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The clinical syndrome of shock is a very dramatic, dynamic, and life-threatening problem faced by emergency medicine physicians. The diagnosis and management of shock in infants, children, and adolescents has undergone a progressive evolution as our knowledge and understanding of the pathophysiology mechanisms, from molecular to cellular to organ systems, has expanded and matured.

Although the focus of therapy remains adequate oxygen delivery and maintenance of perfusion of vital organs, many exciting developments have occurred which expand our ability to accomplish this goal. This article provides a comprehensive review of the pathophysiology of both hypovolemic and septic shock, standard therapeutic options, controversial management approaches, and future research areas.

The author also details outcomes measures – base deficit and serum lactate – and their potential clinical utility. This article provides a complete clinical update on the current status and management of hypovolemic and septic shock.

— The Editor

Current Concepts in the Recognition and Management of Pediatric Hypovolemic and Septic Shock

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Hypovolemic Shock

Hypovolemia is the most common cause of shock in infants and children.[1,2] Hypovolemic shock is best defined as a sudden decrease in the intravascular blood volume, relative to vascular capacity, to such an extent that effective tissue perfusion cannot be maintained. Etiologies include hemorrhage from gastrointestinal disease or trauma, fluid and electrolyte loss, endocrine disease, and plasma loss.[1-4]

Hypovolemia causes a decrease in preload that results in a decrement of stroke volume and reduction in cardiac output. Activation of peripheral and central baroreceptors produces an outpouring of catecholamines, and the resulting tachycardia and peripheral vasoconstriction are usually adequate to support the blood pressure with little or no evidence of hypotension. Another aspect of the body's compensatory mechanism for dealing with hypovolemia is through the activation of the renin-angiotensin-aldosterone system. Angiotensin (a potent vasoconstrictor) promotes the release of aldosterone, which increases the kidney's sodium resorption. This, together with an increase in antidiuretic hormone (ADH) secretion, results in increased water resorption in the kidney.

Reliable indicators of early, compensated hypovolemic shock in children are persistent tachycardia, cutaneous vasoconstriction, and diminution of the pulse pressure. Clinical evidence of decreased tissue perfusion includes skin mottling, prolonged capillary refill, and cool extremities. Systemic arterial blood pressure is frequently normal, the result of increased systemic vascular resistance, making blood pressure monitoring of limited value in managing the patient with compensated hypovolemic shock.[1] Neurological status

is normal or only minimally impaired.

Although capillary refill has long been advocated as an important means of quickly and reliably assessing the hydration and circulatory status of acutely ill or injured children, several important limitations to the use of capillary refill in the assessment of circulatory status in children exist.[5-7] It is necessary to account for the ambient temperature, in addition to the site of measurement, when interpreting the results.

On rare occasions, blood pressure may be paradoxically elevated in hypovolemic children.[8] Recognition of this phenomenon is extremely important because there may be reluctance to fluid resuscitate these patients for fear of exacerbating the hypertension. Treatment of the hypertension, especially with beta-blockers or calcium channel antagonists, may produce hypotension precipitously. Dehydrated, volume-depleted children with paradoxical hypertension should be given a trial of volume expansion; such therapy would cause little harm and could ameliorate the hypertension.

With continued loss of blood volume or with delayed or inadequate blood volume replacement, the intravascular fluid losses surpass the body's compensatory abilities, causing circulatory failure and organ dysfunction. The pronounced systemic vasoconstriction and hypovolemia produce ischemia and hypoxia in the visceral and cutaneous circulations. Altered cellular metabolism and function occur in these areas, resulting in damage to blood vessels, kidneys, liver, pancreas, and bowel. Stroke volume and cardiac output are decreased. Patients are hypotensive, acidotic, lethargic or comatose, and oliguric or anuric. It is important to emphasize that arterial blood pressure falls only after compensatory mechanisms are exhausted, which may occur long after the precipitating event and only after a severe reduction in cardiac output.[9] Terminal phases of hypovolemic shock are characterized by myocardial dysfunction and widespread cell death.

Ischemia develops in various non-vital organs as a result of reduced circulatory blood volume and preferential vasoconstriction. In skeletal muscle during shock, the normal intermittent perfusion pattern in a capillary network has been observed to transform to a marked maldistribution of flow, with the majority of capillaries ceasing to have flow.[10,11] Besides a low and irregular flow state in capillaries, recent findings have demonstrated a progressive narrowing of the capillary lumen during shock. The decrease in lumen diameter of almost 25% after one hour of shock is principally a consequence of swollen endothelial cells, which significantly increases the capillary resistance to flow and contributes to further flow retardation.[10,11] In addition, it has been repeatedly observed, in a variety of organs, that there is impaired microcirculatory blood flow on reperfusion after a period of ischemia ("no reflow" or "slow reflow"). The causes of no reflow include red blood cell aggregation, leukocyte trapping, and edema of tissue and capillary endothelial cells.[11]

In any form of shock, including hypovolemic shock, the end result of hypoperfusion and tissue ischemia is an oxygen and nutrient deficiency that can affect the integrity of cellular function and structure. Anaerobic metabolism results from the decrease in oxygen delivery, leading to glycogen depletion and lactate production. An increase in cytosolic calcium is also evident, which leads to an increase in membrane phospholipid hydrolysis and lysosomal membrane damage.[2] This process eventually progresses to irreversible cellular injury and a host of inflammatory responses, which stimulate further tissue inflammation and injury. Ischemia/reperfusion can also induce expression of inflammatory genes in endothelial cells. Certain animal models demonstrate that fluid resuscitation leads to a decrease in the inflammatory cascade triggered by organ ischemia secondary to hypoperfusion.[2] Because this inflammatory response is of unlikely value in protecting or repairing the organ from the hypovolemic insult, downregulation of this inflammation seen with fluid resuscitation is likely to be of benefit.

Therapy

Initial treatments of the child in hypovolemic shock are similar, regardless of etiology. Therapy begins with the establishment or assurance of adequate oxygenation and ventilation. Oxygen should always be the first drug administered. Once the airway is ensured or established (may require intubation) and

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ventilation is adequate, measures to restore an effective circulating blood volume should begin. Placement of an adequate intravenous or intraosseous catheter and rapid volume replacement are the most important therapeutic maneuvers to reestablish the circulation.

Vascular access is secured using the largest, most easily accessible vein. Peripheral venotomy can be performed in the veins of the hand, foot, arm, leg, or scalp, but these vessels tend to be small and difficult to cannulate in the hypovolemic child, so attempts should be limited.[3,12] In children younger than 6 years of age, in whom peripheral access may be difficult, the preferred site for emergent access is intraosseous.[12]

In children 6 years and older, vascular access may be obtained by central venous cannulation or saphenous cutdown. The femoral vein is often the most easily accessible in emergency situations.[3,12]

The amount of volume required to resuscitate a child who presents in hypovolemic shock is variable. However, the most common error made in resuscitation of hypovolemic shock is inadequate or delayed volume administration. The variance in disease processes that lead to hypovolemic shock may require different treatment and will be discussed separately.

Fluid Therapy – Diarrhea and Dehydration

Diarrhea has the potential to cause a severe disruption in the balance of fluids and electrolytes and remains a leading cause of infant mortality worldwide.[13] Dehydration and shock as a consequence of diarrhea are more likely to occur in the infant or small child than in the adult.

Serum tonicity is important in both the presentation and the management of dehydration. In approximately 80% of cases of dehydration, patients have normal serum osmolarity; 15% are hyperosmolar; and 5% are hypo-osmolar.[3]

The serum sodium level can be used as a rough estimate of serum osmolarity and dehydration, classified as:

	Serum sodium
Hyponatremic	< 130 mEq/dL
Isonatremic	130-150 mEq/dL
Hypernatremic	> 150 mEq/dL

Hyponatremic dehydration occurs secondary to a disproportionate loss of solute to fluid. There is depletion of extracellular fluid volume (ECF) – intravascular and extravascular – relative to intracellular fluid volume (ICF), producing characteristic physical findings – dry mucous membranes, reduced skin turgor, cool extremities, compromised perfusion, and in severe cases, hemodynamic collapse. Hypernatremic dehydration is the result of fluid loss out of proportion to solute loss. There is relative preservation of the extracellular volume. Physical findings include a doughy consistency of the skin and subcutaneous tissues and the apparent maintenance of good hemodynamic function and blood pressure even in the face of large volume losses.

The approach to the infant or child with diarrheal dehydration may be organized using the five-point assessment.[4] *(See Table 1.)* Initial management is guided by a simple history and physical examination, followed by assignment of the patient to one of three groups based on severity of illness. This process provides a framework for the rapid triage of patients. Those who require urgent attention are identified, and candidates for oral rehydration are selected.

Table 1. Rapid Assessment of Dehydration

POINT OF ASSESSMENT	METHOD
Volume deficit	History and physical
Osmolar disturbance	Serum sodium
Acid-base disturbance	Serum pH, PCO_2, bicarbonate
Potassium disturbance	Serum potassium
Renal function	Serum blood urea nitrogen, creatinine
	Urine analysis, specific gravity, sodium

Adapted from Kallen RJ. The management of diarrheal dehydration in infants using parenteral fluids. Pediatr Clin North Am 1990;37:265.

Table 2 lists the signs and symptoms that may be used to group patients by severity of dehydration. Of the 10 findings listed, none is sufficiently accurate to be used in isolation.[15] The presence of fewer than three signs corresponds with a fluid deficit of less than 5%, whereas children with a deficit of 5-9% generally have three or more clinical findings. At least six or seven should be present to diagnose a deficit of 10% or more. A recent study has suggested that it may be possible to rely on a relatively restricted subset of clinical indicators: general appearance, capillary refill, mucous membranes, and tears. Of these four findings, the presence of any two indicates a deficit of 5% or more, and three or more findings indicates a deficit of at least 10%.[15]

Regardless of the serum osmolarity, isotonic crystalloid (20 mL/kg), delivered as a rapid infusion, is effective in the resuscitation of children with shock secondary to dehydration. The use of hypotonic solutions is not only ineffective but also may be harmful in hypernatremic dehydration by reducing serum sodium concentration abruptly. A frequently encountered problem that results from the use of large volumes of isotonic (0.9%) saline is the development of hyperchloremic acidosis. This occurs because isotonic saline contains 154 mEq/L of chloride and its administration results in a dilutional decrease of serum bicarbonate and an increase in serum chloride concentration. Both of these changes will produce metabolic acidosis. Resuscitation with lactated Ringer's solution provides a more balanced electrolyte replacement and is less likely to produce metabolic acidosis. The infusion of lactated Ringer's solution in general does not influence the circulating blood lactate concentration.[16]

The use of colloid is not indicated in the initial resuscitation of the patient with shock secondary to dehydration. Albumin and other colloids have been used effectively for volume replacement in patients with large volumes of non-functional extracellular or "third space" fluid loss or low albumin states.[3,17] "Third space" fluid comprises a pool of water, electrolytes, and protein that is not available for incorporation into

Table 2. Severity of Dehydration Based on History and Physical Exam

	MILD	MODERATE	SEVERE
General Appearance	Alert, restless, thirsty	Lethargic, postural dizziness	Limp, coma, cold and cyanotic extremities
Radial pulse	Full	Thready, weak, rapid	Feeble, inpalpable
Respiration	Normal	Deep	Deep/rapid
Skin elasticity	Pinch retracts immediately	Pinch retracts slowly	Pinch retracts very slowly (> 2 sec)
Eyes	Normal	Sunken	Very sunken
Tears	Present	Diminished	Absent
Mucous membrane	Moist	Dry	Very dry
Urine output	Normal	↓	↓ or absent
Cap Refill	< 2 sec	> 2 sec	Prolonged
Heart rate	Varies with age	Varies with age	Varies with age

the intravascular space. Examples include fluids found in pleural effusions, ascites, and intraluminal fluid in the gastrointestinal tract. Surgical bowel manipulation or trauma can significantly increase the volume of fluid in this potential fluid space.

The first fluid infusion (20 mL/kg) should be administered rapidly and the heart rate, pulse pressure, blood pressure, peripheral perfusion, quality of mentation, and volume of urine output should be monitored. Improvement in these measurements suggests that maintenance fluid administration can then be initiated and vital signs monitored. The appropriate maintenance fluid to be used depends on the measurement of the serum electrolytes. The end point of fluid resuscitation should be normalization of heart rate and respiratory rate, an increase in arterial blood pressure, an increase in pulse pressure and peripheral perfusion, establishment of adequate urine output, and a decrease in the metabolic acidosis. However, if shock persists after the first fluid infusion is completed, a second infusion of 20 mL/kg should be started. If the patient does not improve after 2-3 infusions (40-60 mL/kg) of isotonic crystalloid solution, more aggressive monitoring and therapy are clearly required. If a child is unresponsive to this amount of fluid resuscitation, the child must be evaluated for complicating factors. Causes of unresponsive shock in a patient with adequate oxygenation include unrecognized pneumothorax or pericardial effusion, intestinal ischemia (volvulus, intussusception, necrotizing enterocolitis), sepsis, myocardial dysfunction, adrenocortical insufficiency, and pulmonary hypertension.[1]

Even while the initial 60 mL/kg of fluid is infusing, some children require inotropic or vasopressor support to maintain adequate end-organ perfusion. This subset of patients, who are said to have fluid-refractory shock, may require a combination of large amounts of fluid resuscitation as well as catecholamine support. It is important to be sure of the diagnosis in these cases, as the clinical signs of different types of shock frequently overlap. In addition, reassessment of the patient frequently and thoroughly during the resuscitation is important to guiding additional therapy. For example, children with hypovolemic shock secondary to diarrhea who do not improve despite large amounts of volume may have ongoing gastrointestinal losses that are overlooked, leading to further volume being necessary in order to keep up with the ongoing output. An analogous situation is the child with diabetic ketoacidosis, who continues to have large amounts of ongoing urine losses that, if inadequately replaced, will lead to a decrease in intravascular volume. Children with intravascular dehydration secondary to burns or septic shock frequently require large amounts of fluid secondary to ongoing capillary leak, as well as concurrent inotropic and/or vasopressor support.[18] To guide therapy, it is important to determine if these children have failure of the vasculature, cardiac function, or a combination of both, leading to requirements of additional support other than volume. The cardiac failure seen with thermal injuries, trauma, or sepsis must be further differentiated between intrinsic cardiac dysfunction and decreased cardiac output as a result of external compression (e.g., pericarditis, tamponade).[19] An additional concern in children who have fluid-refractory shock is adrenal insufficiency. With the increased use of chronic steroid therapy in children (e.g., transplantation, malignancy, asthma), there exists the possibility that a relative adrenal insufficiency contributes to the patient's fluid-refractory shock state, and that exogenous steroid therapy may have a role in treatment of these patients.

Fluid Resuscitation in Septic Shock

Carcillo and colleagues found that pediatric patients who presented in septic shock had reduced mortality with rapid fluid resuscitation (> 40 mL/kg within the first hour); yet, these patients had no increase in cardiogenic pulmonary edema or adult respiratory distress syndrome.[18] This association between

vigorous volume resuscitation and improved survival is well supported in animal models of septic shock.

The child who presents in septic shock should be treated aggressively with volume resuscitation. Based on current information, repeated 20 mL/kg fluid boluses may be administered in excess of 60 mL/kg in the first hour and 120 mL/kg the first six hours if blood pressure, peripheral pulses, mental status, arterial blood gas levels, urine output, and peripheral color suggest that perfusion remains decreased.[18]

Fluid Therapy in Hemorrhagic Shock

Shock in the injured child is almost always secondary to hypovolemia, and acute blood loss must always be considered first. With hemorrhagic shock, the source of blood loss may be external and readily apparent, such as a laceration of a major vessel in an extremity or a large scalp laceration. The scalp is often a source of significant blood loss in children, both because of its inherent vascularity and because of the increased percentage of body surface made up by the head in infants and young children. More commonly, however, the source of blood loss is internal and therefore less apparent. Extremity (i.e., femur fracture) and intra-abdominal injuries are common following blunt trauma in children, especially with motor vehicle accidents.[4] Both can result in significant occult blood loss.

Intra-abdominal solid organ injury is a common cause of occult blood loss, and such injuries are probably the most common cause of traumatic shock in this age group.[4] Single or complex fractures of the liver and spleen often result in significant hemorrhage. Associated injury to the inferior vena cava is rare, but if present, usually leads to life-threatening hemorrhage. Mesenteric injury is often seen as part of the "lap belt syndrome," but does not usually result in sufficient blood loss to cause shock. Blunt injury of the kidney may also cause significant blood loss into a retroperitoneal hematoma. Fracture of the bony pelvis is relatively common in older children, and may lead to massive hemorrhage, at times requiring urgent stabilization. Occult blood loss may occur in the chest as well, with laceration of the lung or an intercostal vessel. Great vessel injury secondary to blunt trauma in children is, fortunately, rare. Even in urban trauma centers, penetrating injuries secondary to gunshot and stab wounds account for only a relatively small percentage of all pediatric and adolescent injuries.[20]

Children usually have healthy compensatory mechanisms which maintain peripheral perfusion. First, heart rate increases in order to maintain cardiac output in the face of decreased stroke volume. For this reason, tachycardia is an early sign of acute blood loss and impending shock. Total blood volume in children is generally estimated as 7-8% of body weight or 70-80 mL/kg.

Table 3. Classification of Hemorrhage by Blood Volume Lost

DEGREE OF HEMORRHAGE	BLOOD VOLUME LOST (%)	SIGNS
Class I	< 15	Minimal tachycardia; normal respiration, BP, capillary refill
Class II	15-30	Tachycardia; tachypnea; diminished pulse pressure; systolic BP unchanged; prolonged capillary refill; minimal decrease in urine output; anxiety
Class III	30-40	Tachycardia; tachypnea; decreased BP; decreased urine output; mental status changes
Class IV	> 40	Hypotension; anuria; loss of consciousness

BP = blood pressure.
Adapted from Committee on Trauma, American College of Surgeons. Morgan WM, O'Neill JA. Hemorrhagic and obstructive shock in pediatric patients. *New Horizons* 1998;6:150-154.

With blood loss of 10-15% (class I hemorrhage as defined by Advanced Trauma Life Support), the injured child easily compensates with a 10-20% increase in heart rate. *(See Table 3.)* Blood pressure and peripheral capillary refill are usually unchanged. Even with 20-25% loss of blood volume (class II hemorrhage), there is often little change in the systolic blood pressure as increasing tachycardia and peripheral vasoconstriction mediated through the sympathetic nervous system and other mechanisms serve to maintain perfusion pressure. It is for this reason that one must avoid the tendency to equate hypotension with shock in the pediatric trauma patient. Hypotension is a late finding with ongoing hemorrhage and often signals that the child is near the point of complete decompensation.[4,9] Heart rate is a much more reliable early sign of significant blood loss in this setting.

With any signs of hypovolemic shock (i.e., tachycardia), a fluid bolus of 20 mL/kg of isotonic crystalloid solution should be given. Transfusion of packed red blood cells (PRBCs) or whole blood is indicated for the patient with hemorrhagic shock who shows signs of persistent intravascular depletion despite the rapid administration of 60 mL/kg crystalloid.[3] PRBCs should be given in 10 mL/kg boluses. Type-specific blood is used if available, but typing should not delay resuscitation. Uncross-matched O-negative "universal donor" blood should be immediately available. Aggressive fluid resuscitation is paramount, even when there is associated closed-head injury, since ongoing hypoperfusion leads to secondary hypoxic end-organ injury, especially in the brain.[21-24] This point is highlighted by the shift in emphasis from intracranial pressure to cerebral perfusion pressure in the management of traumatic brain injury.[22]

Although hypovolemia is the most frequent cause of shock, occasionally other causes of hemodynamic compromise may be present. Obstructive shock due to tension pneumothorax or peri-

cardial tamponade, myocardial contusion, and spinal shock may complicate the management of pediatric trauma.[19] Blunt cardiac injury (BCI) can cause myocardial contusion, myocardial concussion, aneurysm, septal defects, chamber rupture, valvular rupture, and damage to the pericardium.[25-27] Each of these entities has separate presentations, although the lesions are often concurrent. The majority of blunt injuries to the heart are myocardial contusions; devastating events such as ventricular rupture are rare.[25,27]

Important clinical implications were presented recently concerning children with BCI:

1. If a child with a suspected BCI is hemodynamically stable and presents with a normal sinus rhythm, then the development of serious arrhythmia or cardiac failure is not likely. In other words, high-risk patients are usually evident from the start.[25]
2. Trauma patients with a suspected cardiac injury should receive prompt evaluation of cardiac function with echocardiography.[25,26] Any patient with unexplained hypotension or diminished periperhal perfusion should be studied using echocardiography.
3. Elevated cardiac isoenzyme values and electrocardiography are nonspecific for clinically significant myocardial injury.[26]

Timing of Fluid Resuscitation in Traumatic Shock

For many years, the preoperative approach to hypotensive patients with trauma has included prompt intravenous infusion of isotonic crystalloid solution in order to restore normal blood pressure as quickly as possible. Several established, long-standing clinical and laboratory studies supporting these guidelines showed the reversal of hemorrhagic shock when 2-3 times the volume of blood lost was replaced using crystalloid solution.[28]

A number of recent studies have challenged the current standard of infusing crystalloid solutions at a rapid rate in attempts to restore normal hemodynamics during hemorrhagic shock from trauma.[28-32] The recommendation that hypotensive patients with suspected acute hemorrhage should receive intravenous fluids before the control of bleeding is based largely upon animal studies in which hypovolemia was produced atraumatically by withdrawing blood through a surgically implanted catheter. Unfortunately, controlled blood withdraw in the laboratory may not have clinical correlation.[32] Blood loss in the trauma victim occurs as the result of injury to blood vessels or solid organs, not from roller pump or syringe withdrawal through a catheter. Until that interruption in the vascular circuit is definitely managed, the possibility of further hemorrhage accentuated by resuscitation exits when the patient has suffered a penetrating injury.[30]

Many authors have expressed concern that intravenous volume infusion may be detrimental in the clinical setting if administered aggressively before the hemorrhage is surgically controlled.[28] The hazards of aggressive crystalloid resuscitation in this situation include:

1. The negative impact of fluid resuscitation on early clot formation;
2. Possible mechanical disruption of blood clot from a vessel injury by rapid volume resuscitation;
3. The dilution of clotting factors by crystalloid resuscitation; and
4. The occurrence of a progressive hemodilution followed by cardiovascular collapse.[9,28]

Recent studies have demonstrated that in uncontrolled hemorrhage, aggressive administration of fluids may disrupt the formation of thrombus, increase bleeding, and decrease survival.[29]

Dries has recently provided a review of the various studies that have led to the concepts of hypotensive resuscitation for uncontrolled hemorrhage.[33] The paper discusses many of the small and large animal studies in the literature, as well as pertinent clinical studies regarding uncontrolled hemorrhage. In several studies there is an apparent improvement in survival for those animals only partially resuscitated from uncontrolled hemorrhage.[28,31] Bickell's 1991 paper and research by Stern and others have shown that there are markedly increased hemorrhage volumes in a swine aortotomy model when the animals are resuscitated with crystalloid in attempts to restore normal blood pressure and that the maintenance of a mild hypotension resuscitation, rather than normotension, resulted in improved short-term survival.[34,35] Another swine study by Owens and associates confirmed the same findings in their model of uncontrolled bleeding and also determined that oxygen delivery could be significantly improved over their non-resuscitated animals by a limited crystalloid resuscitation, without the detrimental effects of their standard crystalloid resuscitation.[36]

The results of these studies may have implications on the treatment of penetrating intrathoracic and intra-abdominal injuries with suspected large-scale hemorrhaging. First, the outcome of an uncontrolled abdominal hemorrhage seems to be optimal when a moderate amount of crystalloid fluid is infused. In a rural situation in which the distance to the hospital is long, fluid therapy given in smaller amounts than previously believed to be necessary is more likely to result in survival than the conventional 3:1 therapy or no therapy. In an urban situation in which the distance to the hospital is short, the considerations become more complex because fluid therapy probably postpones irreversible shock until rebleeding occurs. The risk of rebleeding increases with time and the amount of fluid given, but this complication has the potential of being remedied by timely and adequate surgical intervention. Fluid therapy might "buy time," because rebleeding usually begins approximately 30 minutes after the infusion is started.[31] If a more ambitious fluid program is chosen (than conventional 3:1 replacement), however, it seems important to give definitive treatment in the hospital within 30 minutes of the initial care.

On the basis of these studies, a change in trauma resuscitation for patients sustaining a penetrating torso injury may be indicated. Moderation in the use of intravenous crystalloid for restoring blood pressure, rather than overly aggressive infusion rates, now appears to be an acceptable recommendation.[28] However, the issues regarding the acceptance of a blood pressure that is less than normal during a resuscitation remains less clear, and further research is needed to provide definitive recommendations.[28]

Tailoring of the trauma resuscitation to the individual patients, their pre-existing diseases, the mechanism of injury, and the setting in which the patients have been injured, plus factoring the distance and time they need to be transported, should still be the accepted form of trauma management. Care providers should remain cautious about applying the principle of "delayed fluid resuscitation" or "hypotensive resuscitation" to all patients, especially those who have sustained blunt trauma and have a possible closed head injury.

Crystalloid vs. Colloid

Volume resuscitation may include the use of crystalloid and/or colloid as well as blood products. Crystalloids are electrolyte-containing solutions distributed through the body according to their chemical composition and tonicity. Isotonic solutions (lactated Ringer's solution; 0.9% sodium chloride) are distributed to the extracellular space. Hypotonic solutions have a proportion of water not associated with sodium and are therefore distributed throughout the entire body water. Hypertonic solutions (sodium concentrations in excess of 180 mEq/L) increase serum osmolality and therefore induce movement of water from the intracellular space to the extracellular space.

Colloids used in the treatment of patients in shock include plasma, prepared plasma fractions, and synthetic plasma substitutes. Colloids consist of large molecules that are generally restricted to the intravascular compartment, exerting an oncotic effect on the distribution of water. In doing so, iso-oncotic + solutions (5% albumin, fresh frozen plasma) result in a greater expansion of the intravascular volume than that achieved with isotonic crystalloid solutions when the same volume is infused. Hyperoncotic solutions, such as 25% albumin, move fluid into the vascular compartment from the interstitial space.

Plasma expanders, such as the dextrans and hydroxyethyl starch, are also available for intravascular volume replacement. The dextrans, Dextran-40 and Dextran-70, are available as either 0.9% sodium chloride solutions or 5% dextrose solutions. Hetastarch is amylopectin in which hydroxyethyl starch groups are substituted. It is available as a 6% solution in 0.9% sodium chloride. Use may be limited by hypersensitivity reactions; experience with use of dextrans and hetastarch is pediatrics is limited.

There continues to be an ongoing debate as to the most suitable type of fluid to use for resuscitation. Both choices, crystalloid solutions and colloid solutions, carry with them their own advantages and disadvantages.

The advantages of using crystalloids for resuscitation are both the availability and cost effectiveness of these solutions. The cost of 5% albumin is many times that of the common crystalloid solutions. The main disadvantage is that crystalloids reduce colloid oncotic pressure and may predispose to pulmonary and peripheral edema.[37]

Colloid solutions are useful because they contain relatively large molecules that are impermeable to the capillary membrane, leading to increased volume remaining in the intravascular space. Disadvantages of colloid infusions are chiefly related to cost and the potential exposure to blood products.

Few human clinical trials directly compare crystalloid with colloid infusions. Early trials were flawed by comparing the two types of fluid by the end point of the total amount of volume infused, instead of physiologic parameters, such as central venous pressure or pulmonary capillary wedge pressure. In studies which used physiologic parameters as end points, the same physiologic results can be achieved with either fluid, but 2-4 times as much crystalloid compared with colloid must be infused. In some studies, however, pulmonary edema was more prevalent in patients receiving crystalloids.

Recently, the effects of isotonic crystalloids compared with colloids in fluid resuscitation of adult patients have been systematically reviewed. All of the available studies have been conducted in adult patients, with no pediatric studies present in the published literature.

Choi et al evaluated all randomized, clinical trials of adult patients requiring fluid resuscitation comparing isotonic crystalloids with colloids.[37] Overall, there is no apparent difference in pulmonary edema, mortality, or length of stay between isotonic crystalloid and colloid resuscitation. In addition, crystalloid resuscitation is associated with a lower mortality in trauma patients. Since meta-analysis results may not be replicated in large, modern, randomized trials, rigorous research in this field must be conducted.[38,39]

A similar systematic review synthesized the evidence from randomized, controlled trials comparing colloid and crystalloid fluid resuscitation across a wide variety of clinical conditions requiring fluid resuscitation.[40] Resuscitation with colloid solutions was associated with an absolute increase in the risk of mortality of 4%, or four extra deaths for every 100 patients resuscitated.

The results of these studies differ from those of Velanovich's meta-analysis, which concluded that resuscitation with colloids had a beneficial effect on mortality among non-trauma patients compared with crystalloids.[41] However, Velanovich also showed a relative mortality difference of 12% in favor of crystalloid when only studies of trauma patients were included.

Although there is an association between the extent of hypoalbuminemia and the risk of death, the value of albumin administration in patients with low albumin, burns or in the treatment of hypovolemic shock is uncertain. In view of the high cost of albumin and difficulty with access to this blood product, a very careful process of identifying all published, randomized, controlled trials examining the administration of albumin compared with no colloid or a crystalloid was recently conducted.[42,43] Overall, the risk of death in patients treated with albumin was 6% higher than in patients not given albumin. This review suggests that the indications and use of albumin in critically ill patients should be re-evaluated by a large, blinded, controlled trial.

Certainly the crystalloid-colloid question remains unanswered. Until the proper research is completed, the administration of crystalloids and colloids will likely continue to be individualized to each patient based on pathophysiologic rationale, clinical experience, cost, and other externalities of the health care system.

For the most part, unless the child has an underlying disease that predisposes him or her to a decreased plasma oncotic pressure (e.g., malnutrition, hypoproteinemia, nephrotic syndrome), the initial 40-60 mL/kg of fluid resuscitation should be isotonic crystalloid solution. If additional fluid is necessary, the choice is made according to the signs of interstitial volume status on physical examination. If the child is displaying signs of extravascular hypervolemia, colloid solutions may be considered.

Hemoglobin-based blood substitutes are colloid-containing fluids that have the additional advantage of being able to carry oxygen and release it to tissues.[44] Although still experimental, the prospect of a resuscitative fluid that would expand the plasma volume as well as increase oxygen carrying capacity is truly

Table 4. Hypertonic Saline Solution — Physiologic Effects

IMPROVED CARDIAC OUTPUT AND BLOOD PRESSURE

- Fluid shift to intravascular compartment
- Increased inotropy
- Venoconstriction

ALTERED DYNAMICS OF THE MICROCIRCULATION

- Reduced swelling of endothelial cells

RESTORATION OF CIRCULATION WITHOUT ELEVATING THE INTRACRANIAL PRESSURE

- Less edema of the uninjured brain

IMMUNOLOGIC EFFECTS

- Reduced neutrophil-mediated organ injury

PREVENTION OF PULMONARY OVERHYDRATION

Table 5. Definitions

Systemic Inflammatory Response Syndrome: The systemic inflammatory response to a variety of severe clinical insults. The response is manifested by two or more of the following conditions:

- Temperature > 38°C or < 36°C
- Heart rate > 90 beats/min
- Respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mmHg
- WBC > 12,000 cells/mm^3, < 4000 cells/mm^3, or >10% immature (band) forms

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

- Temperature > 38°C or < 36°C
- Heart rate > 90 beats/min
- Respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mmHg
- WBC > 12,000 cells/mm^3, < 4000 cells/mm^3, or > 10% immature (band) forms

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

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

Hypotension: A systolic BP of < 90 mmHg or a reduction of > 40 mmHg from baseline in the absence of other causes for hypotension.

Adapted from the American College of Chest Physicians (ACCP)/Society of Critical Care Medicine (SCCM) Consensus Conference.[61]

exciting. Further refinement of these products is needed before they can be used clinically.

Hypertonic Saline Solutions

Recent interest in the use of hypertonic saline solutions for the resuscitation of patients in hemorrhagic shock represents the revival of a concept that originated with the shock-study teams of World War I. After the war, doubts regarding the true efficacy of hypertonic resuscitation, coupled with the development of plasma transfusion and a series of landmark papers demonstrating the effectiveness of isotonic saline resuscitation, dampened both interest and research in hypertonic resuscitation for decades.[45]

Large-volume, isotonic crystalloid resuscitation became the foundation of orthodox resuscitation doctrine and little follow-up work was done on hypertonic resuscitation until the resurrection of this concept by Velasco and his colleagues in 1980.[46] These authors described the permanent resolution of an otherwise lethal shock state in hemorrhaged dogs using 7.5% sodium chloride solution at a dose of 4 mL/kg of body weight.

It has since been established in numerous animal models of hemorrhagic shock that the infusion of small volumes of hypertonic solutions (ranging from 3.% to 7.5% saline in most studies), can produce rapid circulatory resuscitation.[45] The results of this work have revealed several aspects of the general physiology of hypertonic solutions on intravascular volume, the heart, the peripheral vasculature, and the microcirculation. *(See Table 4.)*[19,24] The most common hypertonic solutions are hypertonic saline (HTS) solutions with or without added dextran. The most common solution of HTS is a 7.5% saline solution (2400 mosm/L).

Small amounts of HTS intravenously infused produce dramatic and rapid improvement in blood pressure, cardiac output, and systemic oxygen consumption. In most animal models of hemorrhagic shock, HTS restores cardiac output and blood pressure to control levels within minutes.[45,47] Clinical trials in adult victims of trauma have shown that prehospital administration of 7.5% HTS with dextran solution in volumes of as little as 250 mL improves blood pressure and survival rate.[47,48] There are reports in the literature of the effectiveness of HTS administered in volumes equal to one-tenth that of the hemorrhaged volume.[9] Such small volume resuscitation with HTS may be ideal in pediatric patients with severe hemorrhagic shock and vascular access limited to an intraosseous route.[48]

Improvement in cardiovascular function with HTS is probably related to multiple factors: intravascular volume expansion secondary to redistribution of fluid from the extravascular to the intravascular compartment, improved myocardial contractility,

Table 6. Suggested Age-Appropriate Values for Defining Systemic Inflammatory Response Syndrome in Children

AGE	HEART RATE (BEATS/MIN)	RESPIRATORY RATE (BREATHS/MIN)	SYSTOLIC BP (mmHg)
0-1 month	> 180	> 50	< 50
1-12 months	> 170	> 40	< 70
1-5 years	> 150	> 30	< 80
5-10 years	> 130	> 25	< 80
> 10 years	> 120	> 20	< 90

Values suggested are based on >2 standard deviation from mean for age.

and constriction of the central capacitance veins in both systemic and pulmonary circulations.[45]

While the cardiac output and blood pressure rise with infusion of HTS in hemorrhagic shock, it has been consistently observed that hypertonic fluids in general, and HTS in particular, have a vasodilating effect on arterial resistance vessels.[45] A vasodilator effect is seen in renal, mesenteric, and coronary vascular beds.

Hypertonic fluid resuscitation also has a positive effect on the microcirculation. It has been shown that a severe depression of microvascular flow occurs in shock.[49] A cause of post-shock microcirculatory failure is swelling of endothelial cells which produces hydraulic resistance to flow.[10,11] Resuscitation with HTS markedly reduces this swelling.[11] In addition, it has recently been shown that leukocyte-platelet aggregation and neutrophil-endothelium interactions are reduced following HTS shock resuscitation compared with isotonic saline resuscitation.[45]

Review of the current status of hypertonic resuscitation suggests that HTS is more hemodynamically efficacious than conventional resuscitation and, when administered in the prehospital setting, is at least as effective as conventional resuscitation.[47] It is also important to point out that several studies have shown improved survival with HTS in selected subsets: patients with head injury, patients with penetrating injury, patients with penetrating injury undergoing operation, and severely hypovolemic patients.[21,24,45]

The weight of experimental and clinical evidence suggests that HTS may prove to be a valuable resuscitation fluid when shock complicates head injury.[24,50-55] Patients who have traumatic brain injuries in the presence of hypotension and receive HTS are about twice as likely to survive as those who receive standard care.[50] Hypertonic solutions increase blood pressure, decrease intracranial pressure (ICP), and reduce brain water in areas in which the blood-brain barrier is intact.[24] The blood-brain barrier is unique in that it is only minimally permeable to most ions.[51] As a result, it is the osmotic gradient between the blood and the brain that is the major determinant of water flux at the blood-brain barrier.

Recent studies in children suggest that HTS is beneficial in the treatment of infants and children with severe head injury.[53,54]

Based on its efficacy, some authors question why HTS has not become the standard practice in the resuscitation of the severe traumatic brain injured patient.[23]

The potential complications or dangers of HTS most frequently considered include electrolyte disturbances, neurologic dysfunction, and recurrence of bleeding.[45]

Septic Shock

Septic shock is the most complex and controversial type of shock. Septic shock compromises a cascade of metabolic, hemodynamic, and clinical changes resulting from invasive infection and the release of microbial toxins into the bloodstream. Historically, a distinction was made between the clinical findings and the type of invading microorganism. However, on closer analysis, it became apparent that the systemic response was independent of the type of invading organism (bacteria, virus, fungus, rickettsia); rather, it was a host-dependent response.[56-60] The morbidity and mortality are primarily the result of endogenous proteins and phospholipids synthesized by the patient.[56]

One of the factors hampering progress in the understanding of sepsis and septic shock has been the variability of definitions used and patient populations studied. As an approach to standardizing the definitions of sepsis and organ failure, the American College of Chest Physicians and the Society of Critical Care Medicine held a consensus conference to define sepsis and organ failure more precisely.[61] This group proposed the term systemic inflammatory response syndrome (SIRS), recognizing that the inflammatory response can be precipitated by processes other than infection. *(See Table 5.)* The group included in the definition of SIRS abnormalities of temperature, heart rate, respiratory rate, and white blood cell count. While the definitions used were those applied to adults, age-appropriate values can be used to apply the same descriptions to children. *(See Table 6.)*[60,62,63]

The pathophysiology of septic shock isn't completely understood. A combination of the direct effects of microbial agents, microbiological toxins, and the patient's inflammatory response to infection results in the cardiovascular instability and multisystem organ failure seen in septic shock. A key element in the pathogenesis of sepsis is activation of the cytokine network. Cytokines are host-produced, pleomorphic immunoregulatory peptides.[57,58] The most widely investigated cytokines are tumor necrosis factor, interleukin-1, and interleukin-8, which are generally proinflammatory, and interleukin-6 and interleukin-10, which tend to be anti-inflammatory. A trigger, such as a microbial toxin, stimulates the production of tumor necrosis factor and interleukin-1, which in turn promote endothelial cell-leukocyte adhesion, release of proteases and arachidonate metabolites, and activation of clotting.[56,58] Interleukin-1 and tumor necrosis factor are syngeristic, share many biologic functions, and interact to promote positive feedback cascades that result in fever, vasodilation, cardiovascular failure, and lactic acidosis.[56] The cytokines stimulate the production of many important effector molecules, including proinflammatory cytokines, anti-inflammatory cytokines, and nitric oxide (NO). Increased proinflammatory cytokines, anti-inflammatory cytokines, and NO correlate with outcome and the development of multiple

organ failure in pediatric sepsis and septic shock.[56,64-66] Because of the multiple factors involved, the clinical pattern and presentation of septic shock may vary a great deal and depend on the dynamic interplay of the invading organism, elapsing time, and host response.

Abnormal hemodynamic responses constitute a primary hallmark of septic shock. The early stages consist of a hyperdynamic state characterized by an elevated cardiac output, a decreased systemic vascular resistance, and a widened pulse pressure, with episodic hypotension and warm extremities on physical examination.[1,56] In this hyperdynamic stage, the syndrome can also be recognized by the presence of high fever, mental confusion, and hyperventilation. Although these patients are typically tachycardic and tachypneic, the vital signs and clinical examination may not reflect the severity of disease. Mental status changes, a sensitive indicator of hypoperfusion, may present in a clinical spectrum that begins with fussiness, irritability, or hallucinations and, if untreated, evolves to lack of response to parents, noxious stimuli and eventual coma.[1,56,67]

If sepsis is unchecked and uncorrected, steady deterioration in cardiovascular performance occurs, characterized by a decline in cardiac output, hypotension, and metabolic acidosis. Paradoxically, hypotension may occur in the presence of a normal or elevated cardiac output. One fundamental abnormality in patients with septic shock is an altered relationship of systemic vascular resistance and cardiac output.[68] The patient's status deteriorates when cardiac compensation for diminishing systemic vascular resistance is lost. Some patients die of refractory hypotension as a result of very low systemic vascular resistance.[68,69] The progression from high to low cardiac output may occur over any time period. As cardiac output decreases, tissue perfusion worsens, leading to anaerobic metabolism and accumulation of lactic acid.[62] Progressive lactic acidemia may warn of impending death.[68,70,71] Infants, who have limited cardiac reserve, may rapidly progress to this hypodynamic picture.

Survival in septic shock has been related to the host's ability to establish and maintain a hyperdynamic cardiovascular state.[72-74] Even in this "hyperdynamic" shock, when cardiac output is increased and the systemic vascular resistance is decreased, compelling evidence from animal and human clinical studies suggests both the right and left ventricle are dilated and poorly contractile.[63,72] During this time, cardiac output is maintained only at the cost of ventricular dilation and tachycardia. Infants and children may not be fully capable of utilizing or maintaining protective physiologic mechanisms seen in adult patients. For example, infants and children have higher resting heart rates, which can limit the efficiency of a chronotropic protective response. The ability to dilate the ventricle as a protective response may also be less in children.

In early stages of septic shock, hypovolemia or myocardial dysfunction (resulting from preexisting or intercurrent ventricular disease) can blunt or eliminate the hyperdynamic response to sepsis.[68,69] Several factors may contribute to hypovolemia, which commonly occurs in septic shock. Increased microvascular permeability, arteriolar and venular dilation with subsequent peripheral pooling of intravascular blood volume, inappropriate polyuria, and poor oral intake all combine to result in a reduced effective blood volume.[58,69] Fluid loss secondary to fever, diarrhea, vomiting, or sequestered third space fluid also contributes to the hypovolemia.

In some patients without complicating preexisting heart disease, a relative depression in left ventricular contractility exists even in early stages.[63,72] Myocardial contractility is most likely depressed due to the inhibitory effects of one or more circulating substances. In patients who survive, this myocardial depression is transient.

Contrary to adult experience, low cardiac output, not low systemic vascular resistance is associated with mortality in pediatric septic shock.[56,75] Recently, Ceneviva and colleagues, reported outcome data associated with aggressive volume resuscitation and goal-directed therapies in children with septic shock.[76] In this study, 50 children with fluid refractory septic shock were hemodynamically characterized utilizing a pulmonary artery catheter. The majority (58%) showed a low cardiac output, high systemic vascular resistance state (group I); 20% showed the classic adult high cardiac output, low systemic vascular resistance state (group II); and 22% had decreased cardiac output and systemic vascular resistance (group III). Patients in group I responded to inotropic therapy with or without a vasodilator; patients in group II responded to vasopressor therapy but some needed the addition of an inotrope for evolving myocardial dysfunction; and patients in group III responded to combined vasopressor and inotropic therapy. The overall 28-day survival rate was 80% (group I, 72%; group II, 90%; group III, 91%). This study demonstrates that therapies directed at cardiac dysfunction and systemic vasoconstriction are more common in pediatric septic shock.[76]

Cardiovascular abnormalities described in sepsis include alterations of both systolic and diastolic function.[77] Although diastolic performance in sepsis has been less characterized, echocardiographic studies have demonstrated a pattern of abnormal left ventricular relaxation which is more severe in nonsurvivors.

Septic shock is also characterized by abnormal utilization of oxygen.[73,75,78] Although sepsis causes a hypermetabolic stress associated with increased oxygen demand, deterioration characteristically occurs when oxygen consumption falls during a period of increased cardiovascular function and oxygen delivery. This fall in oxygen consumption is the result of decreased oxygen extraction and reflects a severe impairment of oxidative metabolism at a time of major metabolic and physiological stress. The pathophysiology of inadequate oxygen consumption in septic shock remains unclear. The most widely accepted theories to account for this oxygen debt are the redistribution of blood flow, with a consequent decrease in nutrient capillary flow, and the development of a cellular metabolic blockade at the mitochondrial level such that delivered oxygen cannot be used.

Progressive deterioration in oxygen consumption and oxygen extraction portends a poor prognosis for septic shock patients.[73]

Regardless of the cardiac output present in sepsis, this flow is not evenly distributed.[79] Animal studies have demonstrated a reduction in blood flow to the myocardium and skeletal muscle but most notably to the stomach, duodenum, small bowel, and pancreas.[80,81] The reduction in splanchic blood flow remains even with preservation of cardiac output. Factors limiting microvascu-

Table 7. Inotropic and Vasoactive Drugs Utilized in Management of Septic Shock

DRUG	DOSAGE	RECEPTORS	USUAL EFFECT
Dopamine	0.5-3 μg/kg/min	Dopaminergic	Dilation in renal, mesenteric, cerebral vasculature
	5-10 μg/kg/min	β-adrenergic	Mostly inotropic (increased cardiac output)
	10-25 μg/kg/min	α-adrenergic	Increased heart rate, vascular resistance, and blood pressure
Dobutamine	1-20 μg/kg/min	β-adrenergic	Inotropic, vasodilation
Epinephrine	0.02-0.1 μg/kg/min	β-adrenergic	Inotropic
	0.1-1 μg/kg/min	α- and β-adrenergic	Increased vascular resistance and blood pressure
Norepinephrine	0.05-0.5 μg/kg/min	mostly α-adrenergic	Increased vascular resistance
Phenylephrine	0.5-8 μg/kg/min	α-adrenergic only	Increased vascular resistance
Milrinone (Primacor)	Loading dose: 50 μg/kg (slowly) Infusion: 0.25-0.75 μg/kg/min	None	Inotropic, vasodilation
Amrinone (Inocor)	Loading dose: 0.75 mg/kg (slowly) Infusion: 3-10 μg/kg/min	None	Inotropic, vasodilation
Nitroglycerin	1-5 μg/kg/min	None	Systemic and pulmonary vasodilation
Sodium Nitroprusside	0.5-10 μg/kg/min	None	Systemic and pulmonary vasodilation

Notes:
- To mix infusions, the "rule of 6" may be utilized; mix 6 mg/kg in 100 mL D5W; then 1 mL/hr = 1 μg/kg/min.
- For a dosage where < 1 μg/kg/min is indicated, mix 0.6 mg/kg in 100 mL D5W; then 1 mL/hr =0.1 μg/kg/min.
- Dosage ranges are approximate, and effects are simplified. Actual doses must be titrated to the individual patient response.
- All drugs shown may have harmful side effects. Amrinone and milrinone are not rapidly metabolized and can have increased toxicity with prolonged use.

lar blood flow in septic shock are multifactoral and complex.[79] A large number of mediators and inflammatory cells interact with endothelial and vascular smooth muscle cells to interfere with blood flow and ultimately lead to microvascular failure.[82] Rheologic changes, including red blood cell deformability, increased leukocyte aggregation, and endothelial adherence, may contribute to this abnormality by compromising effective capillary cross-sectional area.[83] Although there are numerous changes, slowing of capillary blood flow due to depressed perfusion pressure as a result of systemic pressure reduction and local arteriolar constriction are of critical importance.[79] Use of vasodilator drugs to improve microcirculatory blood flow has long been appealing but is still under investigation.

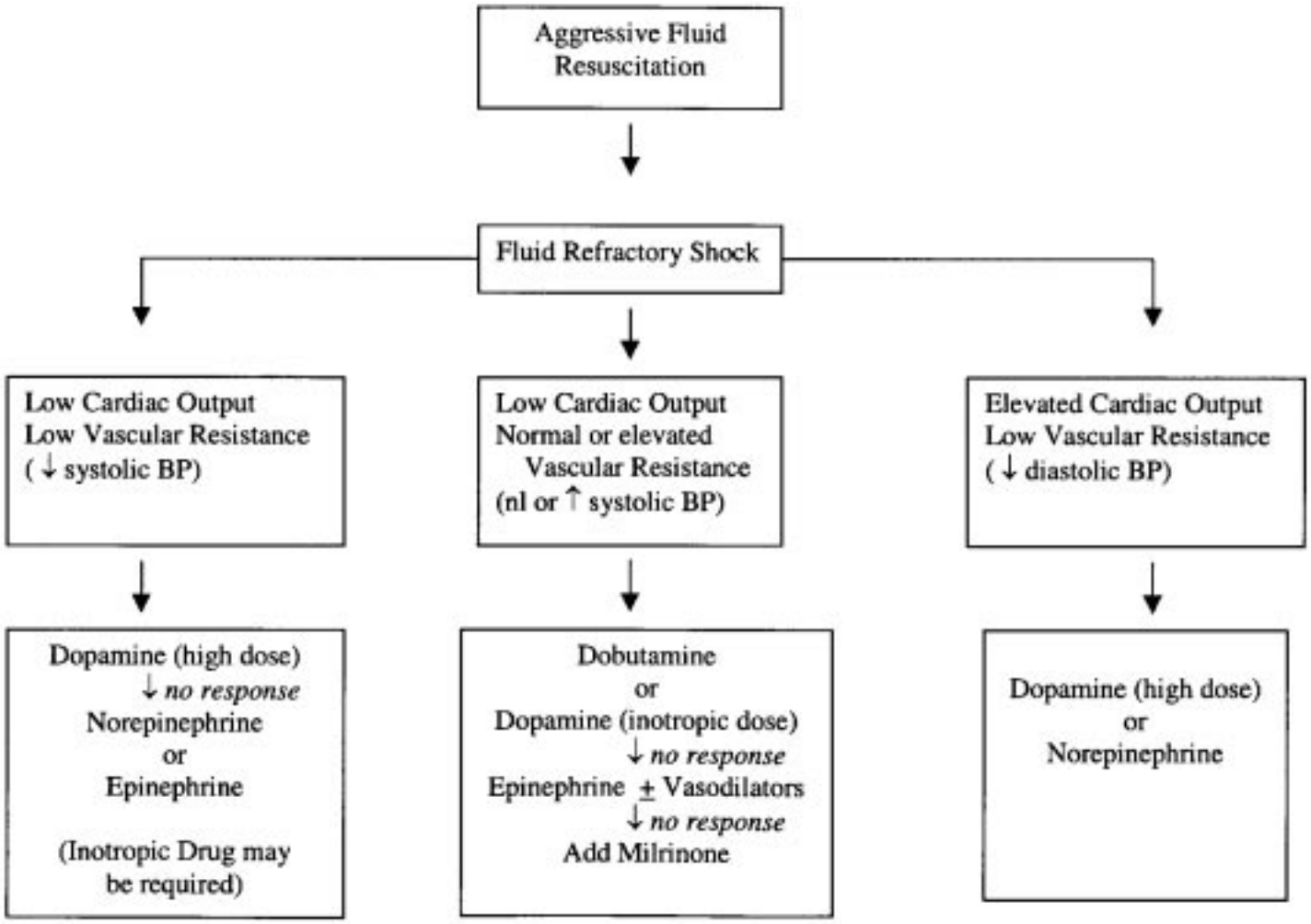
Therapy

Primary therapeutic goals for the initial treatment of septic shock are identification and control of the infection and rapid reversal of cardiovascular dysfunction.

The removal or control of microorganisms by surgical debridement or drainage and antibiotic therapy is a crucial component of the treatment of septic shock. Antibiotic treatment is appropriate in patients with circulatory shock whenever an infectious etiology is suspected. Antimicrobial drugs are necessary but not sufficient for the treatment of sepsis, and paradoxically, may precipitate septic changes by liberating microbial products.[58]

The primary goal in the initial management of septic shock is to restore hemodynamic stability. Increasing oxygen delivery by maximizing cardiac output and arterial oxygen content and minimizing oxygen requirements are fundamentals of management.[1] Detection of septic shock is facilitated by the nearly universal presence of tachypnea.[58] Sepsis places extreme demands on the cardiopulmonary system, requiring a high-minute ventilation precisely when the compliance of the

Figure 1. Suggestions for Hemodynamic Support in Pediatric Septic Shock



respiratory system is diminished, airway resistance is increased, and muscle efficiency is impaired. Timely intubation and mechanical ventilation reduce respiratory-muscle oxygen demand and the risk of aspiration and cerebral anoxia from catastrophic respiratory arrest.

Restoration of preload by volume resuscitation is the first therapeutic measure for a decreased cardiac output.[18,56,84] Early and effective expansion of the circulating blood volume may enhance oxygen delivery and prevent progression of the septic shock state. Placement of a thermodilution pulmonary artery catheter may be indicated in children who demonstrate a sluggish response to fluid infusion, have signs of pulmonary edema with normal CVP, or show clinical or echocardiographic evidence of myocardial dysfunction.[56,76]

Isotonic crystalloid solutions may be used initially to restore intravascular volume in the presence of septic shock if they increase the blood volume and cardiac output. Debate on the relative advantages and disadvantages of crystalloid and colloid fluids for the treatment of sepsis and septic shock continues.[58,60] A meta-analysis has shown no difference in mortality between patients resuscitated with normal saline or albumin, and a multi-disciplinary consensus statement concluded that crystalloid is the preferred solution in septic patients.[85] A recent study showed that either fluid could be used to expand the plasma volume.[85]

Theoretically, transfusion of packed red blood cells to maintain a normal hemoglobin concentration is the most effective means of increasing arterial oxygen content and systemic oxygen availability.[84] Initial guidelines in patients with severe sepsis are a hemoglobin concentration greater than or equal to 10g/dL and an oxyhemoglobin saturation greater than or equal to 95%. However, the concept of a single threshold value for transfusion in all patients has been challenged.[86] A restrictive strategy of red-cell transfusion (hemoglobin values between 7 and 9 g/dL) is superior to a liberal transfusion strategy (hemoglobin values 10-12 g/dL) in critically ill adult patients.

The optimum hemoglobin in sepsis has not been firmly established, but there is no compelling evidence to maintain a hemoglobin concentration greater than 10 g/dL.[84] Although often recommended, 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.[56,68] The majority of trials have not demonstrated a significant increase in systemic oxygen con-

sumption when the major effect of transfusion therapy is to increase oxygen content.[68,87] Critically ill patients may also be at increased risk for the immunosuppressive and microcirculatory complications of red-cell transfusions.[86]

Excessive tachycardia, severe mixed venous desaturation, cardiac systolic dysfunction, and failure to resolve lactic acidosis or failure to improve gastric intramucosal pH may indicate the need to increase hemoglobin concentration to levels above 10g/dL.[68,88]

Although fluid administration and antimicrobial therapy remain the cornerstones of the therapeutic approach to sepsis and septic shock, patients often require therapy with inotropic agents, vasoactive drugs, or both.[56] Children can have predominant cardiac failure, predominant vascular failure, or a combination of cardiac and vascular failure.[56,76,89] Therapeutic approaches differ with each condition.

Inotropic Therapy

Myocardial depression complicates septic shock and may prevent the development of optimal cardiac output despite adequate intravascular volume. The catecholamine and noncatecholamine inotropes may both be effective in reversing myocardial depression and improving contractility. *(See Table 7 and Figure 1.)*

Children in a normotensive, hypodynamic state require an inotrope to increase cardiac output and to reverse shock. Dobutamine or moderate dose dopamine can be used as the first line of inotropic support. Patients with dobutamine-resistant septic shock often respond to the addition of epinephrine with or without vasodilators. When patients remain in a normotensive low cardiac output state, despite epinephrine and vasodilator therapy, then the use of milrinone should be considered.[89]

Catecholamines exert their action via β-adrenergic receptors, elevating intracellular calcium transients through increasing production of intracellular cyclic adenosine monophosphate (cAMP). However, benefits from the application of catecholamines in septic shock may not be sufficient. Myocardial hyporesponsiveness to catecholamine administration during septic shock has been documented by several investigators. This hyporesponsivity of the myocardium to catecholamines may be due to cytokine-induced uncoupling of the β-adrenergic receptor system or due to deranged intracellular calcium metabolism.[89]

The bipyridines (milrinone, amrinone) have no interaction with the adrenergic receptors but rather exert their effects through the inhibition of phosphodiesterases, which degrade cAMP. Milrinone has been shown to improve cardiovascular function in pediatric patients with hypodynamic septic shock who are adequately volume resuscitated and are being treated with catecholamines.[89]

Vasopressor Therapy

Vasopressor therapy is commonly required in children with fluid refractory shock and hypotension. Choices for vasopressor effect include dopamine in a dose range of 10-25 mcg/kg/min, norepinephrine, and epinephrine. Alpha-adrenergic agonists are vasoconstricting drugs that can boost systemic vascular resistance. All the drugs mentioned have marked β-adrengeric properties as well, increasing the heart rate and myocardial contractility.

Dopamine is an α-adrenergic agonist at higher concentrations. It mediates vasoconstriction indirectly by causing the release of norepinephrine from sympathetic vesicles.[90] Dopamine is often used first because it also stimulates dopaminergic receptors (DA), potentially increasing renal blood flow. Apart from the vasoconstricting effect of dopamine, however, its role in protecting the kidneys or augmenting urine output in patients with sepsis remains controversial.[58]

Norepinephrine often reverses dopamine-refractory septic shock.[91] Norepinephrine can also improve urine output and renal function by increasing perfusion pressure in hypotensive patients.

In children who present with a warm vasodilated state after volume resuscitation, norepinephrine can be used to increase diastolic blood pressure while maintaining good perfusion.[56,91]

Use of vasopressors should be titrated to end points of normal perfusion pressure or systemic vascular resistance. Strict end point measures should be used because unnecessary vasoconstriction to key organs can result. A frequent adverse effect of α-agonist treatment is localized severe vasoconstriction after extravasation of the infusion, therefore, these infusions are best administered into deep venous or central venous catheters.[90]

Supraphysiologic Oxygen Delivery

The benefit of manipulating oxygen delivery to achieve supraphysiologic oxygen delivery has not been convincingly demonstrated in patients with septic shock.[58,73,84,92,93]

Corticosteroid Therapy

Interest in the use of corticosteroids as adjunctive therapy for septic shock spans well over three decades. Despite discouraging results of large, randomized, placebo-controlled trials using pharmacologic doses, interest in the use of corticosteroids for the treatment of septic shock has persisted.[94]

Table 8. Factors Contributing to the Development of Relative Hypoadrenalism in Critically ill Patients

DAMAGE OF THE ADRENAL CORTEX

- Pre-existing or previously undiagnosed diseases of the adrenal gland
  - Polyglandular endocrinopathies
  - Adrenoleukodystrophy
- Acute, partial destruction of the adrenal gland
  - Hemorrhage
  - Bacterial, viral, or fungal infections

HYPOTHALAMIC-PITUITARY DISEASE/DAMAGE

- Trauma
- Tumor

DRUG-RELATED FACTORS

- Corticosteroid use
- Change in cortisol synthesis or metabolism

CYTOKINE-MEDIATED FACTORS

- Interference with glucocorticoid receptor binding

There is interest in using corticosteroids in late or refractory septic shock at physiologic doses.[95] Evidence exists that suggest a role for occult adrenal insufficiency in the pathophysiology of septic shock. *(See Table 8.)*[94-97] Several reports have demonstrated an attenuated response to ACTH stimulation in some patients with septic shock and a higher mortality in some of these patients.[95-97] In addition, both temperature and cytokines may decrease glucocorticoid receptor binding affinity.[94] This would cause a relative glucocorticoid insensitivity not related to serum cortisol levels which may be responsive to exogenous supplementation of physiologic doses of glucocorticoids.

Although the incidence of adrenal hemorrhage and necrosis in septic shock is rare, it must be considered in rapidly progressive shock which is unresponsive to fluids and inotropic/vasopressor therapy.[98] Other disease entities may increase the risk of adrenal insufficiency in children with septic shock, however, the most common is chronic steroid use with subsequent suppression of the hypothalamic-pituitary-adrenal axis.[56,94]

No large, randomized, placebo-controlled trials have addressed the use of corticosteroids in pediatric patients with septic shock. However, there are populations of children at risk for adrenal insufficiency for which the use of stress doses of corticosteroid during septic shock is warranted. Cortiocosteroid therapy should be considered in children with vasopressor-dependent septic shock.[97,99]

Table 9. Immunotherapy for Sepsis

AGENT	SITE OF ACTION
Antiendotoxin Antibodies E5 (murine) HA-1A (human)	Neutralize endotoxin
Bactericidial permeability-increasing (BPI) protein	Neutralize endotoxin
Tumor necrosis factor (TNF) antibodies	Block TNF
Interleukin-1 receptor antagonists (IL-1 ra)	Inhibit action of IL-1 on cellular receptors
IL-1 antibodies	Block IL-1 receptor interaction
IL-6 and IL-8 antibodies	Block IL-6, IL-8 receptor interaction
Bradykinin-receptor antagonists	Prevent vasoactive effects of bradykinin
Platelet activating factor (PAF) antagonists	Block platelet activation and platelet aggregation
Cyclooxygenase inhibitors (ibuprofen)	Block pyrogen, thromboxane, and prostaglandin production
Nitric oxide (NO) synthase inhibitors	Block production of NO, restore vascular tone
Inhibitors of leukocyte-adhesion molecules	Prevent endothelium-leukocyte interaction
Corticosteroids	Promote an anti-inflammatory response
Anti-inflammatory cytokines (IL-6, IL-10)	Inhibit inflammatory response; reduce production of proinflammatory cytokines

Immunotherapy

Since septic shock may be primarily the result of endogenous proteins and phospholipids synthesized by the patient, it has been hypothesized that diminution or elimination of the host response will lessen morbidity and mortality.[57,66] The hypothesis is currently being tested, but early results are discouraging.[59,66,100-104] Some of the experimental therapies and their therapeutic targets are listed in Table 9.

Despite the initial failure of immunotherapies, much knowledge has been gained.[103] The mechanisms of sepsis have been elucidated more clearly, and the roles of new cytokines in this process have been discovered. Better approaches to patient selection, subgroup analysis, and end point identification are being applied more uniformly. Our understanding of cytokine regulation, transcription, and translation is improving constantly. In the future, combination immunotherapies may be used and determined on a case-by-case basis. In addition, it is clear that earlier detection of patients at risk for sepsis ultimately may improve the efficacy of existing agents.

End Points of Shock Resusitation

The ability to treat shock properly requires a thorough understanding of the pathophysiology underlying the shock state and being able to identify standard end points for resuscitation, thus minimizing the morbidity and mortality associated with ongoing under-resuscitated shock. Even after decades of research, no one resuscitation end point has been identified which can consistently serve as a marker of adequate tissue perfusion and reestablishment of the homeostatic state.[105] The spectrum of resuscitation end points that have been studied range from the simplest, such as heart rate, blood pressure, urine output, central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), oxygen delivery (DO^2), oxygen consumption (VO^2), and lactate levels, to the more elaborate end points, such as near infrared spectroscopy (NIR), gastric tonometry, and more.[105,106] Currently, most physicians use a

combination of some or all of these factors as each of these end points has its associated advantages and disadvantages, and no single one has proven to be consistently accurate in defining an adequate resuscitation.

Clinical Examination

Traditionally, when blood pressure, heart rate, and urine output were used to define shock, the resuscitation was complete when these values were normalized. A positive response to volume administration includes a decrease in heart rate, correction of hypotension, and improvement in the warmth of extremities, the quality of peripheral pulses, the child's general color, and the briskness of capillary refill. In addition, the child's urine volume should increase. Hourly urine output and urine specific gravity measurements can serve as markers for response to volume resuscitation as these reflect renal perfusion. As shock is successfully treated, the child's level of consciousness should improve. If the child's neurologic function fails to improve or deteriorates during shock therapy, neurologic complication or inadequate resuscitation should be ruled out. Capillary refill and core-peripheral temperature gap may not correlate with measured hemodynamic variables and, therefore, their use as indicators of successful resuscitation may be limited.[7]

However, evidence of ongoing inadequate tissue perfusion may persist despite the normalization of blood pressure, heart rate, and urine output (compensated shock).[106] The body functions to preserve blood flow to the heart and brain until all compensation fails, while flow to other nonvital tissues, such as the skin, skeletal muscle, and splanchnic circulation remains diminished. Thus, under-resuscitation of the shock state allows cellular dysfunction to progress to cell death. Tissue death can lead to organ failure and subsequent multisystem organ failure can ultimately result in the patient's demise.

Bedside Hemodynamic Measurements

Several studies have looked at optimizing delivery and consumption of oxygen to improve outcome in critically ill patients.[105,106] Controversy remains, as some studies have shown significant decreases in patient's morbidity and mortality with optimization of oxygen delivery and consumption, while others have found no improvement.[105] The use of inotropes to raise oxygen delivery to improve patient outcomes has also remained an unclear area.

Another issue that complicates the use of oxygen delivery and consumption as end points of resuscitation is that measurements of systemic values may not reflect the true state of tissue oxygenation in all the organs at any given time. There may be microscopic areas of hypoxia while the majority of tissues are adequately perfused.

The search for better end points of resuscitation has led to a search for better markers of inadequate tissue perfusion. When looking at the body as a whole, base deficit and serum lactate levels have been identified as indicators of generalized hypoperfusion. Other researchers have looked for markers of inadequate regional tissue perfusion which perhaps could be more sensitive; foremost among these markers is gut mucosal pH, which can be approximated by using gastric or rectal tonometry. Other researchers are beginning to use NIR to evaluate oxygen delivery and consumption at the tissue level.

Base Deficit

One of the clinical signs of inadequate tissue perfusion is tissue acidosis. The magnitude of the metabolic acidosis, which has been shown to correlate with the amount of oxygen debt, can be estimated by the base deficit on an arterial blood gas. Base deficit is thus widely available and readily obtained even though it is only an approximation of global tissue acidosis, not directly measured.

Despite not being directly measured, there is work showing that serum lactate has a nearly stoichiometric relationship to base deficit and as such, an increase in the calculated base deficit may be a valuable indicator for shock.[106] To apply this clinically one must remain aware of other causes of metabolic acidosis that have nothing to do with shock or under-resuscitation (drug ingestions, iatrogenic hyperchloremia).

Experimental models of hemorrhagic shock have demonstrated that base deficit correlates with oxygen debt and survival better than cardiac output, systolic arterial pressure, and lactate.[105] Base deficit corrects more rapidly than lactate and correlates better with the amount of oxygen debt during resuscitation. Clinical studies have similarly found that the base deficit more accurately reflects the severity of oxygen debt compared to standard hemodynamic variables such as mean arterial pressure, mixed venous oxygen saturation, and arteriovenous oxygen difference. Davis and colleagues first reported that stratification of the base deficit into mild (-2 to -5), moderate (-6 to -14), and severe (< -15) correlated with the amount of crystalloid and blood replacement over the initial 24-hour period after trauma.[107] They also found that a worsening base deficit correlated with ongoing hemorrhage 65% of the time, concluding that despite appearance of stability, a patient who has an increasing base deficit requires a diligent evaluation for ongoing hemorrhage. Base deficit has also been found to correlate with survival after hemorrhagic shock.

Studies using laboratory values to predict fluid deficits in pediatric patients are scant. Teach and colleagues studied 40 children requiring fluid resuscitation and found that the laboratory values they targeted (serum blood urea nitrogen to creatinine ratio, total serum CO_2, serum uric acid, serum anion gap, urine anion gap, venous pH, venous base deficit, urine specific gravity, and fractional excretion of sodium) were poor predictors of fluid deficits.[108]

Despite the limitations mentioned, the data supports the use of the base deficit as an easily obtained, inexpensive, and useful guide to the magnitude of a physiologic insult and to the effectiveness of an ongoing resuscitation.

Serum Lactate

Anaerobic glycolysis results in the accumulation of hydrogen ions and pyruvate and generation of a very little ATP. In the absence of sufficient oxygen, pyruvate is converted to lactate. The lactate diffuses out of the cell and into the bloodstream. When lactate is released into the circulation it can probably be taken up and metabolized by most cells.[105] However, quantitatively the liver and kidney cortex are the most important organs

in lactate removal.

The association between serum lactate levels and hypovolemic shock and the relationship between lactic acidosis and death in critical illness have been well established.[105,106,109-111] In 1964, Broder and Weil correlated increasing serum lactate with increasing mortality.[110] They reported that only 11% of patients with lactate levels greater than 4 mmol/L survived circulatory shock. In addition, the time interval to normalize the serum lactate has been correlated to patient survival. In one such study, when the data was analyzed by the time to normalization of the serum lactate (≤ 2 mmol/L), they found 100% survival among patients if normalization occurred within 24 hours, 78% survival when normalized between 24 and 48 hours, and only a 14% survival if it took longer than 48 hours to normalize the serum lactate.[112] The usefulness of lactate as a prognostic variable has also been reported in septic patients.[70,71]

One should realize that lactate levels can increase with improved perfusion due to lactate washout. In addition, lactate levels can remain elevated even with completed resuscitation in the presence of unrecognized tissue death and, finally, splanchnic ischemia may be present in critical illness in the absence of increased blood lactate.[109]

In summary, an elevated serum lactate identifies patients at risk for development of organ failure and death. As a prolonged elevation of lactate is associated with a higher mortality rate, serial lactate levels are a useful guide to the adequacy of an ongoing resuscitation.

Gastric Tonometry

Both lactate and base deficit are global markers of the adequacy of tissue perfusion. However, blood flow is not uniformly distributed to all tissue beds. Therefore, even though the aggregate of all tissue beds may be normal, as measured by the global markers of lactate and base deficit, there may be regions with inadequate tissue perfusion. Consequently, it may be advantageous to have a regional marker for tissue perfusion. Of all the various tissue beds that can be monitored, the splanchnic bed or, more specifically, the gut mucosa is ideally suited. This mucosa is a region of the body that is among the first to be affected during shock and the last to be restored to normal after resuscitation.[113] The intramucosal pH of the gut lies within normal limits when there is adequate perfusion to the splanchic bed and falls below normal as perfusion becomes inadequate. Gastric intramucosal pH has been used as measurement for the adequacy of perfusion of the splanchnic bed as a whole.

Tissues that are inadequately perfused have an accumulation of hydrogen ions and carbon dioxide molecules, which lowers the tissue pH. The carbon dioxide produced by the mucosa of the intestinal tract diffuses into the gas and liquid present in the gut lumen and reaches equilibrium. This concentration of carbon dioxide can be measured by inserting a balloon of carbon dioxide permeable silicone attached to a gas-impermeable sampling tube (tonometer) into the gut, filling it with saline and allowing it to come into equilibrium. Once the mucosal PCO_2 is estimated by measuring the PCO_2 in the balloon; the pH may be calculated by the Henderson-Hasselbach equation. Clinically, the tonometer is placed in the same manner as a conventional nasogastric tube.

It is clear from a variety of studies that intramucosal pH of the gut is a good prognostic indicator; it is a slightly better predictor of mortality than either lactate or base deficit.[105,113,114] However, it is not clear if the use of gastric tonometry as a resuscitation end point results in lower morbidity and mortality.[105] The use of gastric tonometry during the acute resuscitation may not offer substantial benefits over the use of other less expensive, more easily obtained end points.

Near Infrared Spectroscopy

A technique that may be able to reflect the adequacy of oxygen delivery at the cellular level is near infrared (NIR) spectroscopy. Essentially, the probe emits several wavelengths of light in the near infrared spectrum (650-900 nm) that are able to penetrate tissue. These photons are then absorbed or reflected back to the probe. By measuring the various ratios of absorption and reflectance for several different wavelengths, a computer is able to determine the local arterial oxygen saturation, the local tissue oxygen saturation, and the redox state of cytochrome aa3, the terminal electron acceptor in the mitochondrial process of oxidative phosphorylation [105]

Constraints Upon Resuscitation

While a considerable amount of time and energy has been spent looking for end points of resuscitation that indicate adequate tissue resuscitation, there is also concern that resuscitation with excessive amounts of fluid may result in adverse consequences in some patients.[105,115] Patients with pulmonary or brain injury and patients with uncontrolled hemorrhage may not tolerate the massive fluid resuscitation that is sometimes required. In such situations, in order to avoid inadequate fluid resuscitation, the administration of fluid, whether isotonic or hypertonic, should be guided by every available method, including the measurements made possible by a pulmonary artery catheter.

Conclusion

The clinical syndrome of shock is one of the most dramatic, dynamic, and life-threatening problems faced by the physician in the emergency care setting. Although untreated shock is universally lethal, with proper recognition, diagnosis, monitoring, and treatment, the mortality may be considerably reduced.

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Physician CME Questions

22. A 4-month-old presents to the emergency department with a 24-hour history of fever, decreased oral intake, and progressive lethargy. On evaluation you find the following:

    Vital signs: HR 180, BP 112/71, RR 36, grunting is present, temperature 102.9°F, oximetry 95% with no supplemental oxygen.

    Physical: Lethargic infant with minimal response to painful stimulation. Fontanelle is bulging. Wandering eye movements, does not focus. Bilateral otitis media. Chest is clear to auscultation. Cardiovascular — no murmur, no gallop, poor peripheral perfusion, decreased peripheral pulses, prolonged (> 5 sec) capillary refill time, mottling. Abdomen is soft, no organomegaly, skin — no rash present.

Each of the following is appropriate in the diagnosis and management of this infant *except*?
   a. Obtain cultures of blood and cerebrospinal fluid.
   b. Establish vascular access using intraosseous needle if necessary.
   c. Provide a rapid fluid infusion (20 cc/kg) using D5.2 NS.
   d. Start third generation cephalosporin, consider vancomycin.
   e. Provide supplemental oxygen and prepare for intubation.

23. Each of the following is a hazard of aggressive crystalloid resuscitation in uncontrolled hemorrhagic shock *except*:
   a. disruption of a blood clot from a vessel injury.
   b. dilution of clotting factors.
   c. hemoconcentration.
   d. hemodilution.
   e. rebleeding.

24. Each of the following is an effect of isotonic crystalloids compared with colloids in fluid resuscitation of hypovolemic shock *except*:
   a. 2-4 times as much crystalloid compared with colloid must be infused to achieve the same physiologic end points.
   b. Crystalloids reduce colloid oncotic pressure and predispose to pulmonary edema.
   c. Crystalloid resuscitation has been associated with a lower mortality rate in adult trauma patients.
   d. The indications and use of albumin in critically ill pediatric patients has been carefully studied.
   e. Resuscitation with colloid solutions has been associated with an increase in the risk of mortality across a wide variety of clinical conditions requiring fluid resuscitation.

25. Physiologic effects of hypertonic saline include each of the following *except*:
   a. increased cardiac output and blood pressure.
   b. venoconstriction.
   c. reduced swelling of endothelial cells.
   d. vasoconstriction of the coronary vascular bed.
   e. less edema of uninjured brain.

26. The systemic inflammatory response syndrome (SIRS) is defined by abnormalities in each of the following *except*:
   a. blood pressure.
   b. temperature.
   c. heart rate.
   d. respiratory rate.
   e. white blood cell count.

27. Which one of the following statements concerning fluid resuscitation in septic shock is true?
   a. Colloid solutions are preferred solutions in septic shock resuscitation.
   b. Aggressive fluid resuscitation in the first hour reduces mortality in pediatric septic shock.
   c. Blood transfusion to maintain hemoglobin concentration greater than 10 g/dL is indicated.
   d. Proper fluid resuscitation eliminates the need for inotropic drug therapy.
   e. Because of increased vascular permeability, fluids must be restricted to prevent excessive accumulation of pulmonary extravascular fluid.

28. Which one of the following statements concerning pharmacologic therapy in septic shock is true?
   a. Use of inotropic drugs to achieve supraphysiologic oxygen delivery improves survival in pediatric septic shock.
   b. Corticosteroid therapy is contraindicated in septic shock.
   c. Milrinone has been shown to improve cardiovascular function in pediatric patients with hypodynamic septic shock.
   d. Norepinephrine should be avoided in septic shock because it causes renal dysfunction.
   e. Vasodilator drug therapy is contraindicated in the management of pediatric septic shock.

29. A 4-year-old child in septic shock remains hypotensive after aggressive fluid resuscitation. Which pharmacologic agent is most likely to improve his blood pressure?
   a. Milrinone
   b. Isoproterenol
   c. Dobutamine
   d. Renal dose dopamine
   e. Norepinephrine

In Future Issues: Pediatric Back Pain