be recommended on the basis of existing data.[28-31]

Goals and Monitoring of Vasopressor Therapy in Sepsis

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

Patients requiring vasopressor therapy for shock should have an arterial cannula for measurement of blood pressure. In shock states, estimation of blood pressure using a cuff is commonly inaccurate, and use of an arterial cannula provides a more appropriate measurement of intra-arterial pressure. These catheters also allow beat-to-beat analysis, so that decisions regarding therapy can be based on immediate and reproducible blood pressure information. Such monitoring makes it possible to give optimal quantities of fluids and potent vasopressor and inotropic agents safely to critically ill patients.[2]

Arterial pressure is the end point of vasopressor therapy, and the restoration of adequate pressure is the criterion of effectiveness. Blood pressure, however, does not always equate to blood flow, and the precise level of MAP to aim for is not necessarily the same in all patients. Animal studies suggest that below an MAP of 60 mm Hg, autoregulation in the coronary, renal, and central nervous system vascular beds blood flow is compromised, and blood flow may be reduced. Some patients, however, may require blood pressures higher than 60 mm Hg to maintain adequate perfusion. Thus, it is important to supplement end points such as blood pressure with assessment of regional and global perfusion by a combination of the methods outlined previously.

Goals and Monitoring of Inotropic Therapy in Sepsis

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 and are aimed at restoring normal physiology. Because of the complexity of assessment of clinical parameters in septic patients, direct measurement of cardiac output by invasive hemodynamic monitoring is advisable, but other end points of global perfusion should be followed as well. When global hypoperfusion is manifested by decreased mixed venous oxygen saturation, this measure may be followed. Similarly, although lactate production in sepsis is complex, a decrease in blood lactate concentrations concomitant with increased cardiac output is a good prognostic sign.

Some critically ill septic patients are hypermetabolic and may require high levels of oxygen delivery to maintain oxidative metabolism. Accordingly, it has been hypothesized that increasing oxygen delivery to "supranormal" levels may be beneficial. Retrospective analyses showed that achievement of a cardiac index of >4.5 L/min/m^2, oxygen delivery of >600 mL/min/m^2, and oxygen consumption of >170 mL/min/m^2 correlated with improved survival.[32] Randomized studies[33-36] to test the strategy of routinely increasing oxygen delivery to these predefined levels in all critically ill patients have produced conflicting results. It is unclear if increases in cardiac index and oxygen delivery are the cause of increased survival or represent the underlying physiologic reserve of the patient. Thus, 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.[37] Nonetheless, some clinicians believe that this issue has not been settled definitively in those patients with septic shock, and they argue that a subset of these patients may benefit from therapy aimed at supranormal oxygen delivery. Such therapy would need to be guided by invasive hemodynamic monitoring to measure cardiac output and systemic and mixed venous oxygen saturation.

Despite seemingly adequate resuscitation, some septic shock patients develop multiple organ failure, resulting in death. It has been argued that even after hypotension has been corrected and global oxygen delivery is adequate in patients with septic shock, blood flow and tissue perfusion can remain suboptimal. No current evidence supports improved outcome with empiric therapy to increase cardiac output in patients with normal blood pressure, but a subpopulation of patients might have regional hypoperfusion that would respond to additional therapy. Such therapy would need to be titrated to an index of regional perfusion such as gastric tonometry, although the precise end points are unclear. In this context, it is important to realize that different interventions to increase oxygen delivery, such as fluid resuscitation, blood transfusion, or infusion of vasoactive agents, can have different effects on regional perfusion.[38-40] Different vasoactive agents have been shown to have divergent effects on gastric intramucosal pH. This is an area of controversy and ongoing research; randomized controlled trials, with clear, reproducible treatment

algorithms and use of defined measures of regional perfusion are necessary. In the interim, clinicians should define the goals and desired end points of inotropic therapy in septic patients and use these end points to monitor and titrate therapy.

FLUID RESUSCITATION IN SEPSIS

Septic shock is characterized by decreased effective capillary perfusion resulting from both global and distributive abnormalities of systemic and microcirculatory blood flow. An important factor contributing to the impairment in tissue perfusion is hypovolemia.[41-44] The initial phases of experimental and clinical septic shock present as a low cardiac output syndrome with low filling pressures and evolve to a hyperdynamic state only after volume repletion.[41, 42] Increased blood and plasma volumes are associated with increased cardiac output and enhanced survival from septic shock.[45] Failure to appreciate the degree of underlying hypovolemia may result in a low cardiac output.

Large fluid deficits exist in patients with septic shock. Crystalloid solutions (6 to 10 L) and colloid solutions (2 to 4 L) are usually required during the initial resuscitation.[27] Volume repletion in patients with septic shock produces significant improvement in cardiac function and systemic oxygen delivery, thereby enhancing tissue perfusion and reversing anaerobic metabolism.[46] Despite sepsis-induced myocardial depression, cardiac index will improve by 25% to 40% during fluid resuscitation.[26] In approximately 50% of septic patients who initially present with hypotension, fluids alone will reverse hypotension and restore hemodynamic stability.[47]

In sepsis, increases in interstitial fluid volume may already exist and changes in venous capacitance play a major role in contributing to hypovolemia. Therefore, repleting the interstitial space, which may have a role in hemorrhagic shock, does not appear to be as important in septic shock. Intravascular volume can be repleted either through the use of packed red blood cells, crystalloid solutions, and colloid solutions.

Fluid infusion is best initiated with predetermined boluses titrated to clinical end points of HR, 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 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 filling pressures between 12 and 15 mm Hg.[26] Increases above this range usually do not significantly enhance end-diastolic volume or stroke volume and increase the risk for developing pulmonary edema.

Resuscitation should be titrated to end points of oxygen metabolism and organ function. Associations have been observed between improved survival and increased levels of systemic oxygen delivery, reversal of lactic acidosis and increases in gastric intramucosal pH.[17, 24, 32] However, the specific choice of end points remains controversial.

Transfusion Therapy

The optimal hemoglobin and hematocrit for patients with septic shock is uncertain. This is a major clinical issue, since 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. Decreases in hemoglobin in the range of 1 to 3 g/dL can be expected during resuscitation of septic shock with either crystalloids or colloids.[27]

In most patients, this degree of anemia is usually 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 serve to compensate for the rheologic changes that occur in patients with septic shock and may enhance microvascular blood flow. However, several factors may affect the ability of the patient to tolerate the decrease in hematocrit and should be considered. Cardiac dysfunction will limit the increase in cardiac output in response to decreased viscosity and may result in inadequate levels of systemic oxygen delivery. In markedly hypermetabolic states, the increase in cardiac output may not be adequate to compensate for the decrease in arterial oxygen content, potentially compromising systemic oxygen metabolism. The inability to extract oxygen, related

either to anatomical abnormalities (as in coronary artery diseases) or physiologic concerns (as in sepsis), may result in greater dependence on oxygen content to maintain oxidative metabolism.[48,49]

To date, studies examining the effects of transfusing critically ill patients with hemoglobin concentrations in the range of 8 to 10 g/dL, have not demonstrated any consistent benefit in tissue perfusion. The majority of trials have not demonstrated a significant increase in systemic oxygen consumption when the major effect of transfusion therapy is to increase oxygen content.[28-30] Other studies[50] suggest that increasing oxygen content by transfusion therapy is not as effective in restoring splanchnic perfusion as it is in increasing cardiac output. The transfusion of aged, more rigid, red blood cells has been associated with decreased gastric intramucosal pH and may act to accentuate the rheologic abnormalities seen in sepsis.[31] Moreover, a study[51] randomizing critically ill patients to transfusion thresholds of 7.0 and 10 g/dL failed to demonstrate any differences in clinically significant outcomes.

Accordingly, the optimal hemoglobin for sepsis has not been defined. Most patients will tolerate hemoglobin concentrations in the range of 8 to 10 g/dL. Excessive tachycardia, severe mixed venous desaturation, cardiac dysfunction, underlying coronary artery disease, and failure to resolve lactic acidosis or failure to improve gastric intramucosal pH may indicate the need for increased oxygen content.

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 lactated Ringer's solution is the extracellular compartment. Under ideal conditions, about 25% of the infused amount remains in the intravascular space while the rest is distributed to the extravascular space. Clinically, 100 to 200 mL of intravascular volume expansion can be expected after the infusion of 1 L of isotonic crystalloids.[52, 53] Resuscitation from septic shock frequently requires crystalloid volumes ranging from 6 to 10 L during the initial 24-hr period, which results in significant hemodilution of plasma proteins and decreases in colloid osmotic pressure.

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 vasodilation. The primary risk when using these fluids is iatrogenically induced hypertonic states. Experience with hypertonic solutions in septic shock is limited.

Colloids

There are many different colloidal solutions available including: a) plasma protein fraction; b) albumin; c) gelatins; d) dextrans; and e) hydroxyethyl starch. The principal solutions used in clinical resuscitation are albumin and hetastarch.

Albumin is a naturally occurring plasma protein that accounts for approximately 80% of the plasma colloid osmotic pressure in normal subjects. The normal albumin concentration is from 3.5 to 5.0 g/dL with 40% of the albumin pool being intravascular and the rest being extravascular. Human serum albumin is available in the United States in 5% and 25% solutions; other concentrations are available in Europe. The 5% solution contains 12.5 g of albumin diluted in 250 mL of normal saline and has a colloid osmotic pressure of 18 to 20 mm Hg. The 25% solution contains 12.5 g of albumin in 50 mL of normal saline and has a colloid osmotic pressure of 100 mm Hg. The 5% solution, rather than the 25% solution, should be used for initial resuscitation. After 1 L of 5% albumin has been infused, plasma volume expansion ranges from 500 to 1000 mL.[52, 53] 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 to 500 mL in the intravascular volume 1 hr after infusion.[53] In the setting of increased vascular permeability, such as septic shock, significantly smaller amounts of fluid may be mobilized.

Hydroxyethyl starch (hetastarch) is a synthetic colloid formed from hydroxyethyl-substituted branch-chain amylopectin. It is available in a 6% solution of normal saline, which contains 60 g/L of hetastarch and has a colloid osmotic pressure of approximately 300 mOsm/L. One liter of hetastarch expands plasma volume by 700 mL to 1 L, with as much as 40% of maximum volume expansion persisting for 24 hrs.[52] Hydroxyethyl starch molecules may also affect endothelial cell activation through mechanisms yet to be determined. In patients with sepsis, the infusion of hydroxyethyl starch, as compared with albumin, was associated with reduced release of circulating soluble adhesion molecules, suggesting a reduction in endothelial cell activation and injury.[54] This mechanism may partially account for a preservation of microvascular cross-sectional area that has been observed with hydroxyethyl starch solutions in experimental sepsis.[55]

Hetastarch can cause dose-dependent decreases in factor VIII activity and prolongation of partial thromboplastin time (PTT). In the majority of clinical trials, these changes appear to be largely related to hemodilution after large volumes of hetastarch.[56] Only minor abnormalities in clotting parameters and no increased frequency of bleeding have been observed in patients with hypovolemic and traumatic shock treated with hetastarch.

The possible immunosuppressive effect of the long-term deposition of higher molecular weight hetastarch particles in the reticuloendothelial system have been of concern. In a laboratory study[57], macrophage function and reticuloendothelial clearance of lipid emulsions were not altered in animals receiving hetastarch.

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.[27] Crystalloid solutions will require 2 to 4 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. Five percent albumin and 6% hetastarch are equivalent in the amount of fluid required during resuscitation.

Complications

The major complications of fluid resuscitation are pulmonary and systemic edema. 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. Large-volume crystalloid resuscitation results in significant decreases in plasma colloid osmotic pressure, while plasma colloid osmotic pressure is maintained with colloid infusion.[27] 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.[58,59] Some[60-62], but not all clinical reports, have observed a correlation between decreases in the colloid osmotic pressure-pulmonary arterial occlusion pressure gradient and the presence of pulmonary edema. Several clinical studies[27,63,64] have randomized subjects to receive crystalloid or colloid infusion and examined the development of pulmonary edema with mixed results, either demonstrating no differences between solutions or an increased frequency 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.[65] Taken 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.[27]

The acute respiratory distress syndrome occurs in 30% to 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 of studies[28,66-68], including a variety of models of increased microvascular permeability as well as 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.

Systemic edema is a frequent complication of fluid resuscitation. The relative roles of increased microvascular permeability, increases in hydrostatic pressure, and decreases in plasma colloid osmotic pressure in the development of this complication during sepsis are unclear. Tissue edema may reduce tissue PO_2 values by increasing the distance for diffusion of oxygen into cells. During experimental peritonitis, crystalloid therapy was associated with increased endothelial cell swelling and decreased systemic capillary cross-sectional area when compared with colloid infusion.[55] In contrast, other studies[69, 70] comparing the impact of large-volume crystalloid infusion on skeletal muscle and intestinal oxygen metabolism have observed no impairment of oxidative metabolism despite significant edema formation.

The integrity of the gastrointestinal mucosa as a barrier to bacterial translocation also does not appear to be affected by decreases in colloid osmotic pressure and the development of tissue edema after crystalloid resuscitation. A comparison of crystalloid and colloid resuscitation in thermal injury found that the extent of resuscitation and not the choice of fluids was the major determinant of bacterial translocation.[71]

Vasopressor Therapy

Overview of Vasopressor Therapy

When fluid administration fails to restore an adequate arterial pressure and organ perfusion, therapy with vasopressor agents should be initiated.[72] Potential agents that can be selected include dopamine, norepinephrine, epinephrine, and phenylephrine. Vasopressor therapy may be required transiently even while cardiac filling pressures are not yet adequate, in order to maintain perfusion in the face of life-threatening hypotension. Although the use of these drugs has the potential to reduce organ blood flow through arterial vasoconstriction, their final effects depend on the sum of the direct effects and any increase in organ perfusion pressure. In settings where organ autoregulation is lost, organ flow becomes linearly dependent on pressure[73,74] and organ perfusion pressure should be preserved if flow is to be optimized.[75-77]

Whether or not a potent vasopressor also has positive inotropic effects is of clinical importance in patients with low cardiac output.[4] From a practical point of view, when a vasopressor infusion is started, doses should be carefully titrated to restore MAP, without impairing stroke volume. Should this occur, the dose of vasopressor should be lowered, or the use of dobutamine considered.[78] If right ventricular dysfunction occurs during vasopressor infusion, one should keep pulmonary vascular resistance at the lowest values compatible with the restoration of normal systemic hemodynamics.[40,79-81]

Attention should be paid to the renal and splanchnic circulation during vasopressor infusion. Although no prospective, randomized studies have demonstrated a significant improvement in renal function with increase in renal perfusion pressure, a number of open-label clinical series support this notion.[78,82-91] Urine output and creatinine clearance are increased after the restoration of MAP. Thus, vasopressor agents can be effective tools for the augmentation of renal perfusion pressure. In some patients, the renal autoregulation curve may be shifted to the right, demanding a greater perfusion pressure for a given renal blood flow. The precise mean blood pressure level targeted depends upon the premorbid blood pressure but can be as high as 75 mm Hg.[78,82-90] However, individual responses should be kept at the minimum level required to reestablish urine flow, and in some patients, this re-establishment of urine flow can be achieved with an MAP of 60 or 65 mm Hg.

The gastrointestinal tract, particularly splanchnic bed perfusion and the integrity of the gut mucosa, occupies a key position in the pathogenesis of multiple organ failure in sepsis. Various vasopressor agents have different effects on splanchnic circulation, which may play a role in their selection for a given patient.

Individual Vasopressor Agents

Dopamine

Dopamine is the immediate precursor of norepinephrine and epinephrine. Dopamine possesses several dose-dependent pharmacologic effects. At doses of <5 µg/kg/min, the predominant effect of dopamine is to stimulate dopaminergic DA_1 and DA_2 receptors in the renal, mesenteric, and coronary beds, resulting in vasodilation. Infusion of low doses of dopamine causes an increase in glomerular filtration rate, renal blood flow, and sodium excretion.[92, 93] At doses of 5 to 10 µg/kg/min, β_1-adrenergic effects predominate, producing an increase in cardiac contractility and HR. Dopamine causes the release of norepinephrine from nerve terminals, which contributes to its effects on the heart. At doses above 10 µg/kg/min, α-adrenergic effects predominate, leading to arterial vasoconstriction and an increase in blood pressure. However, there is much overlap in these effects, particularly in critically ill patients.

Hemodynamic Effects

The hemodynamic effects of dopamine in patients with septic shock have been reported in a number of open-label trials. Dopamine has been shown to produce a median increase in MAP of 24% in patients who remained hypotensive after optimal fluid resuscitation.[39,43,92-102] Dopamine increased MAP primarily by increasing cardiac index, with minimal effects on systemic vascular resistance. The increase in cardiac index was primarily due to an increase in stroke volume, and to a lesser extent, to increased HR.[39,43,92-102] The median dose of dopamine required to restore blood pressure was 15 µg/kg/min. In most studies, central venous, pulmonary artery, and pulmonary artery occlusion pressures, as well as systemic vascular resistance and pulmonary artery resistance indices, were unchanged. In patients with increased pulmonary artery occlusion pressures, dopamine may further increase wedge pressure by increasing venous return. Patients receiving dopamine infusion rates of >20 µg/kg/min showed increases in right heart pressures as well as in HR. Dopamine has been shown to improve right ventricular contractility in patients with underlying right ventricular failure.[40]

Regnier et al.[101] compared the hemodynamic effects of dopamine and isoproterenol in patients with septic shock. Dopamine increased cardiac output by 34%, which was attributable to an increase in stroke volume and, to a lesser extent, to an increase in HR. Isoproterenol increased both stroke volume index and HR, but decreased systemic vascular resistance by a mean of 40%. Regnier et al.[98] also compared the effects of dopamine and dobutamine in patients with septic shock and depressed cardiac function. Both agents increased stroke volume by 25%, HR by <10%, and cardiac output by 33%. MAP was unchanged with dobutamine, and so systemic vascular resistance was decreased by 19%, whereas MAP increased by 17% with dopamine, leading to unchanged systemic vascular resistance. Filling pressures decreased in all cases with dobutamine and tended to increase with dopamine, but this was not statistically or clinically significant.

Gas Exchange

In studying the effect of dopamine on pulmonary gas exchange, dopamine has been shown to consistently increase pulmonary shunt fraction, decrease arterial-venous oxygen difference, and increase mixed venous oxygen saturation with the Pao_2 decreasing or remaining unchanged.[95,96,101] Dopamine also inhibits the ventilatory response to hypercarbia. The increase in cardiac output after dopamine administration reduces pulmonary vascular resistance, increasing pulmonary blood flow and increasing intrapulmonary shunt by reopening vessels in poorly ventilated areas of the lung,[95,101] which may play a major role in increasing pulmonary shunt fraction.[96] The relatively constant effect on Pao_2 may relate to the increase in mixed venous oxygen content offsetting the increase in shunt or may be due to a hemodynamic improvement without a change in oxygen consumption.[95,101]

Oxygen Delivery

Dopamine has been shown to increase oxygen delivery above pretreatment levels or levels obtained with concurrently administered catecholamines.[39,92,93] Its effects on calculated or measured oxygen consumption, however, have been mixed. Oxygen extraction ratio typically decreases, suggesting no improvement in tissue

oxygenation.[92,93] This decrease may be due to a failure to improve microcirculatory flow in vital organs or lack of a meaningful tissue oxygen debt in some patients.[93]

Splanchnic Perfusion

The effect of dopamine on splanchnic perfusion, as assessed by gastric tonometric parameters, has also been mixed. Roukonen et al.[94] and Meier-Hellmann et al.[92] documented that dopamine can increase splanchnic blood flow. Roukonen et al.[94] reported that splanchnic oxygen delivery increased as a result of the increase in splanchnic blood flow, with no significant increase in splanchnic oxygen consumption. Meier-Hellmann et al.[92] reported that dopamine increased fractional blood flow if the baseline was <0.30, but had no effect if the baseline fractional blood flow was >0.30. They[92] also reported an increase in splanchnic oxygen delivery without an effect on splanchnic oxygen consumption and a consequent reduction in splanchnic oxygen extraction. There was no effect on pHi or systemic or splanchnic lactate values. Maynard et al.[103] were unable to show any effect on splanchnic blood flow, intramucosal pH, lidocaine metabolism, or indocyanine clearance with low-dose dopamine therapy.

Marik and Mohedin,[39] on the other hand, reported a reduction in pHi associated with an increase in systemic oxygen delivery and oxygen consumption with dopamine. They suggested that dopamine caused an increase in splanchnic oxygen utilization that was not compensated for by an increase in oxygen delivery, resulting in an increase in splanchnic oxygen debt. They speculated that dopamine might have redistributed blood flow within the gut, reducing mucosal blood flow and increasing mucosal oxygen debt.

Neviere et al.[104] reported that dopamine was associated with a reduction in gastric mucosal blood flow. There were changes in gastric P_{CO_2}, gastric-arterial P_{CO_2} difference, and calculated intramucosal pH. Because there were no changes in the acid-base parameters of the patients, the authors could not determine if the reduction in gastric mucosal blood flow was critical.

In summary, dopamine appears to be very effective in increasing MAP in patients who remain hypotensive after optimal volume expansion. Since MAP increases primarily as a result of increasing cardiac index, it should be most useful in patients who are hypotensive with reduced cardiac function. It may be used as an alternative agent in patients with hyperdynamic septic shock who require a vasopressor agent but would not benefit from a further increase in cardiac inotropic function. The major undesirable effects of dopamine are tachycardia, increased pulmonary artery occlusion pressure, increased pulmonary shunt, decreased Pa_{O_2}, and the potential to decrease pHi.

Epinephrine

In patients unresponsive to volume expansion or other catecholamine infusions, epinephrine can increase MAP, primarily by increasing cardiac index and stroke volume with more modest increases in systemic vascular resistance and HR.[87,105-107] Although systemic vascular resistance has increased with increasing doses of epinephrine, there appears to be no predictable dose-response relationship.[87,105] However, Moran et al.[106] showed a linear relationship between epinephrine dose and HR, MAP, cardiac index, left ventricular stroke work index, and oxygen delivery and consumption. In patients with right ventricular failure, epinephrine increases right ventricular function by improving contractility.[108] Epinephrine can increase oxygen delivery, but oxygen consumption may be increased as well.[105-109]

Epinephrine decreases splanchnic blood flow, with transient increases in arterial, splanchnic, and hepatic venous lactate concentrations, decreases in pHi, and increases in P_{CO_2} gap.[38,92] However, Levy et al.[38] documented that the arterial lactate concentration and pHi returned to normal values within 24 hrs. These increases were thought to be due either to increases in splanchnic oxygen utilization and CO_2 production secondary to the thermogenic effect of epinephrine or to epinephrine-induced reduction in gut mucosal blood flow. The reduction in splanchnic blood flow has been associated with a decrease in oxygen delivery and a reduction in oxygen consumption. 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,[38,92] and may potentially be reversed by the concomitant administration of

dobutamine.[110] The addition of dobutamine to epinephrine-treated patients has been shown to improve gastric mucosal perfusion, as assessed by improvements in pHi, arterial lactate concentration, and P_{CO_2} gap.

Epinephrine administration has been associated with increases in systemic and regional lactate concentrations.[38, 105, 109] The etiology of the increase in lactate concentration is unclear.[105] The monitoring periods were short, and so it is unclear if these increases are transient. Despite respiratory compensation and decreased arterial P_{CO_2}, the increase in plasma lactate concentration was associated with decreases in arterial pH and base excess.[109] Other adverse effects of epinephrine include increases in HR, but electrocardiographic changes indicating ischemia[105] or arrhythmias[106] have not been reported in septic patients. Epinephrine has had minimal effects on pulmonary arterial pressures and pulmonary vascular resistance in sepsis.[105,106]

In summary, epinephrine increases blood pressure in patients unresponsive to traditional agents. However, because of its effects on gastric blood flow and its propensity to increase lactate concentrations, the use of epinephrine should be limited to patients who are failing to respond to traditional therapies for increasing or maintaining blood pressure.

Norepinephrine

Norepinephrine is a potent α-adrenergic agonist with less pronounced β-adrenergic agonist effects. In open-label trials, norepinephrine has been shown to increase MAP in patients who remained hypotensive after fluid resuscitation and dopamine. Due to concerns about potential adverse vasoconstrictive effects on regional vascular beds, such as the liver and the kidney, norepinephrine traditionally had either not been used or had been reserved as a last resort in a moribund patient, with predictably poor results.

The recent experience with norepinephrine in septic shock strongly suggests that this drug can successfully increase blood pressure without causing deterioration in organ function. In most studies, septic patients were given fluid to correct hypovolemia before dopamine was titrated to achieve the target blood pressure. When dopamine failed, norepinephrine was added to the dopamine regimen.[38, 40, 78, 82, 86, 89, 90, 94, 97]

In most studies of septic patients, norepinephrine was used at a mean dose of 0.2 to 1.3 μg/kg/min. The initial dose can be as low as 0.01 μg/kg/min [89], and the highest reported norepinephrine dosage was 3.3 μg/kg/min.[78] Thus, large doses of the drug may be required in some patients with septic shock, possibly due to α-receptor down-regulation in sepsis.[111]

Cardiovascular Effects

Norepinephrine therapy usually causes a clinically significant increase in MAP attributable to its vasoconstrictive effects, with little change in HR or cardiac output, leading to increased systemic vascular resistance. Several studies demonstrated increases in cardiac output ranging from 10% to 20% and increases in stroke volume index of 10% to 15 %.[78,80,82,83,86,89] Since cardiac output is either increased or unchanged and MAP is consistently increased, left ventricular stroke work index is increased with norepinephrine therapy. Clinical studies have reported either no change.[40,82,83,86,89] or modest increases (1 to 3 mm Hg)[39,78,90,94,97] in pulmonary artery occlusion pressure. Mean pulmonary arterial pressure is either unchanged[78,82,.86,90,112], or increased slightly.[40,89,90,97]

Norepinephrine, like all other vasopressors, should be used only to restore normal (or low normal) levels of MAP and systemic vascular resistance. Titration to MAP, rather than systemic vascular resistance, a derived parameter[113], is advised. The optimal target MAP depends on many factors, including age and premorbid condition.

Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in septic shock patients. Martin et al.[97] prospectively randomized 32 volume-resuscitated patients with hyperdynamic sepsis syndrome to receive either dopamine or norepinephrine to achieve and maintain normal hemodynamic and oxygen transport parameters for at least 6 hrs. Dopamine administration (10 to 25 μg/kg/min) resulted in successful treatment in only 31% (5 of 16) of patients, whereas norepinephrine administration (1.5±1.2 SD μg/kg/min) was

successful in 93% (15 of 16 of patients) ($p < 0.001$). Of the 11 patients who did not respond to dopamine, ten patients responded when norepinephrine was added.

Renal Effects

In patients with hypotension and hypovolemia, e.g., during hemorrhagic or hypovolemic shock, the vasoconstrictive effects of norepinephrine can have severe detrimental effects on renal hemodynamics, with increased renal vascular resistance and renal ischemia.[114-116] Norepinephrine has been demonstrated to cause ischemia-induced acute renal failure in rats.[117] The situation is different in hyperdynamic septic shock, in which it is believed that urine flow decreases mainly as a result of lowered renal perfusion pressure.[88] Since norepinephrine has a greater effect on efferent arteriolar resistance and increases the filtration fraction, normalization of renal vascular resistance could effectively reestablish urine flow.

In the high output–low resistance state of septic shock patients, norepinephrine can markedly improve MAP and glomerular filtration. In the studies by Redl-Wenzl et al.,[90] Desjars et al.,[83] and Martin et al.[88] of septic shock patients treated with dopamine (and some also treated with dobutamine), the addition of norepinephrine (0.5 to 1.5 μg/kg/min) significantly increased urine output, creatinine clearance, and osmolar clearance. In a study by Fukuoka et al.[85], the addition of norepinephrine to dopamine and dobutamine increased systemic vascular resistance and urine flow only in patients with normal serum lactate concentrations, although this study was small and is at variance with other studies[39,40,43,97] in which vascular resistance and urine flow were increased in patients with increased lactate concentrations. These studies[83, 88, 90] support the hypothesis that renal ischemia observed during hyperdynamic septic shock is not worsened by norepinephrine infusion and even suggests that this drug may effectively optimize renal blood flow and renal vascular resistance.

Combination therapy employing vasoactive agents with different vascular actions has been suggested as a way to maximize therapeutic benefit while minimizing undesirable effects. In that regard, the use of low-dose dopamine (1 to 3 μg/kg/min) may be considered.[73, 118] In a recent study[119], the addition of low-dose dopamine to norepinephrine in healthy volunteers significantly increased renal blood flow and sodium excretion. Thus, the renal vasodilating action of low-dose dopamine may persist despite the infusion of a potent vasopressor. Whether these findings can be extended to patients with sepsis will require further study.

Effects on Lactate Concentrations

The effects of norepinephrine on serum lactate concentrations were assessed in five studies. In four of these studies, changes in lactate concentrations were assessed over a relatively short period of time (1 to 3 hrs), and although blood flow tended to improve significantly, the decrease in serum lactate concentration was not significant.[39,40,86,94] It is worth noting that initial values were not very high (1.8 to 2.3 mmol/L), and it is unclear if sufficient time elapsed between measurements to see a significant norepinephrine-induced change in serum lactate concentration. In the fifth study[97], initial lactate concentrations were elevated (4.8 ± 1.6 SD mmol/L) and a statistically and clinically significant decrease (2.9 ± 0.8 SD mmol/L) was observed at the end of the 6-hr study period. The results of these five studies suggest that the use of norepinephrine does not worsen, and can even improve, tissue oxygenation of septic shock patients.

Effects on Splanchnic Circulation

The effects of norepinephrine on splanchnic blood flow were evaluated in two elegant studies. In a study by Ruokonen et al.[94] in septic shock patients receiving either norepinephrine (0.07 to 0.23 μg/kg/min) or dopamine (7.6 to 33.8 μg/kg/min) to correct hypotension, the effect of norepinephrine on splanchnic blood flow was considered unpredictable (increased in three patients, decreased in two patients, with no change in mean splanchnic blood flow, oxygen consumption, or oxygen extraction), while dopamine caused a consistent and statistically significant increase in splanchnic blood flow. Meier-Hellman et al.[92] showed that septic patients switched from dobutamine to norepinephrine, or from dobutamine and norepinephrine to norepinephrine alone, had a decrease in cardiac output and a decrease in splanchnic blood flow that paralleled the decrease in cardiac output. Splanchnic oxygen consumption remained unchanged due to a regional increase in oxygen extraction. The authors concluded that

provided cardiac output is maintained, treatment with norepinephrine alone is without negative effects on splanchnic tissue oxygenation. This result was confirmed in the study by Marik and Mohedin[39] in which gastric mucosal pHi was significantly increased during a 3-hr treatment with norepinephrine while it was significantly decreased during treatment with dopamine. Reinelt et al.[120] showed that the addition of dobutamine to norepinephrine to obtain a 20% increase in cardiac index in septic shock patients could increase splanchnic blood flow and oxygen consumption and improve hepatic metabolic activity (as assessed by hepatic glucose production). Splanchnic blood flow and cardiac index increased in parallel, but there was no effect on splanchnic oxygen consumption and hepatic glucose production decreased.

Levy et al.[38] compared the effects of epinephrine with the combination of norepinephrine and dobutamine on gastric tonometric variables in 30 septic shock patients and found that while systemic hemodynamics were similar, pHi and gastric P_{CO_2} gap were normalized within 6 hrs with norepinephrine and dobutamine while pHi decreased and gastric P_{CO_2} gaps increased in epinephrine-treated patients. Changes in the epinephrine group were transient and were corrected within 24 hrs, but might have induced splanchnic ischemia and injury. The authors concluded that the splanchnic effects of the combination of norepinephrine-dobutamine were more predictable than epinephrine.

Conclusions on the Use of Norepinephrine in Septic Shock Patients

The clinical experience with norepinephrine in septic shock patients strongly suggests that this drug can successfully increase blood pressure without causing a deterioration in cardiac index and organ function.[121] Used in doses of 0.01 to 3 µg/kg/min, norepinephrine reliably improves hemodynamic variables in the great majority of patients with septic shock. The effect of the drug on oxygen transport variables cannot be determined fully from the available data. However, other clinical parameters of peripheral perfusion, such as urine flow and lactate concentration, are significantly improved in most studies. Unfortunately, only one report was controlled[97], and whether using norepinephrine in septic shock patients affects mortality as compared to dopamine or epinephrine still requires a prospective clinical trial. When the use of norepinephrine is contemplated, it should be used early and not withheld as a last resort.[122]

Phenylephrine

Phenylephrine, a selective α-1 adrenergic agonist, has been used by rapid intravenous administration to treat supraventricular tachycardia by causing a reflex vagal stimulation to the heart resulting from a rapid increase in blood pressure. Phenylephrine is also used intravenously in anesthesia to increase blood pressure. Its rapid onset, short duration, and primary vascular effects make it an attractive agent in the management of hypotension associated with sepsis. However, there are concerns about its potential to reduce cardiac output and lower HR in these patients.

Unfortunately, there are only a few studies evaluating the clinical use of phenylephrine in hyperdynamic sepsis. As such, guidelines on its clinical use are limited. One study[123] evaluated short-term phenylephrine therapy in hyperdynamic septic patients who were not hypotensive at the time of drug administration. Phenylephrine, at a dosage of 70 µg/min, increased MAP, cardiac index, and stroke index. HR was statistically significantly lower but the decrease averaged only 3 beats/min. There was no change in systemic vascular resistance. In comparison, the response of normotensive patients with cardiac disease to the same phenylephrine dosing was an increase in blood pressure and systemic vascular resistance, a decrease in cardiac index, and no change in HR. In a dose-response study, phenylephrine was administered to hyperdynamic septic patients who were normotensive at the time of drug therapy.[124] In incremental doses of 0.5 to 8 µg/kg/min, phenylephrine increased MAP, systemic vascular resistance, and stroke index, while no change was seen in cardiac index. HR was slightly but significantly lower, with a decrease ranging from 3 to 9 beats/min. This study evaluated oxygen transport parameters and found no statistical changes in either oxygen delivery or consumption. However, a clinically significant (>15%) increase in oxygen consumption was seen in eight of ten patients in at least one dosage.

There is only one study[91] evaluating the clinical effects of phenylephrine in treating hypotension associated with sepsis. This was a small study of 13 patients with septic shock who received either low-dose dopamine or dobutamine, and who remained hypotensive despite fluid administration. Their baseline cardiac index was 3.3 L/min/m^2 and MAP was 57 mm Hg. Phenylephrine was begun at 0.5 µg/kg/min and was titrated to maintain an MAP of more than 70 mm Hg. Patients required phenylephrine for an average of 65 hrs, and the maximum dosage in each patient averaged 3.7 µg/kg/min (range 0.4 to 9.1). Phenylephrine resulted in an increase in MAP, systemic vascular resistance, cardiac index, and stroke index. There was no change in HR. Clinically, a significant increase in urine output, and no change in serum creatinine were seen during phenylephrine therapy. Increases in oxygen delivery and consumption were reported.

The limited information available with phenylephrine suggests that this drug can increase blood pressure in fluid-resuscitated septic shock patients. 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.

Complications of Vasopressor Therapy

All of the catecholamine vasopressor agents can cause significant tachycardia, especially in patients who are inadequately volume resuscitated. In patients with coexisting coronary disease, vasopressor-induced increases in myocardial oxygen consumption may precipitate myocardial ischemia and infarction. In the presence of myocardial dysfunction, excessive vasoconstriction can decrease stroke volume, cardiac output, and oxygen delivery. When a vasopressor infusion is started, doses should be carefully titrated to restore MAP, without impairing stroke volume. Should the stroke volume become impared, the dose of vasopressor should be lowered, or the use of dobutamine considered.[78] In the presence of right ventricular dysfunction in septic shock, increased right ventricular afterload could worsen ventricular function.[79,81] During vasopressor infusion, one should keep pulmonary vascular resistance at the lowest values compatible with the restoration of normal systemic hemodynamics.[40, 80]

Potent vasopressors, such as norepinephrine, decrease renal blood flow in human and canine studies.[115] While the patient is receiving vasopressor therapy, cardiac index should be maintained at normal levels to optimize renal blood flow.[78]

Administration of vasopressors may impair blood flow to the splanchnic system, and this impairment can be manifested by stress ulceration, bowel ileus, and malabsorption.[109,110] Gut mucosal integrity occupies a key position in the pathogenesis of multiple organ failure, and countercurrent flow in splanchnic microcirculation gives the gut a higher critical threshold for oxygen delivery than other organs. If possible, episodes of intramucosal acidosis, which might be detected either by a decrease in gastric mucosal pHi or an increase in gastric mucosal P_{CO_2}, should be avoided, although no prospective, randomized, controlled trial has demonstrated a decrease in mortality with pHi or gastric P_{CO_2}-directed care in the management of patients with septic shock.

Inotropic Therapy in Sepsis

Overview

Sepsis is characterized by a hyperdynamic state, with normal-to-low blood pressure, normal-to-high cardiac index, and a low systemic vascular resistance.[1,43] Although cardiac output is usually maintained in the volume-resuscitated septic patient, a number of investigations[4,125,126] 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 (a load-independent measure of ventricular function).[127-129] The mechanism of this cardiac dysfunction is unclear. Myocardial ischemia is unlikely, as coronary blood flow is normal and there is no net lactate production across the coronary vascular bed.[130,131] Animal studies of endotoxemia or bacterial infection have suggested that myocardial edema,[132] alterations in sarcolemmal or intracellular calcium homeostasis,[133] and uncoupling or disruption of ß-adrenergic signal transduction may contribute to the cardiac contractile dysfunction.[134] A variety of inflammatory mediators, including prostanoids,[135] platelet-activating factor,[136] tumor necrosis factor (TNF)-α, interleukin (IL)-1 and IL-2, [137] and nitric

oxide (NO),[138, 139] have been shown to cause myocardial depression in a number of animal models.

Although it is clear that myocardial performance is altered during sepsis and septic shock, end points for cardiac resuscitation are uncertain. Data from the 1980s and early 1990s suggested that a linear relationship between oxygen delivery and oxygen consumption ("pathologic supply dependency") was common in septic patients;[46,140] i.e. oxygen delivery was insufficient to meet the metabolic needs of the patient. These observations led to the hypothesis that resuscitation to predetermined elevated end points of cardiac index and oxygen delivery and consumption ("hyperresuscitation") might improve patient outcome. More recent investigations,[33-35,141] however, have challenged the concept of pathologic supply-dependency and hyperresuscitation. Although cardiac index and oxygen delivery are correlated with outcome,[32] it is unclear if increases in these variables are the cause of increased survival or represent the underlying physiologic reserve of the patient.

Uncertainty exists in regard to other end points for inotropic therapy. Deficits in oxygen delivery can cause a lactic acidosis, but the converse is not true: increased lactate concentrations in patients with sepsis or septic shock do not necessarily reflect deficits in oxygen delivery. In septic patients, mixed venous oxygen saturation is usually high, and this value correlates poorly with cardiac output. Several studies have questioned the value of mixed venous oxygen saturation as the end point for inotropic therapy in critically ill patients.[142,143] Low mixed venous oxygen saturation may indicate decreased global oxygen delivery, however.[142] Global oxygen delivery may be adequate in many septic patients but regional perfusion may be suboptimal. Gastric tonometry monitors gastric intramucosal pH (pHi) as a proxy for determining the adequacy of gut perfusion. Although gastric tonometry is a good predictor for the ultimate outcome of critically ill patients and may be useful in the resuscitation of such patients,[22-25] its utility to guide therapy in patients with sepsis and septic shock has not been proven.

With the above considerations in mind, precise recommendations regarding specific end points for cardiac index, oxygen delivery, oxygen consumption and mixed venous oxygen saturation are difficult to formulate based on currently available data. An inotropic agent should be considered to maintain an adequate cardiac index, MAP, mixed venous oxygen saturation and urine output.

Therapies and efficacy

Most investigations evaluating inotropic agents have been observational and have used the baseline hemodynamic characteristics of the patient as the controls. The majority of these studies have used HR, cardiac index or cardiac output, and/or stroke volume or stroke volume index as the outcome variables. A minority of studies have assessed ventricular function by reporting left (or right) ventricular stroke work index, which may be a more accurate approach. The results are summarized in **Table 2.**

Individual inotropic agents

Catecholamines

Isoproterenol

Isoproterenol is a $ß_1$- and $ß_2$-adrenergic receptor agonist. Few studies have evaluated isoproterenol in sepsis and septic shock. In septic shock patients with a low cardiac index (mean of < 2.0 L/min/m^2), isoproterenol (2 to 8 µg/min) significantly increases cardiac index without decreasing blood pressure but at the expense of increasing HR.[43,144] In patients with a normal cardiac index, however, isoproterenol can decrease blood pressure through its $ß_2$-adrenergic effects. In addition, the chronotropic effects of $ß_1$-adrenergic stimulation can precipitate myocardial ischemia.

Dopamine

Dopamine is an adrenergic agonist with predominant dopaminergic properties at doses of <5 µg/kg/m and increased ß and α activity at doses of >5 µg/kg/min. Even at low doses, significant α and ß agonism may occur.

In patients with severe sepsis and/or septic shock, most studies[39,40,94,95,97,99,100,102,109,145-147] have shown that dopamine increases cardiac index in the range of 20% to 30%, left ventricular stroke work index by 20% to 60%, and right ventricular stroke work index by a modest 5% to 10%. These improvements in cardiac performance come at the expense of an increase in the HR by approximately 15%. The greatest increase in these variables occurs at doses ranging from 3 to 12 µg/kg/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 $ß_1$- and $ß_2$-adrenergic effects, and an L isomer with $ß_1$- and α_1-adrenergic effect. The predominant effect of dobutamine is inotropic via stimulation of $ß_1$ receptors, with a variable effect on blood pressure.

A number of studies[78,148-153] have investigated the effect of dobutamine on cardiac function during sepsis or septic shock at doses ranging from 2 to 28 µg/kg/min. In the majority of these studies, increases in cardiac index ranged from 20% to 66%. However, HR often increased significantly (10% to 25%). Two studies[148,149] reported that left ventricular stroke work index increased by 23% to 37% at mean dobutamine doses of 5 to 12 µg/kg/min. Similar increases in right ventricular stroke work were also observed in these studies.

Epinephrine

Epinephrine stimulates both α and ß receptors. At low doses, the ß adrenergic effects predominate. A few recent studies[106, 107, 109] have examined the hemodynamic effects of epinephrine in septic shock at doses ranging from 0.1 to 0.5 µg/kg/min. The increase in cardiac index varied from 23% to 54%, and the HR response was variable. Only one study[107] reported left ventricular stroke work index and noted a 95% increase. Another study[109] suggested that lactic acidosis is increased and perfusion to the gut is altered with the use of epinephrine.

Norepinephrine

Like epinephrine, norepinephrine stimulates both α and ß receptors; however, the α-adrenergic response is the predominant effect.

The effect of norepinephrine on cardiac index is modest, with the majority of studies[39,40,78,80,89,94,97] showing no change or increases of 10% to 12%, while HR is unaffected or even decreases by ≤10%. However, several studies[39,40,80,89] have shown a marked increase in left and right ventricular stroke work index due to increased blood pressure.

Combination and Comparative Studies

A significant number of studies[38,82,90,120,154-157] have investigated catecholamine combinations. The majority of these studies did not study the catecholamine combination in a standardized fashion, thus limiting the conclusions that can be drawn about the effects of these catecholamine combinations on cardiac function. Two studies suggest that a norepinephrine/dobutamine or norepinephrine/dopamine combination is no better than norepinephrine or dopamine alone, respectively, at improving cardiac index.[78,97]

A few investigations[38-40,84-87,109] have been performed comparing different inotropic regimens. Epinephrine appears to be as good, if not better, at improving cardiac performance than dopamine or a dobutamine/norepinephrine combination.[38,109] However, epinephrine is associated with increases in arterial lactate concentration and decreases in gastric intramucosal pH, suggesting that perfusion to regional vascular beds may be impaired.[38,109] In several studies,[39, 40] dopamine increased cardiac index and stroke volume index to a greater extent than norepinephrine but increases in left and right ventricular stroke volume index were about the same with the two agents. There was less prominent tachycardia with norepinephrine,[39,40] and one study suggested that mesenteric perfusion is impaired with dopamine compared to norepinephrine.

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 have been no studies of amrinone in patients with sepsis. There has been one published study[158] evaluating milrinone in pediatric patients with sepsis. However, catecholamines were also administered to the majority of these patients. After a bolus (50 µg/kg) and infusion (0.5 µg/kg/m) of milrinone, cardiac and right and left ventricular stroke work indices improved significantly with little change in HR.

Miscellaneous Agents

No studies have examined the role of calcium or glucagon in the septic patient. One investigation[146] of digoxin in hypodynamic septic patients demonstrated significant improvement in cardiac performance.

Complications.

In the septic patient who has been inadequately volume resuscitated, all of the inotropic agents can cause significant tachycardia. In patients with coexisting coronary disease, the change in myocardial oxygen consumption may precipitate myocardial ischemia and infarction.[34] 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) are likely to reduce blood pressure. These reductions can be long lasting with agents that have a long half-life.

Administration of inotropic agents that have pressor activity may impair blood flow to other organ beds, such as the splanchnic circulation.[109,110] Efforts to ensure adequate volume resuscitation and to assess end-organ function must be made.

EXPERIMENTAL THERAPIES

Introduction:

This document has provided guidelines and recommendations regarding currently available therapeutic approaches to treat hemodynamic instability in septic patients. The past decade has witnessed a profound increase in the understanding of the pathophysiology of sepsis and of the biological, biochemical, pharmacologic, and molecular mechanisms that mediate the deleterious effects of infectious agents. This understanding provides the basis for several potential therapeutic strategies to interrupt the pathogenic sequence leading to septic shock.

In keeping with the goals of this practice parameter, this section will focus on several experimental strategies aimed at improving hemodynamics in sepsis. These strategies include dopexamine, inhibitors NO_2, and use of extracorporeal circuits to remove toxic mediators. Therapies aimed at inhibiting or neutralizing the effects of specific inflammatory mediators of sepsis such as endotoxin, TNF, IL-1 and other cytokines will not be reviewed, although it is recognized that any intervention which ameliorates the septic process will likely improve hemodynamics. Similar considerations pertain for other experimental approaches.

Dopexamine:

Dopexamine is a synthetic catecholamine that has a unique combination of adrenergic effects: strong β-adrenergic and dopaminergic effects without any α-adrenergic effects. Dopexamine stimulates β_2 adrenoreceptors and DA_1 and DA_2 receptors and hence, may restore organ flow because of its vasodilating properties.[159] It is theorized that dopexamine may increase hepatosplanchnic perfusion, either alone or in combination with other vasoactive agents, and may thus potentially mitigate some of the untoward effects and sequelae of sepsis and septic shock.

Dopexamine has been shown to increase oxygen delivery in animal trials. Lund et. al.[160] documented improved tissue oxygenation in gut, liver, and skeletal muscle with dopexamine in septic rabbits in a dose-dependent manner.[161] Similarly, Cain and Curtis[161,162] observed an increase in systemic oxygen delivery and oxygen consumption with dopexamine and suggested improved gut mucosal perfusion in endotoxemic dogs. Palsson et. al.[163] compared the

renal effects of dopexamine with both dopamine and dobutamine in an experimental model of sepsis in conscious rats after *Escherichia coli* infusion, and concluded that the renal excretory function was improved to a greater extent with dopexamine than the other two agents. Dopexamine preserved blood pressure better than dobutamine, although no differences were noted in MAP between dopexamine and dopamine.[163] In contrast, however, Van Lambalgen et al.[163] observed no differences between dopexamine and dobutamine in organ perfusion in endotoxemic rats.

Dopexamine has been evaluated in several small human trials. Colardyn et al.[165] evaluated the use of dopexamine in ten patients with septic shock and observed a short-term increase in cardiac index and HR and a dose-dependent decrease in systemic vascular resistance. Over the long term, tolerance may have developed, as these effects gradually diminished.[165] Hannemann et al.[159] evaluated the effects of a 30-min infusion of dopexamine (2 μg/kg/min) in 29 postoperative patients with septic shock and noted an increase in cardiac index and oxygen delivery, and a slight (4%) but statistically significant increase in oxygen consumption; the oxygen extraction ratio decreased by approximately 8%. More recently, Smithies et al.[166] evaluated the effects of raising cardiac index with dopexamine in ten patients with sepsis syndrome, acute respiratory failure, and at least one other organ system failure. With dopexamine hepatic blood flow was increased, and gastric intramucosal pH also improved significantly; these effects were sustained after discontinuation of dopexamine, suggesting that dopexamine may improve splanchnic oxygenation independent of its effects on systemic hemodynamics.[166] These studies are small, and the effects of dopexamine on gastric intramucosal pH have not been consistently reproducible.

These[159,165,166] and other studies seem to suggest a potential benefit from dopexamine in patients with sepsis and septic shock. The use of dopexamine in these patients, however, can be limited by a significant increase in HR[167] and by the potential for hypotension. Clear and convincing evidence is lacking in regard to improved efficacy over other agents, and a benefit in terms of improved or altered clinical outcome has not been demonstrated. Dopexamine has been available in some countries in Europe for several years, but it is still considered experimental in the United States. Although potentially promising, dopexamine cannot be considered part of the standard therapeutic regimen for the treatment of hemodynamic insufficiency in patients with sepsis on the basis of current evidence.

Nitric Oxide Inhibition:

Cytokines and other mediators of inflammation stimulate macrophages, monocytes, smooth muscle cells, and vascular endothelial cells to produce nitric oxide NO, a potent endogenous vasodilator.[168] Increased NO production, as evidenced by increased serum nitrate and nitrite concentrations, has been observed in patients with septic shock[169, 170] Vasodilation stimulated by NO is important in the initiation and maintenance of hypotension in sepsis, and NO is also an important mediator of sepsis-induced refractoriness to the vasopressor effects of catecholamines.[168,171] Nitrate concentration in septic patients have been shown to correlate with systemic vascular resistance.[172] Thus, concentrated efforts have been devoted to the full elaboration of the pathways involved in NO synthesis and activation, in the belief that inhibition of this pathway may reduce the incidence of hemodynamic insufficiency in septic shock.

NO is synthesized from endogenous L-arginine by the enzyme nitric oxide synthase (NOS), which can be inhibited in a competitive fashion by analogues of L-arginine.[173] NOS inhibition, using these agents, has improved blood pressure and increased systemic vascular resistance in animal models,[174-176] but can decrease cardiac output and increase pulmonary arterial pressure.[177]

Several small trials of short-term administration of NOS inhibitors to pressor-dependent septic patients have been conducted, with similar findings. Petros et al.[178] gave the NOS inhibitor N^G-methyl-L-arginine to 12 patients with septic shock requiring pressor therapy. They obtained an increase in MAP from 81 to 101 mm Hg, with a decrease in cardiac output from 11.2 to 8.9 L/min and an increase in pulmonary vascular resistance (PVR) from 122 to 238 dyne·sec·cm^{-5}. Lorente et al.[179] found a similar pattern after bolus infusion of N^w-nitro-L-arginine to eight patients with sepsis syndrome, with an increase in MAP of 57%, a decrease in cardiac output of 24%, and an increase in pulmonary vascular resistance of 53%.[180]

Despite their effects on blood pressure, convincing data that NOS inhibitors improve mortality is lacking, even in animal models. Production of NO by constitutive NOS in endothelial cells is an important modulator of both vascular permeability and leukocyte adherence, and inhibits platelet aggregation and adherence.[180] Thus, NO is important in maintaining microvascular blood flow. Production of NO by the constitutive enzyme may protect the liver from endotoxin-induced damage as well.[181] Accordingly, use of arginine analogues that inhibit both the constitutive and inducible isoforms of NOS may not be beneficial in sepsis. Detrimental effects of such nonselective NOS inhibition have been seen in some animal models.[181-183] A large, randomized trial of nonselective NOS inhibition with N^G-methyl-L-arginine in patients with septic shock was recently terminated due to excess mortality in the treatment group.[184] Selective inhibition of the cytokine-inducible form of NOS has shown some promise in rodent models[185, 186] but needs further testing in appropriate large-animal models before clinical trials can be contemplated.

NO relaxes vascular smooth muscle by activating soluble guanylate cyclase and increasing intracellular cyclic guanosine monophosphate (GMP). Methylene blue inhibits the effects of NO on guanylate cyclase and may inhibit NOS as well. Preiser et al.[187] infused methylene blue as a 2-mg/kg bolus into 14 patients with severe septic shock requiring adrenergic therapy. They showed that methylene blue increased MAP without decreasing cardiac output or oxygen consumption. These effects were transient, and mortality was not examined in this small pilot study.

The full effects, interactions, and an understanding of the risks and benefits of NO inhibition require further understanding and scientific inquiry. Data are most prominent in animal models, but even in these models, results are mixed. The benefits of this approach in patients remain to be demonstrated in clinical trials.

Extracorporeal Membrane Oxygenation Therapy and Related Interventions

Extracorporeal circuits and related techniques, such as continuous veno-venous hemofiltration, continuous arteriovenous hemofiltration, and extracorporeal membrane oxygenation (ECMO), can potentially remove mediators in the septic cascade responsible for hemodynamic decompensation. Data are promising in animal models and in certain specific clinical settings, such as meningococcal disease and the treatment of neonates and other pediatric populations. However, studies still yield conflicting evidence. Extracorporeal support, especially that using nonbiocompatible membranes, can trigger the release of inflammatory mediators.

Stein and colleagues[188] evaluated the effects of hemofiltration on hemodynamic and central blood volume in a swine model of endotoxic shock, and showed that pulmonary arterial pressure, wedge pressure, pulmonary vascular resistance, and systemic vascular resistance were lowered while central blood volume remained unchanged. A trend toward higher survival was noted in the group receiving hemofiltration, although this trend did not reach statistical significance.[188] Grootendorst et al.[189] showed an improvement of right ventricular ejection fraction and cardiac performance in a swine model of endotoxic shock with high-volume venovenous hemofiltration, presumably by removal of vasoactive mediators responsible for the adverse sequelae. Griffin et al.[190] evaluated the effect of ECMO in immature piglets subjected to fecal-*E. coli* peritonitis, and found that although ECMO was associated with improved cardiopulmonary support, mortality was unaffected. Similarly, in an evaluation of continuous venovenous hemofiltration in endotoxic swine, Bottoms et al.[191] failed to demonstrate any reductions in plasma concentrations of TNF, lactate concentration, or eicosanoids. Hence, although results in some animal models are promising, which extracorporeal circuits and regimens work best is not entirely clear, and the benefit from these circuits is still uncertain.

Some small clinical studies suggest a potential benefit from extracorporeal circuits in certain settings, although as with animal data, results are still inclusive. Beca and Butt[192] performed a retrospective analysis on nine children who received ECMO for refractory septic shock, and found that five children were long-term survivors, indicating that ECMO is not contraindicated in this setting.[192] Another retrospective analysis by McCune et al.[193] observed a 100% survival rate in ten neonates with septic shock who received ECMO, although these patients required a longer period of ventilatory support after the ECMO was discontinued. ECMO has also been shown to provide hemodynamic support for pediatric patients with meningococcal disease who failed to respond to conventional therapy, with eight of 12 patients surviving.[194]

In adult patients, Bellomo et al. showed increased clearance of TNF critically ill patients who underwent continuous hemodiafiltration,[195] and a subsequent study[196] of 18 critically ill patients with sepsis and renal failure compared with six critically ill controls showed removal of TNF and IL-1 from the circulation in the experimental group. Comparable findings were also was noted by Hoffmann et al.[197] with hemofiltration in a similar septic adult sample.[197]

However, convincing evidence is still lacking regarding the efficacy of extracorporeal circuits; controlled trials have not been reported. Studies have only been performed in relatively limited situations, and thus cannot be extrapolated to the general septic population. Outcome data are particularly limited in adult populations. Whether endogenous production and clearance of mediators in septic patients is too great to be influenced by extracorporeal clearance is uncertain. Data on the kinetics of inflammatory mediators in septic patients are sparse. In addition, removal of cytokines and mediators that have been linked to the adverse sequelae of septic shock may not translate into beneficial clinical outcomes such as reduced mortality, improvement in hemodynamic status, or resolution of organ failure. Hence these therapies and modalities, while potentially promising, need additional evaluation in randomized and controlled trials before recommendations can be tendered as to their appropriate use.

RECOMMENDATIONS FOR HEMODYNAMIC SUPPORT OF SEPTIC PATIENTS

Basic Principles

1. Patients with septic shock should be treated in an intensive care unit, with continuous electrocardiographic monitoring and monitoring of arterial oxygenation.

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

3. Resuscitation should be titrated to clinical end points of arterial pressure, HR, urine output, skin perfusion, and mental status, and indices of tissue perfusion such as blood lactate concentrations and mixed venous oxygen saturation.

4. 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.

Fluid Resuscitation

Recommendation 1- Level C

Fluid infusion should be the initial step in hemodynamic support of patients with septic shock. Generation of the hyperdynamic state is dependent on fluid repletion.

Recommendation 2 - Level C

Initial fluid resuscitation should be titrated to clinical end points. Isotonic crystalloids or iso-oncotic colloids may be used for fluid resuscitation. These 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 promptly responding 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 to 15 mm Hg.

Recommendation 4 - Level D

Hemoglobin concentrations should be maintained above 8 to 10 g/dL. In patients with low cardiac output, mixed venous oxygen desaturation, lactic acidosis, widened gastric-arterial P_{CO_2} gradients, or coronary artery disease, transfusion to a higher level of hemoglobin may be desired.

Vasopressor Therapy

Recommendation 1- Level E

In patients with clinical signs of shock and hypotension not initially responsive to aggressive empiric fluid challenge, dopamine is the first-line agent for increasing blood pressure. Pulmonary artery catheterization is useful to guide therapy.

Recommendation 2 - 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. Phenylephrine is another alternative, especially in the setting of tachyarrhythmias, although experience in patients with septic shock is limited.

Recommendation 3 - Level D

Epinephrine should be considered for refractory hypotension, although adverse effects are common.

Recommendation 4 - Level E

Routine administration of low doses of dopamine to maintain renal function is not recommended but low-dose dopamine may increase renal blood flow in some patients when added to norepinephrine.

Inotropic Therapy

Recommendation 1- Level E

Dobutamine is the first choice for patients with low cardiac index (<2.5 L/min/m^2) after fluid resuscitation and an adequate MAP. Dobutamine may cause hypotension and/or tachycardia in some patients, especially those with decreased filling pressures.

Recommendation 2- Level D

In patients with evidence of tissue hypoperfusion, the 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^2) has not been shown to improve outcome.

Recommendation 3 - Level D

A vasopressor, such as norepinephrine, and an inotrope, such as dobutamine, can be titrated separately to maintain both MAP and cardiac output.

Recommendation 4 - Level C

Epinephrine and dopamine can be used to increase cardiac output, but mesenteric perfusion may be decreased with epinephrine, and gastric mucosal perfusion may be decreased with dopamine.

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Table I - The guidelines of Evidence-Based Medicine's rating system for strength of recommendation and quality of evidence.

Rating System for References:

Level I: Large, randomized trials with clear-cut results; low risk of false-positive (α) error or false-negative (β) error
Level II: Small, randomized trials with uncertain results; moderate to high risk of false-positive (α) error and/or false-negative (β) error
Level III: Non-randomized, contemporaneous controls
Level IV: Non-randomized, historical controls and expert opinion
Level V: Case series, uncontrolled studies, and expert opinion

Rating System for Recommendations:
A: Supported by at least two level I investigations
B: Supported by only one level I investigation
C: Supported by level II investigations only
D: Supported by at least one level III investigation
E: Supported by level IV or level V investigations only

Table 2:

Summary of cardiac effects of inotropes used in sepsis and septic 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 mg/min	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

*With other inotropes including dopamine, dobutamine, norepinephrine and/or epinephrine

These practice parameters have been developed by a task force of the American College of Critical Care Medicine, Society of Critical Care Medicine, and thereafter reviewed by the Council of the Society of Critical Care Medicine. The opinions expressed herein reflect the official opinion of the Society of Critical Care Medicine, and should not be construed to reflect the views of the specialty boards or any other professional medical organization.

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