Chapter 12
Shock in the Gynecologic Patient

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DEFINITIONS

Categories of the etiologies of shock—

- Hypovolemic
  - Blood loss, dehydration, and diarrhea
- Distributive
  - Sepsis, endocrine, spinal, and anaphylaxis
- Obstructive
  - PE, tamponade, pericarditis, and pulmonary hypertension
- Cardiogenic
  - MI, myopathy, and valvular lesions

Classification of the severity of hemorrhagic shock—

- Class I—up to 15% of blood volume

  Compensation maintains normal cardiac output and blood pressure

- Class II—15% to 30% of blood volume

  Compensation cannot maintain normal cardiac output, but systolic blood pressure is maintained; pulse pressure is narrowed (compensated shock)
- Class III—30% to 40% of blood volume

  Cardiac output and blood pressure are decreased; significant tachycardia (uncompensated shock)
- Class IV—greater than 40% blood loss

  Cardiac output and blood pressure are profoundly decreased; very significant tachycardia

Compensated shock—A state of global, inadequate organ perfusion, and oxygen delivery with normal blood pressure.

Cytopathic hypoxia—A state of mitochondrial injury and dysfunction resulting from hypoxia and oxidative stress where oxidative phosphorylation is interrupted, thus mandating ATP generation through lactate generation.

Sepsis—The presence of SIRS due to an infectious etiology.

Septic shock—Sepsis advanced to the point of distributive shock.

Severe sepsis—When sepsis has progressed to a severity to manifest organ dysfunction such as delirium, acute lung injury, or acute kidney injury.

Severe SIRS—When SIRS has progressed to a severity to manifest organ dysfunction such as delirium, acute lung injury, or acute kidney injury.

Severe SIRS with shock—SIRS advanced to the point of distributive shock.

Shock—A state of global inadequate organ perfusion and oxygen delivery.

Systemic inflammatory response syndrome (SIRS)—Global activation of the inflammatory cascade, by a variety of stimuli, manifest by two or more of the following:

- Hyper- or hypothermia (>38°C or <036°C)
- Tachycardia (heart rate >90)
- Increased minute ventilation (respiratory rate >20)
- Leukocytosis or leukopenia (WBC > 12,000 or <4,000, or >10% bands)

Shock is defined as a state of global inadequate organ perfusion and may arise from a variety of diverse etiologies. Regardless of the etiology, the shock state will contribute to oxidative stress, cellular injury, and systemic activation of the inflammatory cascade (SIRS) and potentiate or lead to multisystem organ dysfunction syndrome (MODS). Both uncompensated and compensated shock will contribute to cellular changes that potentiate the severity of shock itself. An understanding of the physiologic derangements introduced by shock as well as the therapeutic interventions to mitigate the various etiologies of shock is required to optimally manage patients with this condition. In the chapter to follow, the etiologies, the physiologic cellular and organ derangements caused by the shock state, the interaction with the inflammation and organ injury, and the therapeutic interventions to target each are discussed.

DEFINITION AND ETIOLOGIES OF SHOCK

Shock is defined as a state of systemic or global inadequate organ perfusion and may be caused by a variety of insults. Most commonly, shock is recognized by hypotension, defining *uncompensated shock.* However, inadequate organ perfusion can occur with relatively normal vital signs, as occurs in *compensated shock.* Recognition that shock may exist without significant alterations in hemodynamics is critical to minimizing cellular and organ injury that may be introduced by occult hypoperfusion.

The various etiologies of shock are most frequently classified into four different categories based upon the underlying pathophysiologic alteration: hypovolemic, cardiogenic, obstructive, and distributive. Common causes of *hypovolemic shock* include hemorrhage, dehydration, and diarrheal diseases. *Cardiogenic shock* may be caused by an acute myocardial infarction, valvular lesions, and myopathies induced by ischemia, viral diseases, and inflammatory conditions. Causes of *obstructive shock* include tension pneumothorax, cardiac tamponade, constrictive pericarditis, acute pulmonary embolism, and severe pulmonary hypertension. The various causes of *distributive shock* include sepsis, spinal cord injury with neurogenic shock, adrenal insufficiency, vasopressin deficiency, anaphylaxis, and ischemia/reperfusion. Distributive shock physiologically differs from the other three classifications of shock in that a decline in cardiac output is not universally present. In fact, due to the decrease in systemic vascular resistance, cardiac output is frequently increased unless an underlying cardiac dysfunction also exists.

Appropriate therapeutic interventions for the treatment of shock should be directed toward the underlying pathophysiologic defect, which varies between and within classifications. While shock may be induced by a single etiology, recognizing that multiple etiologies may coexist and that one type of shock may cause or exacerbate a second is crucial to decisions regarding appropriate therapy. Changes induced by shock and the interdependence that may exist are outlined below.

PHYSIOLOGIC RESPONSE

Response to Decreased Cardiac Output

The predominant response to decreased cardiac output is to preserve perfusion to the heart and brain. This

acute physiologic response is best characterized and understood in the context of hemorrhagic shock. Additionally, compensated shock is most easily understood in acute hemorrhagic shock, although inadequate organ perfusion with normal hemodynamics clearly exists in other forms of shock.

Acute hemorrhagic shock may be classified into four classes (**Table 12.1**). In *class I* shock, less than 15% of blood volume (approximately 750 mL in a 70 kg individual) has been lost. At this degree of blood loss, an increase in cardiac contractility and heart rate can maintain cardiac output and thus organ perfusion. In *class II* hemorrhagic shock, 15% to 30% of blood volume (approximately up to 1,500 mL in a 70-kg individual) has been lost. At this magnitude of blood loss, the acute compensatory mechanisms of increased heart rate and contractility can no longer maintain cardiac output. To maintain perfusion pressure, vasoconstriction of peripheral and mesenteric vascular beds increases resistance to blood flow, maintaining systolic blood pressure and increasing diastolic pressure (narrowed pulse pressure). While systolic blood pressure is preserved, cardiac output and delivery are decreased. This is the state of *compensated shock. Class III* hemorrhagic shock is defined as blood loss at 30% to 40% (approximately >1,500 mL in a 70-kg individual) of total body blood volume. At this degree of blood loss, cardiac output is severely altered and vasoconstriction can no longer maintain systolic pressure. Thus, perfusion pressure of the brain and heart are both now altered. Mental status changes and obvious signs of shock ensue. *Class IV* hemorrhagic shock is defined as greater than 40% of blood volume. At this degree of shock, profound hypotension, tachycardia, and severely depressed level of consciousness are manifested.

TABLE 12.1 Hemorrhagic Shock: Estimated Blood Loss[a] Based on Patient's Initial Presentation

	CLASS I	CLASS II	CLASS III	CLASS IV
Blood loss (mL)	<750	750-1,500	1,500-2,000	>2,000
Blood loss (% blood volume)	≤15%	15%-30%	30%-40%	≥40%
Pulse rate	<100	100-120	120-140	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (mm Hg)	Normal or increased	Decreased	Decreased	Decreased
Capillary refill	Normal	Delayed	Delayed	Delayed
Respiratory rate	14-20	20-30	30-40	>35
Urine output (mL/h)	>30	20-30	5-15	Negligible
CNS/mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic

Fluid replacement	Crystalloid	Crystalloid	Crystalloid and blood	Crystalloid and blood

[a]Estimate based upon a 70-kg male.

It is important to recognize that greater than roughly 1,500 mL of blood in a 70-kg individual must be lost before compensatory mechanisms are overwhelmed and hypotension develops. Significant blood loss with associated hypoperfusion of vital organs may exist prior to the development of hypotension. Inadequate organ perfusion induces cellular insult, as outlined below, regardless of blood pressure and must be recognized and treated.

Cellular Biochemical Changes

Shock, or inadequate perfusion, creates hypoxia of the cells involved, which results in anaerobic rather than aerobic metabolism for cellular functions. This period of anaerobic metabolism produces “hypoxic priming” within the affected cells, characterized by a marked reduction in adenosine triphosphate (ATP) generation by the cell, an increase in oxidative stress, loss of antioxidant potential, and a buildup of acidic by-products, including lactic acid. The decrease in ATP production within hypoxic cells leads to a cascade of events including decreased ion exchange by the sodium-potassium adenosine triphosphatase pumps (Na^+/K^+-ATPase), calcium (Ca^{2+}), cellular swelling, Ca^{2+} activation of phospholipases with activation of the arachidonic acid cascade, and generation of fatty acid reactive oxidant species. Additionally, cellular hypoxia leads to the ischemic generation of *xanthine oxidase* by irreversible proteolytic cleavage of xanthine dehydrogenase, the enzyme that normally catalyzes the metabolism of hypoxanthine (product of ATP utilization) to xanthine and subsequently uric acid via the generation of NADH from NAD+.

Reperfusion of cells following a period of hypoxic priming induces further oxidant injury and activation of the inflammatory cascade through several mechanisms. The xanthine oxidase enzyme, generated during hypoxia, catalyzes the conversion of hypoxanthine and oxygen to xanthine and subsequently uric acid and generating the oxidative species, superoxide (O_2^-). Additionally, hypoxia followed by reperfusion induces increased activity of nitric oxide synthetase and enhanced production of nitric oxide (NO), another oxidative species. NO and O_2^- interact to form yet another oxidative species, peroxynitrite (ONOO). These oxidative species generated by hypoxia and reperfusion directly injure mitochondria, proteins, chromosomes, and membrane structures. In severe shock states, oxidative stress can be greatly potentiated by cellular mitochondrial injury, a condition known as *cytopathic hypoxia.* Oxidative species, such as ONOO, can oxidize the components of the electron transport chain and open pores in the mitochondrial membrane, both contributing to mitochondrial dysfunction and loss of aerobic metabolism by the affected cells. The loss of mitochondrial function mandates anaerobic metabolic pathways by the affected cells, an ongoing reduction of ATP generation, thus further potentiating oxidative stress. The oxidative cellular injury introduced by shock potentiates oxidative injury produced by tissue trauma, infection, and sepsis as shown in **Figure 12.1.**

Global hypoxia and reperfusion directly activates the proinflammatory nuclear transcription factor NF-κB with increased production of cytokines (TNF, IL-1, IL-6, IL-8), chemokines, coagulation factors, adhesion molecules, and activation of tissue macrophages and neutrophils. The shock state also directly activates the innate immune system through the release of a variety of substances (referred to as “damage-associated molecular patterns” or DAMPs) that are recognized by tolllike receptors (particularly TLR4) expressed on endothelial cells, neutrophils, and tissue macrophages. Systemic activation of macrophages and neutrophils results in direct tissue damage and still further cellular oxidant injury. As in the case oxidant generation, activation of the proinflammatory state

and the innate immune system by shock potentiates the activation of the inflammatory cascade caused by other insults such as tissue trauma, infection, and sepsis.

Shock and SIRS

The persistence of the shock state creates a nonlinear increase in oxidative injury and activation of the inflammatory cascade and innate immune system. Increasing severity and persistence of shock will produce systemic inflammatory response syndrome (SIRS) and organ dysfunction, culminating in MODS.

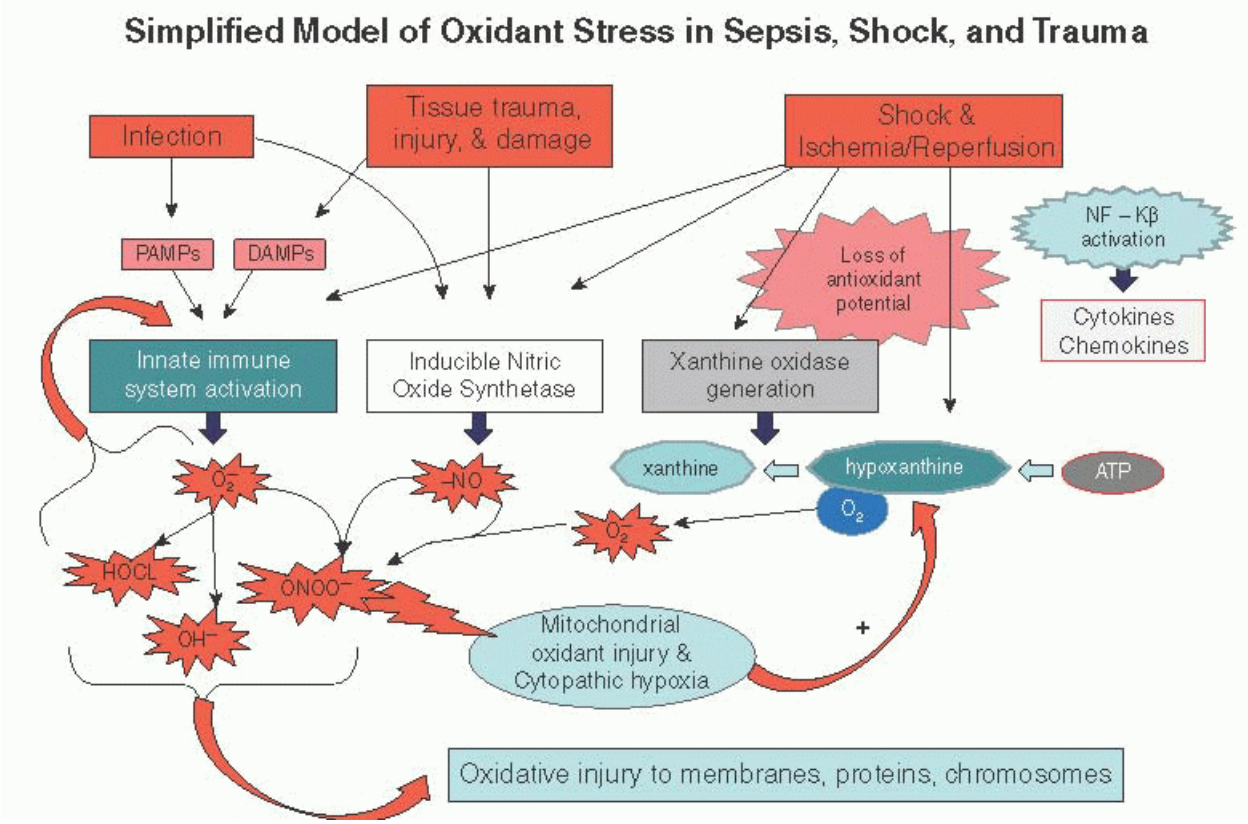

FIGURE 12.1 This simplified model of oxidant stress in sepsis, shock, and trauma demonstrates the overlapping nature of oxidant generation from these insults. Infection, tissue injury, and ischemia/reperfusion injury all activate the innate immune system via the molecular patterns recognized by toll-like receptors on immune cells which in turn produce several oxidative species. Additionally, nitric oxide production is up-regulated. Shock and ischemia/reperfusion injury may also irreversibly cleave xanthine dehydrogenase to xanthine oxidase, increasing the production of oxidant stress. Finally, significant cellular oxidative stress can induce mitochondrial injury and cytopathic hypoxia. PAMPs, pathogen-associated molecular patterns, DAMPs, damage-associated molecular patterns. Oxidative species: HOCL, hypochlorous acid; O_2^-, superoxide; NO, nitric oxide; OH^-, hydroxide; $ONOO^-$, peroxynitrite.

Additionally, shock also creates and enhances vasodilation resulting in distributive shock. SIRS can result from or be exacerbated by shock. Activation of the inflammatory cascade and the subsequent proinflammatory state outlined above produces physiologic changes in temperature (hyperthermia, temperature > 38°C or less commonly hypothermia, temperature < 36°C), heart rate (tachycardia HR > 90), minute ventilation (respiratory rate > 20), and changes in white blood cell count (leukocytosis WBC > 12,000, bandemia > 10% bands, or less commonly leukopenia WBC < 4,000), with two or more of these changes defining *SIRS.* As the severity of this process progresses, organ dysfunction will be manifest, thus defining *severe SIRS.* The presence of SIRS and severe SIRS in which the etiology is infectious defines *sepsis* and *severe sepsis,* respectively. In critically ill patients, SIRS and sepsis are very common, occurring in roughly 75% to 80% of this population. However, SIRS

is significantly more common than is sepsis, a fact that should be considered when making decisions regarding empiric antibiotics in response to fever and leukocytosis.

Vasodilation

During shock, vascular smooth muscle function is altered leading to vasodilation. Vascular smooth muscle function is directly altered by a loss of ATP production, decreased cytoplasmic calcium and decreased phosphorylation of myosin, decreasing smooth muscle contraction. The resulting vasodilation is propagated by the up-regulation of nitric oxide synthetase and subsequently increased nitric oxide production, resulting in even greater vascular smooth muscle relaxation. As a result, systemic vascular resistance falls and distributive (or vasodilatory) shock develops. Thus, a distributive shock state may develop secondary to other forms of shock. The vasodilated state may persist for days and may require prolonged vasoconstrictive agents to ensure adequate mean arterial pressure (MAP) to ensure tissue perfusion. Increasing severity and length of hypoperfusion increases the magnitude of this series of events. Thus, hypovolemic, obstructive, and cardiogenic shock may all initiate a state of distributive or vasodilatory shock following resuscitation. After correction of the original underlying physiologic defect (e.g., hemorrhagic shock), subsequent therapy may be required to correct the vasodilatory component rather than continuing pure volume replacement.

Additionally, tissue hypoxia and sepsis both may lead to defects in the production of *vasopressin* by the hypothalamus and *cortisol* by the adrenal glands. Additionally, the use of etomidate as an induction agent for endotracheal intubation is commonly associated with a period of adrenal insufficiency. Deficiencies of either vasopressin or cortisol will produce vasodilation and distributive shock that is refractory to inotropic support. These deficiencies will coexist with the distributive shock resulting from nitric oxide-induced vasodilation and may complicate management of other forms of shock.

Coagulopathy

While large volumes of blood loss may be sustained without the development of coagulopathy if normotension is maintained, coagulopathy develops at much a much smaller volume of blood loss if shock is present. Tissue hypoxia directly potentiates coagulopathy, and on-going shock will worsen derangements that are introduced by blood loss, hypothermia, and infection. Significant overlap of the coagulation system, the anticoagulant and fibrinolytic pathways, and the inflammatory system exists, and hypoperfusion and tissue hypoxia will potentiate alteration in both pro- and

anticoagulation arms of the coagulation system via multiple mechanisms. Hypoxia may directly alter the release of tissue factor, tissue plasminogen activator, and activation of protein C. These changes overlap and exacerbate those introduced by hemorrhage, hypothermia, and sepsis. Thus, during resuscitation and treatment of patients in shock, recognition that coagulopathy may develop during and be exacerbated by the shock state is important to minimize the chance of potentiation of bleeding and complications related to the derangements in the coagulation system.

Cardiac and Renal Dysfunction

In general, the physiologic response to decreasing perfusion or perfusion pressure is to preserve blood flow and pressure to the brain and the heart. As delivery becomes inadequate, organs that require consistently high levels of ATP production to maintain normal function become altered, specifically the heart and kidney. The alteration in cardiac and renal function following shock complicates the resuscitation of patients with shock, particularly if shock has been prolonged or severe.

Cardiac dysfunction following shock may be quite significant but unrecognized after resuscitation. Cardiac dysfunction may occur even in previously young, healthy individuals and is typically severe in patients who are

elderly or have underlying cardiac disease. At rest, the heart has the highest oxygen extraction ratio of all the organs. The increased heart rate that occurs as a consequence of shock greatly increases oxygen demand by the heart, while decreasing the diastolic perfusion time. In shock states, decreasing perfusion pressure and increasing demands coupled with increasing heart rate quickly create hypoxic conditions, necessitating anaerobic metabolism and a loss of ATP production. Sodium/potassium (Na/K) and sodium/calcium (Na/Ca) ATPase pumps become dysfunctional. Thus, cellular swelling, a loss of contractility, and a decrease in compliance of the heart develop. To achieve adequate filling of the ventricles postshock, higher central venous pressures (CVP) are required, and to achieve adequate contractility, inotropic agents may be necessary. Assessing adequacy of delivery by specific measures of perfusion such as trends in serum lactate, mixed venous or central venous oxygen saturation, and cardiac index or oxygen delivery may be necessary.

Renal function and renal concentrating ability may be significantly altered during periods of either compensated or uncompensated shock. To maintain normal function, the kidneys also require consistent ATP generation. The kidneys concentrate urine by maintaining concentration gradients within the renal medulla; under normal conditions, the renal medulla is relatively hypoxic. During limited perfusion, ATPase pumps cannot maintain adequate concentration gradients; upon reperfusion, urine output may be excessive and dilute. Thus, urine output by the kidney may be a measure of adequate perfusion following periods of shock.

Assessment of Organ Perfusion

The goal of therapeutic interventions for shock, regardless of etiology, is to restore adequate tissue perfusion in order to limit cellular and organ injury because sustained tissue hypoxia is one of the most important cofactors in the development of multiple organ injury. Tissue perfusion is dependent upon forward flow of oxygenated blood and adequate perfusion pressure. As noted in sections above, assessment of adequate organ perfusion during and after resuscitation may be complicated by (a) the presence of compensated shock, (b) changes in cardiac compliance and function, (c) alteration in renal function, and (d) the distributive shock that develops secondary to tissue hypoxia. Unfortunately, no single measure is adequately sensitive or specific in all settings to document adequacy of organ perfusion. Thus, an array of techniques may be required. A brief overview of commonly employed measures is provided below, outlining settings in which measures are adequate and inadequate.

The most commonly used measures of organ perfusion are the assessment hemodynamic parameters and organ function. Significant tachycardia, hypotension, low urine output, cool extremities to physical exam, and alteration in mental status all indicate inadequate perfusion absent conditions that specifically alter each individual measure. However, as noted above, significant limitations to organ perfusion may exist despite all of these being normal. In young, otherwise healthy patients without a period of significant shock, these parameters are most likely adequate, if normal. However, if a period of significant shock is suspected, these measures lose their value. Additionally, in geriatric patients suffering significant stress or insult, these measures are frequently inadequate.

One approach to assessing adequacy of perfusion is to assess the accumulation of by-products of inadequate perfusion through the assessment of either *serum lactate* or *base deficit* (BD). Cells with inadequate perfusion must undergo anaerobic metabolism to continue ATP production. By-products of anaerobic metabolism include the generation of lactic acid as well as the buildup of other acids generated by ATP metabolism and accumulation of acids used in the mitochondrial respiratory process that contribute to BD. While these two measures are similar, they have different characteristics and limitations. Additionally, while these measures may indicate inadequate perfusion, they do not indicate the physiologic defect or defects contributing to the tissue hypoxia such as hypovolemia, cardiac dysfunction, or distributive shock. Thus, they typically must be used in the context of additional information that provides assessment of the underlying defect.

BD can be a sensitive measure of hypoperfusion but, unfortunately, lacks specificity. BD is calculated by the

formula BD = -[(HCO_3) – 24.8 + (16.2 × (pH – 7.4))] and reflects the buildup of acids within the circulation. In the setting of inadequate tissue perfusion and hypoxia, numerous acids accumulate including lactic acid, by-products of ATP metabolism, and products used by the mitochondria. BD tends to change more rapidly than does serum lactate and may reflect hypoperfusion even when lactate is within normal limits. During pregnancy, recognition that maternal circulation is preserved over fetal circulation and that elevated BD or a decline in serum bicarbonate is important to ensure fetal perfusion. However, numerous therapeutic interventions may alter BD independent of adequacy of perfusion, including the choice of fluid provided to the patient (lactated ringers versus normal saline). Elevated BD predicts poor outcome in acutely injured patients, even in the setting of normal lactate. Thus, this measure can alert the practitioner to occult hypoperfusion but must be interpreted with caution, particularly after resuscitation has been initiated.

Serum lactate is a more specific measure of the adequacy of organ perfusion than is BD but does have significant limitations. Lactate is generated under conditions of anaerobic metabolism to allow ongoing glycolysis and generation of 2 ATP through the conversion of pyruvate by the lactate dehydrogenase enzyme and the generation of NAD from NADH. Serum lactate elevation and its persistence in sepsis and trauma strongly correlate with organ dysfunction and death.

Studies suggest that resuscitation efforts directed to normalize serum lactate improve outcome, but this remains inadequately studied. Lactate is effectively metabolized and cleared from the serum by the liver; thus, it only rises if hepatic clearance is exceeded and may rise relatively slowly. Metabolic processes that convert NAD to NADH, such as alcohol metabolism, limit the mitochondrial oxidative phosphorylation by consuming NAD and limiting pyruvates conversion to acetyl-CoA and entry into the tricarboxylic acid cycle (TCA or Krebs cycle). Additionally, epinephrine can directly elevate lactate. Other processes that confound the use of lactate as a marker of adequacy of perfusion include hepatic insufficiency and cytopathic hypoxia. In both cases, lactate may be elevated despite normal organ perfusion. In cytopathic hypoxia, the inability of the mitochondria to utilize oxygen mandates ongoing glycolysis and lactate generation.

Venous Oxygen Saturation

Another measure of adequacy of delivery and resuscitation is the use of venous oxygen saturation as a surrogate for the balance between systemic oxygen delivery (D_{O2}), global oxygen consumption (V_{O2}), and the fraction of delivered oxygen that is consumed (extraction ratio—ER_{O2}) in critically ill patients. As oxygen consumption increases relative to delivery, the extraction ratio increases and is reflected as a decline in venous saturation. The most precise measurement of global venous saturation is the mixed venous oxygen saturation (SvO_2), reflecting venous blood from all portions of the body, including the coronary sinus. However, its measurement requires the placement of a pulmonary artery catheter. An alternative is the use of central venous oxygen saturation ($ScvO_2$) via a central line positioned in the superior vena cava or right atria. The two differ slightly, and some data suggest that they may not be interchangeable. The $ScvO_2$ may be up to 6% higher than SvO_2, but trends in either appear to adequately reflect resuscitation. Generally, values of less than 70% for both measures reflect increased, compensatory extraction. Changes in SvO_2 and $ScvO_2$ occur rapidly; thus, venous saturation can be used as a real-time assessment of resuscitative efforts. The use of venous saturation as a guide to resuscitation in sepsis and other forms of shock has been shown to improve targeted resuscitation and outcomes and may outperform lactate in certain settings.

Limitations to venous saturation include its requiring invasive procedures for placement of either a pulmonary catheter or central line. Additionally, in patients with true shunts (e.g., patients with liver failure) and in patients who have developed cytopathic hypoxia, extraction oxygen extraction will be diminished and venous saturation

may be supranormal.

Assessments of Cardiac Filling and Function

Assessments of cardiac filling and cardiac output are both frequently used to guide resuscitation. To maintain adequate oxygen delivery to tissues, the heart must maintain adequate cardiac output. Output by the heart is determined by heart rate and stroke volume, and stroke volume is determined by filling and contractility. CVP, pulmonary artery pressure, and pulmonary wedge pressure, pulse pressure variation and pulse contour analysis, and ultrasound and echocardiography may all be used to estimate filling. The first three measures all provide an assessment of pressure and one must recognize that pressures do not directly assess volume. With changes in the compliance of the heart, as occurs during shock and resuscitation, the volume for a given pressure changes as well. This is very significant limitation of these values when used to assess adequacy of filling. Ultrasound and echocardiography may be used to provide an estimate of filling but may be technically difficult in many settings of critical illness.

Assessment of cardiac output and function may be determined by pulmonary artery catheter, pulse pressure variation and pulse contour analysis, and transesophageal echocardiography. However, each method has settings in which accuracy of these values may be limited. Additionally, knowledge of the cardiac output does not necessarily equate to adequate oxygen delivery. Tissue perfusion is dependent upon both delivery and perfusion pressure. Oxygen demand by tissues also is not static, and no specific cardiac output is indicative of adequate perfusion in all settings.

Other Assessments of Oxygen Delivery

Research to identify noninvasive measures that can detect occult tissue hypoxia and assure adequacy of resuscitation continues. Additional tools that have been or continue to be investigated include regional capnometry, near-infrared spectroscopy, and sidestream dark-field video microscopy. However, none have achieved widespread acceptance or use.

TREATMENT OF SHOCK

The treatment of shock should be directed toward correcting the underlying physiologic defect or defects that are contributing to inadequate organ perfusion, such as (a) hypovolemia, (b) vasodilatation, or (c) cardiac dysfunction. Both compensated (or occult) and uncompensated shock should be corrected expeditiously to prevent exacerbation of organ dysfunction and propagation of the derangements outlined above. Additionally, during pregnancy, care must be taken to ensure adequate fetal perfusion. While a single underlying insult, such as hemorrhage or infection, most frequently initiates the development of shock, understanding that the physiologic derangements introduced by severe shock frequently include more than one type of shock (i.e., hypovolemic, distributive, and cardiogenic components) is paramount to achieving the best outcome. These secondary components of shock develop as a result of tissue hypoxia; thus, aggressive correction of the underlying primary cause of the shock may fail to improve or even aggravate the other components of shock in the complex patient. The magnitude of each of the various components changes during the course of the illness and recognition of the dynamic nature of the process is important.

While the appropriate treatment of the underlying defect will improve the shock state, incorrectly treating the combination of physiologic defects may worsen hypoperfusion or contribute to other secondary problems such as abdominal compartment syndrome or acute volume overload. For example, treatment of patients with hypotension due to low cardiac output with vasoconstrictive agents will increase systemic vascular resistance, raising blood pressure, but actually decrease cardiac output and delivery. This circumstance may occur when either hemorrhagic shock or cardiogenic failure is treated with high-dose Levophed rather than appropriately treating with either blood products or medications to specifically improve inotropy.

Hemorrhagic Shock

The most common cause of shock in the obstetric and gynecologic patient is hemorrhage. In 2005, hemorrhagic shock was the third leading cause of maternal death due to obstetric factors in the United States. Significant advances in

our understanding of resuscitation of patients with severe hemorrhagic shock have been made in the past decade, predominately through the trauma literature. The expected signs and symptoms for the degree of shock is provided in **Table 12.1**, as put forth in the ATLS guidelines. While patients with limited blood loss, class I and class II hemorrhagic shock, may respond to crystalloid resuscitation, patients with larger volume of hemorrhage will require blood and blood component therapy. Goals during the resuscitation of patients in hemorrhagic shock are to achieve replacement of adequate circulating volume while avoiding coagulopathy, hypothermia, progressive acidosis, and excessive crystalloid administration.

Patients with significant hemorrhagic shock may have alterations in their level of consciousness, and an assessment of the safety of their airway and ability to maintain oxygenation should be undertaken and an airway established as required. Two large bore IVs (18 gauge or larger) should be established to ensure the ability to provide crystalloid and blood products without limitation of flow and cell lysis by the catheter. Efforts should be made to maintain patient normothermia. These may include (a) warm fluids, (b) fluid warming devices, (c) heated ventilator circuits with temperature turned to 38°C to 40°C, (d) forced air warming devices, and (e) ambient room temperature set at 26.5°C to 29°C. While beyond the scope of this chapter, prompt intervention to control the source of hemorrhage is required while resuscitative efforts are continued.

As noted in **Table 12.1**, patients with hemorrhage of up to 30% of their blood volume may be treated with crystalloid resuscitation without necessarily requiring blood products, assuming on-going hemorrhage has been controlled and preexisting ischemic cardiac disease is not present. Patients with blood loss greater than 30% will require blood and blood product administration. The approach to transfusion in a patient with hemorrhagic shock with ongoing blood loss should be different than in those patients with large volume blood loss without shock. Traditionally, resuscitation for hemorrhage has been centered on replacing circulating volume with crystalloid and packed red blood cells (PRBCs). In situations in which blood loss has been matched by fluid and blood replacement without limitations in blood flow (isovolemic blood loss), large volumes of blood may be administered without the development of coagulopathy, and administration of other blood products like fresh frozen plasma (FFP), cryoprecipitate, and platelets should be based upon abnormal laboratory analysis. However, as outlined above, the presence of shock and tissue hypoxia contributes to coagulopathy, and empiric treatment with other components may be indicated. Data predominately from civilian and military trauma literature support an approach in patients with massive hemorrhage which limits crystalloid resuscitation and provides replacement of blood products approximating a 1:1:1 ratio of PRBCs, FFP, and platelets. To achieve this, most centers have developed massive transfusion protocols (MTPs) to provide the correct ratios of products, once activated. An example of the MTP implemented at Vanderbilt University Medical Center is provided in **Figure 12.2**. Absolute activation points are difficult to establish for all patients. The use of MTPs should be considered in patients with ongoing hemorrhage (or risk of ongoing hemorrhage) and hypotension (systolic blood pressure <90 mm Hg) after initial 2 U of PRBCs. The use of MTPs should be considered in a bleeding patient with severe acidosis, existing coagulopathy, thrombocytopenia, or hypothermia[444]. The use and timing of other products such as cryoprecipitate or recombinant factor VII remains controversial and variable in practice.

Distributive Shock

The most common cause of distributive shock in obstetric and gynecologic patients is sepsis although other etiologies should also be considered such as severe SIRS following ischemia/reperfusion, adrenal insufficiency,

vasopressin deficiency, and anaphylaxis. In all cases of distributive shock, the underlying problem is predominantly vasodilation with inadequate perfusion pressure. Thus, therapy should be directed predominantly to increasing vascular vasomotor tone. The therapeutic agents and approach to achieve appropriate vasoconstriction vary depending on the cause and are discussed below.

Sepsis and Septic Shock

Sepsis is a common problem and is one of the most common causes of critical illness in both obstetric and gynecologic surgery patient populations. The diagnosis of sepsis may be difficult to establish in critically ill patients with insults that may initiate the SIRS. Diagnostic criteria for sepsis, severe sepsis, and septic shock are outlined in **Tables 12.2** and **12.3**. The treatment of *septic shock* involves three critical components: (a) source control, (b) appropriate empiric antibiotic therapy, and (c) restoration of cellular perfusion. While beyond the scope of this chapter, the importance of adequate *source control* cannot be overemphasized. Elimination of necrotic or infected tissues, elimination of infected fluid collections, elimination or control of enteric connections, and reduction of bacterial load are all components of adequate source control. A specific anatomical diagnosis for the source of infection should be sought, either establishing or excluding potential sources within the differential as soon as possible and interventions to establish control within 12 hours after the diagnosis of sepsis as possible. Critically ill patients with previous efforts to establish source control and with an appropriate course of antibiotic therapy who are not responding appropriately should be evaluated for failure of primary source control, typically with diagnostic imaging such as computed tomography.

Empiric Antibiotic Therapy

Timely and appropriate *empiric antibiotic therapy* is also critical in patients with septic shock. Significant observational data demonstrate that inadequate empiric antibiotic coverage (not active against all pathogens) significantly increases mortality, despite altering therapy when sensitivities return. Thus, broad empiric antibiotic coverage targeted to cover all likely pathogens should be initiated and then de-escalated once culture and sensitivity data are available. Additionally, antibiotics should be initiated as soon as sepsis and septic shock is suspected, ideally within 1 hour. In one large observational study of critically ill patients with septic shock, each 1 hour delay in antibiotic therapy from the onset of shock was associated with a 12% increase in mortality. Appropriate culture data should be obtained to allow de-escalation of therapy and the antibiotic regimen narrowed to the least number of agents required to appropriate treat the pathogens involved. As noted above, patients not responding to therapy in an appropriate manner should be evaluated for inadequate source control rather than simply extending antibiotic courses beyond 7 days.

Background: Protocolized transfusion has been shown to improve clinical outcomes as well as transfusion efficiency in patients who require massive transfusion (>10 U in 24 hours). This document provides guidelines for utilization of the massive transfusion protocol (MTP).

1. Patient selection
   a. Patients with current, ongoing, or impending massive blood loss should be considered for activation of MTP.
   b. Activation of massive transfusion protocol should be considered for patients who received greater than 2 u of blood in the emergency department (1).
2. Activation
   a. MTP may be activated by the attending surgeon, intensivist or designated surrogate. If surrogate activates MTP, attending surgeon of record must be provided to blood bank (BB).
   b. MTP may be activated by trauma/surgical cc faculty, fellows and instructors; anesthesiology faculty; and selected surgical faculty ONLY.
   c. Upon suspicion of MTP activation, type and screen must be sent to BB as soon as possible.
   d. To activate MTP, call BB at _____ and provide the following information
      i. "This is Dr. _____ activating the MTP….."
      ii. Patient name
      iii. Patient MRN. This will be repeated by BB personnel for verification purposes.
      iv. Patient age
      v. Patient gender
      vi. Current or intended location
3. Product breakdown
   a. Each round of MTP provides 6U PRBC, 4U FFP, 1 dose pack of platelets Repeat rounds of MTP contain identical product "doses"
4. Administration
   a. Products are delivered, and BB calls patient location to verify continuation of MTP. Default is to continue MTP until verbally discontinued by faculty physician.
   b. MTP boxes are intended to be given in their entirety until completed. If not all products are desired, strong consideration should be given to MTP discontinuation.
5. Endpoints/termination
   a. When appropriate endpoints are reached, the MTP must be discontinued to limit resource utilization.
   b. Most reliable transfusion endpoint is a collaborative decision based on operative field examination, laboratory results, and clinical parameters.
   c. Premature discontinuation of MTP should be avoided to minimize catch-up reactive transfusion.
6. Pitfalls, common errors
   a. Failure to send type and screen.
      i. T&S must be sent upon suspicion of MTP requirement.
   b. Returning platelets on ice.
      i. Cold temperature destroys platelets. Must be returned in cooler side pouch.
   c. Failure to identify significant hemorrhage, delayed MTP activation.
      i. Result in delayed activation, over activation is anticipated
   d. Premature termination.
      i. Consider continuing MTP until patient stabilizes in the ICU.
   e. Failure to provide entire box/dose.
      i. If not all products are required, d/c MTP and transfuse PRN.
      ii. Collaborate with intensivist/anesthesiologist regarding transfusion plan.
   f. Reliability on laboratory tests alone for transfusion indication.
      i. Laboratory tests are unreliable in the hyperacute setting.
   g. Inappropriate personnel activating MTP.
      i. BB personnel are empowered to refuse MTP to callers who are not authorized to activate protocol.

References:

1. Nunez, TC, Voskresensky, IV, Dossett, LA, et al. Early prediction of massive transfusion in trauma: simple as ABC (assessment of blood consumption)? *The Journal of Trauma* 2009;66:346–352.
2. Vanderbilt University Medical Center Trauma and Surgical Critical Care, Nashville, TN.

FIGURE 12.2 Massive Transfusion Protocol.

TABLE 12.2 Diagnostic Criteria for Sepsis

Infection, documented or suspected, and some of the following:

General variables

Fever (>38.3°C)

Hypothermia (core temperature < 36°C)

Heart rate > 90/min^{-1} or more than two SD above the normal value for age

Tachypnea

Altered mental status

Significant edema or positive fluid balance (>20 mL/kg over 24 h)

Hyperglycemia (plasma glucose > 140 mg/dL or 7.7 mmol/L) in the absence of diabetes
Inflammatory variables
Leukocytosis (WBC count > 12,000 μL^{-1})
Leukopenia (WBC count < 4,000 μL^{-1})
Normal WBC count with >10% immature forms
Plasma C-reactive protein more than two SD above the normal value
Plasma procalcitonin more than two SD above the normal value
Hemodynamic variables
Arterial hypotension (SBP < 90 mm Hg, MAP < 70 mm Hg, or an SBP decrease > 40 mm Hg in adults or <2 SD below normal for age)
Organ dysfunction variables
Arterial hypoxemia (PaO_2/FIO_2 < 300)
Acute oliguria (urine output < 0.5 mL/kg/h for at least 2 h despite adequate fluid resuscitation)
Creatinine increase > 0.5 mg/dL or 44.2 µmol/L
Coagulation abnormalities (INR > 1.5 or aPTT > 60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count < 100,000 μL^{-1})
Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 µmol/L)
Tissue perfusion variables
Hyperlactatemia (>1 mmol/L)
Decreased capillary refill or mottling

WBC, white blood cell; SBP, systolic blood pressure; MAP, mean arterial pressure; INR, international normalized ratio; aPTT, activated partial thromboplastin time.
Adapted from Dellinger RP, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41:580-637.

Restoration of Cellular Perfusion

The third critical component of the treatment of patients with septic shock is the *restoration of cellular perfusion.* Septic patients typically have both volume depletion and vasodilatory components to their shock. Additionally, some patients may also have altered cardiac function. Thus, a quantitative resuscitation managed by a specific protocol should be undertaken. As resuscitation precedes, an evaluation of volume status, blood pressure, organ function, and organ perfusion should be constantly monitored to access the effectiveness of the resuscitation and provide indicators to adjust therapy. General recommended goals of resuscitation include the following:

TABLE 12.3 Severe Sepsis and Septic Shock

Severe sepsis definition = sepsis-induced tissue
hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)
Urine output < 0.5 mL/kg/h for >2 h despite adequate fluid resuscitation
Acute lung injury with PaO_2/FIO_2 < 250 in the absence of pneumonia as infection source
Acute lung injury with PaO_2/FIO_2 < 200 in the presence of pneumonia as infection source
Creatinine > 2.0 mg/dL (176.8 µmol/L)
Bilirubin > 2 mg/dL (34.2 µmol/L)
Platelet count < 100,000 µL
Coagulopathy (international normalized ratio > 1.5)
Lactate above upper limits laboratory normal (tissue hypoperfusion)
Sepsis-induced hypotension (septic shock)

Adapted from Dellinger RP, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41:580-637.

a. CVP of 8 to 12 mm Hg
b. MAP of ≥65 mm Hg
c. Urine output ≥0.5 mL/kg/h
d. Normal assessment of tissue oxygenation
   - Central venous (superior vena cava) or mixed venous oxygen saturation of 70% or 65%, respectively
   - Normalization of serum lactate

Recognition that preexisting comorbidity or other clinical conditions may require an alteration of these end points is important to appropriately target resuscitation. For instance, during the third trimester of pregnancy, the normal values for the end points cited above are altered: CVP 4 to 10 mm Hg, MAP 84 to *96* mm Hg, mixed venous saturation >80%.

An example of an algorithm to direct resuscitation in patients with severe sepsis and septic shock is provided in **Figure 12.3.** Initial therapy is directed at replacing the volume deficits with crystalloid fluid resuscitation in a volume of up to 30 mL/kg. Additional crystalloid may be required based upon the analysis of volume status.

Additional fluid resuscitation should be based upon ongoing assessments of volume responsiveness; excessive crystalloid administration may worsen acute lung injury, edema, and increase the risk of abdominal compartment syndrome. Patients with large fluid requirements may benefit from provision of albumen. Patients with hypotension or hypoperfusion after adequate fluid resuscitation should have vasopressor therapy added. Norepinephrine is the first-line vasopressor of choice, demonstrating better return of splanchnic perfusion than do other agents. Patients with depressed cardiac function may require the addition of an inotropic agent to achieve adequate cardiac output. Epinephrine may be required in addition to or instead of norepinephrine. Alternative inotropic agents may be considered in combination with norepinephrine such as dobutamine or milrinone.

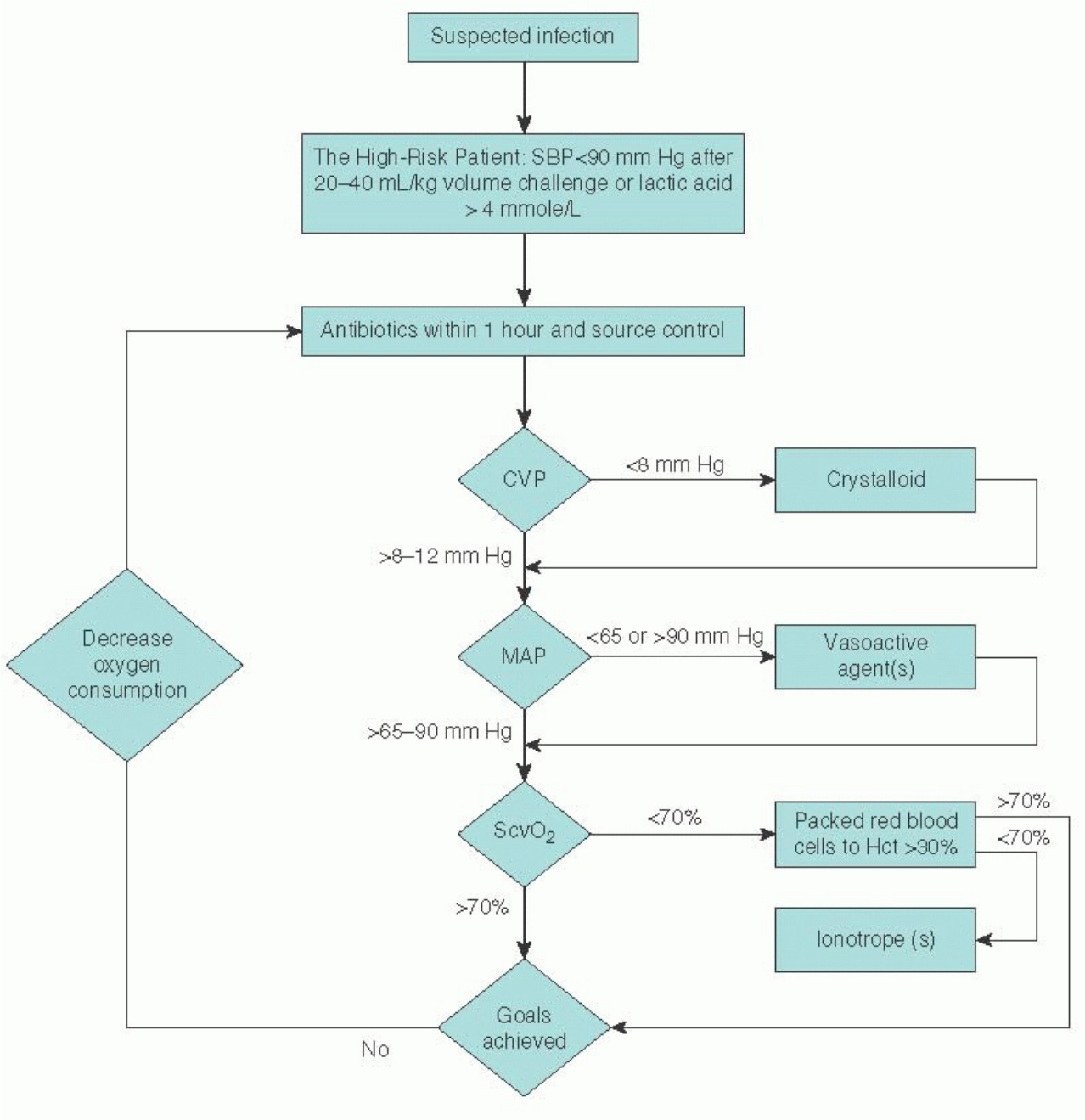

FIGURE 12.3 Algorithm for the goal-directed resuscitation of patients with severe sepsis and septic shock.

Vasopressin and Adrenal Insufficiency

Patients with severe sepsis and septic shock may develop distributive shock related to either vasopressin deficiency or adrenal insufficiency. Patients in whom blood pressure is poorly responsive to or requires high

doses of norepinephrine may be *vasopressin deficient.* The addition of a vasopressin infusion at 0.03 to 0.04 units/min may be initiated with responsiveness determined by a decline in norepinephrine requirements. Due to the pronounced vasoconstrictive effects of vasopressin, this agent should not be used as a first-line agent and the use of doses above the recommended range should only be used as salvage therapy. *Adrenal insufficiency* may also develop as a result of sepsis and be a cause of inadequate response to vasopressor therapy. An absolute value of serum hydrocortisone that indicates either adequate or inadequate production is not currently assessable. Thus, presumptive therapy of adrenal insufficiency is currently recommended in patients who appear unresponsive to vasopressor support. Recommended treatment is with hydrocortisone (50 mg every 6 hours) and tapered when vasoactive support is no longer needed and blood pressure is normal.

Other conditions may lead to either vasopressin or adrenal insufficiency. Tissue hypoxia and severe shock may contribute to both. Assessment of serum cortisol levels in these settings remains controversial as an absolute level of serum cortisol for a given state is difficult to establish.

SUMMARY

An understanding that compensated and uncompensated shock create a nonlinear increase in cellular and organ dysfunction is important for the practicing obstetrician and gynecologist. Persistent shock is a self-replicating process, and prompt, targeted therapy directed toward the appropriate contributing components is paramount. Early correction of cellular perfusion limits organ dysfunction and improves outcomes.

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