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Shock in the Critically Ill Neonate

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Shock is a clinical disorder that challenges caregivers in the neonatal intensive care unit. Critically ill neonates may develop shock due to a variety of causes but the predominant cause of shock in neonates is sepsis. This article provides the neonatal nurse with basic knowledge of the pathophysiology and the types of shock seen in the critically ill neonate. Treatment and supportive care of the neonate in shock is determined by the underlying cause of shock with the ultimate goal of treatment being adequate perfusion of tissues to deliver oxygen to the cells and remove metabolic waste products. **Key words:** *hypotension*, *neonate*, *shock*, *treatment*

Shock is a complex cluster of clinical signs that results in death if not treated. Physiologically, oxygen and nutrient delivery to cells is inadequate to meet the needs of cellular aerobic metabolism and removal of metabolic wastes is impaired.[1,2] Consequently, anaerobic metabolism ensues, resulting in the accumulation of lactic acid. The buildup of lactic acid alters delivery of energy to cellular components resulting in a disruption of cellular pumps and pathways and an accumulation of sodium and calcium within the cell. The end result is cellular swelling, cell membrane breakdown, and cell death.[3,4]

Shock may result from an infection or from disorders of the heart, vasculature, or nervous system, or a combination of these. The incidence of shock in neonates is unknown; however, the incidence of sepsis in neonates, which often leads to shock, is between 1.9% and 21% with death rates between 10% and 18%.[5–7] Mortality due to shock in neonates is also difficult to ascertain but Watson reported mortality of 10.3% in neonates with sepsis and organ dysfunction.[8] This article provides the neonatal nurse with an overview of the causes of shock, classification of shock, and the management and goals of treatment. Newer treatments are also described.

CAUSES OF SHOCK

In order for adequate tissue perfusion to occur, cardiac output and vasomotor tone in vascular beds must be sufficient to deliver nutrient- and oxygen-rich blood to the tissues. Shock occurs when the blood volume in the vasculature falls to levels below that for which adequate blood flow to the tissues and cells is maintained. As a result, oxygen and nutrient delivery is not sufficient to nourish the cells and cellular metabolic wastes are not removed from the cells for excretion.[9,10] Although the end result of shock is cell death due to lack of nutrients and inadequate removal of cellular waste, the events leading to a state of shock may be due to cardiogenic, hypovolemic, and/or distributive or vasogenic causes.

CARDIOGENIC SHOCK

Cardiogenic shock is a consequence of myocardial cell injury that impairs the pumping ability of the myocardium. When myocardial contractility is impaired, oxygen delivery to tissues is reduced. Myocardial dysfunction may be due to direct myocardial cell injury, as seen in intrapartum asphyxia, or due to structural heart defects or cardiac arrythmias.[9] In neonates,

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myocardial cell toxicity is commonly the result of mediators and cytokines released during septic shock.[11] Children with septic shock have elevated troponin I levels with myocardial cell dysfunction, suggesting that these children experience a level of cardiogenic shock in addition to shock secondary to sepsis.[11] Little is known about the relationship between troponin levels and myocardial cell function in neonates.

Obstructive heart lesions are another common cause of neonatal cardiogenic shock. These lesions create cardiac dysfunction via mechanical obstruction of ventricular filling and/or emptying. Circulatory compromise due to obstructive cardiac lesions is caused by hypoplasia, stenosis, or atresia that decreases cardiac output and oxygen delivery to tissues.[12,13] Specifically, obstructive heart lesions that may lead to cardiogenic shock include coarctation of the aorta, aortic valvular stenosis, and interrupted aortic arch. However, signs of shock may not appear until the patent ductus arteriosis closes.[14] Pulmonary congestion and hypoperfusion develop upon closure of the patent ductus arteriosis and cause congestive heart failure and would progress to shock if left untreated. Treatment of cardiogenic shock resulting from an obstructive cardiac lesion is correction or palliation of the lesion causing the obstruction and is beyond the scope of this article.

HYPOVOLEMIC SHOCK

Hypovolemic shock is the most common type of shock seen in the neonate. It results from the depletion of intravascular blood volume due to fluid losses from hemorrhage or gastrointestinal losses or due to fluid shifts among the fluid compartments in the body.[3] The loss of intravascular volume leads to decreased cardiac output and decreased oxygen delivery to the tissues resulting in inadequate tissue oxygenation. Hemorrhage is the most obvious cause of hypovolemic shock and may be seen in neonates delivered to mothers with placental abruption or delivered with an umbilical cord tear. Internal fluid shifts that are not corrected may also lead to hypovolemic shock. For example, a neonate may experience plasma loss from the intravascular space into the interstitial space or into a closed cavity, such as the peritoneal or thoracic cavities. Fluid shifts between body fluid compartments may be referred to as "third spacing." "Third spacing" is used in clinical practice to describe the edema that results from fluid shifts between body fluid compartments.[3,4] It is a misnomer because technically, the body only has 2 major fluid compartments: (1) intracellular (inside the cell) and (2) extracellular. The extracellular fluid compartment has 4 components: (1) interstitial fluid, (2) plasma, (3) transcellular fluid, and (4) lymph.[10] The literature does not identify any of those components as a "third space." Therefore, nurses should avoid the use of this term when describing fluid shifts in neonates with shock.

DISTRIBUTIVE OR VASOGENIC SHOCK

Distributive shock is caused by abnormalities within the vascular bed that lead to vasodilation and pooling of blood, which decreases tissue perfusion. Abnormalities of autoregulation and vasomotor responsiveness create a maldistribution of peripheral blood flow.[15] Consequently, vital organs do not receive adequate blood flow if hypotension develops. The 3 types of distributive shock are neurogenic, anaphylactic, and septic.[3]

NEUROGENIC SHOCK

Neurogenic shock is characterized by hypotension and bradycardia, secondary to decreased sympathetic outflow as seen with spinal cord injury.[10,16] Decreased sympathetic activity in neurogenic shock leads to a lack of vascular tone and vasodilation with decreased tissue perfusion. Neurogenic shock is rare in neonates.

ANAPHYLACTIC SHOCK

Anaphylactic shock is the end result of hypersensitivity response to an environmental substance or agent. Rare in neonates, histamine, proteases, platelet-activating factor, leukotrienes, and other chemical mediators released in response to the environmental substance leads to widespread vasodilation, increased capillary permeability, fluid shifts into the interstitial space, severe hypotension, and circulatory collapse.[10,17] In addition to these massive fluid shifts, the bronchioles constrict and respiratory failure ensues. An individual suffering from anaphylactic shock must first be sensitized to the agent that leads to the release of chemical mediators. Sensitization occurs with the first exposure to the agent such as penicillin with anaphylaxis occurring at a subsequent exposure to the sensitizing agent.[17]

SEPTIC SHOCK

Septic shock is the third type of distributive or vasogenic shock. The inflammatory response to an infection may be exaggerated in septic neonates and cause a diffuse pathophysiologic reaction known as systemic inflammatory response syndrome (SIRS).[18] Hypotension and hypoperfusion ensue because of systemic

vasodilation and damage to endothelial vasculature respectively. This pathophysiologic response causes septic shock if not treated promptly.

In adults, *septic shock* is defined as hypotension secondary to sepsis that persists despite resuscitation with fluids or volume.[19] Although Dellinger et al[19] define septic shock in terms of blood pressure and treatment response, septic shock is a more complex syndrome involving organ dysfunction as well as hypotension. Sepsis, as it relates to shock, is defined as SIRS due to suspected or proven infection. SIRS includes (*a*) either an abnormal temperature or an abnormal white cell count, (*b*) tachycardia or bradycardia, and (*c*) tachypnea or mechanical ventilation.[20] This definition was developed by the "Surviving Sepsis Campaign" members. This particular definition is problematic when applied to neonates and children because (1) the definition was based on adult data and was developed for adults and (2) hypotension may or may not be associated with shock in these 2 groups. Thus a definition for pediatric patients was still needed.[20]

Goldstein et al[20] developed a revised definition of septic shock specifically for pediatrics, defined as sepsis and cardiovascular dysfunction. In an effort to clarify various processes leading to shock, definitions of pediatric SIRS, infection, sepsis, severe sepsis, and septic shock were developed.[20] These definitions were necessary because of the differences in physiology among neonates, children, and adults, largely due to different developmental processes that occur in neonates and children. Because of these age-dependent developmental differences, Goldstein et al[20] developed 6 age groups with age-specific normative values for vital signs and laboratory values. These age groups are newborn (0–7 days of life), neonate (1 week to 1 month of age), infant (1 month to 1 year of age), toddler and preschool (age 2–5 years), school-aged child (age 6–12 years), and adolescent/young adult (age 13 to <18 years). Septic shock in the pediatric patient, adopted by members of the International Pediatric Sepsis Consensus group, is defined as severe sepsis and cardiovascular dysfunction. Severe sepsis for the purposes of this definition is suspected or proven infection with SIRS.[20] Cardiovascular dysfunction is defined as hypotension and vasoactive drug therapy to maintain normotension plus at least 2 of the following findings: (1) unexplained base deficit of >5 mEq/L, (2) arterial lactate level >twice the upper normal value, (3) urine output <0.5 mL/kg/h, (4) capillary refill time >5 seconds, or (5) a core to peripheral temperature difference >3°C.[20] Unfortunately, the consensus document did not include normative data for newborns born at <37 weeks' gestation.

The use of the aforementioned definition of septic shock works well for the term neonate or young child but is problematic for the premature neonate in large part due to the definition of normal and abnormal blood pressure in these neonates. Normative blood pressure values are not available for the preterm neonate. In clinical practice, it is common for providers to use the preterm neonate's gestational age as a guide for mean arterial blood pressure but this value is rarely useful after the first day of life as it increases to 30 mm Hg or more by the third day of life.[2] Many other factors such as intravascular volume, myocardial function, adrenal response to stress, and vasomotor tone influence blood pressure in the preterm neonate. In addition, poor outcomes associated with low blood pressure are difficult to determine because of the many extraneous factors that influence them.[1,21] Oxygen delivery to cells is more dependent upon cardiac output and systemic blood flow than on blood pressure and a neonate may be hypotensive but still have adequate oxygen delivery. For these reasons, the use of blood pressure as part of the definition of septic shock is problematic in the preterm neonate.

The above definition of *shock* serves as a guideline for the practitioner, but shock will often be classified in other domains. Goldstein et al[20] recognized the classifications and presentation of shock in children but believed that the differentiation of shock into various presentations and classifications was beyond the scope of the consensus statement. However, for the purpose of this article, a brief mention and definition of these classifications is warranted.

OTHER CLASSIFICATIONS OF SHOCK

Warm vs. cold shock

Shock is divided into 2 phases: early and late shock. Each phase of shock is characterized by specific hemodynamic changes.[22] During the early phase of shock, also known as warm shock, there is peripheral vasodilation, tachycardia, and loss of vascular tone associated with low to normal blood pressure and increased systemic blood flow.[22,23] The extremities are warm, hence the term *warm shock*. Cold shock is the late phase of shock. During this phase, there is a reduction of myocardial contractility that leads to vasoconstriction, decreased systemic blood flow, decreased pulse volume, cold periphery, prolonged capillary refill time, and increased vascular tone. Low blood pressure is not seen initially in cold shock but eventually occurs if shock is left untreated.[4,22–24] On the basis of this classification of shock, Otieno and colleagues conducted a study

to evaluate an agreement among clinicians in assessing clinical characteristics of shock.[24] They reported only moderate agreement among clinicians for capillary refill time and weak pulse volume ($\kappa = 0.42$, $\kappa = 0.40$, respectively). Therefore, while the terms *warm shock* and *cold shock* are still seen in the literature, the use of these terms may not be appropriate in the clinical setting due to the subjective nature of the clinical definitions of shock.

Compensated, uncompensated, irreversible shock

Shock that is not recognized and treated early progresses from early to late stages, referred to as compensated, uncompensated, and irreversible shock. A neonate in compensated shock clinically presents with pallor, tachycardia, cool extremities, and capillary refill time more than 4 seconds. During this stage, the neonate's sympathetic reflexes preserve perfusion of the brain, heart, and adrenal glands. These homeostatic mechanisms will eventually become exhausted and the neonate will progress to uncompensated shock.[2]

Uncompensated or progressive shock is characterized by insufficient oxygen delivery to tissues to meet the demand and multiple organ dysfunction ensues.[2,3] Anaerobic metabolism occurs, lactic acid production increases, myocardial contractility is reduced secondary to metabolic acidosis, and the myocardium becomes poorly responsive to catecholamines. During this stage, inflammatory mediators are released leading to a cascade of metabolic abnormalities that further impairs tissue perfusion.[2] As uncompensated shock progresses, the endothelial cascade is activated and vascular dysfunction occurs, which leads to further release of cytokines and mediators and ultimately capillary leak.[25] Ultimately, irreversible shock occurs with irreversible and extensive damage to major organs despite restoration of adequate circulating blood volume.[2] The neonate exhibits signs of profound multiorgan system failure, is severely hypoxemic, and eventually develops refractory circulatory failure and dies.[3]

GOALS OF TREATMENT AND MANAGEMENT OF THE NEONATE IN SHOCK

The definitive goal, when managing a neonate in shock, is to treat the underlying cause of shock. While this is the main objective, prompt supportive treatment measures are necessary to restore blood flow and oxygen delivery to tissues so that perfusion and aerobic cellular metabolism are restored and preserved.[3] The therapeutic interventions chosen are dependent upon the type of shock present. Establishing and maintaining an airway for adequate ventilation and oxygenation is the first step in managing a patient in shock. Treatment of specific causes of shock is beyond the scope of this article but supportive therapies will be described.

Volume replacement

Neonates in shock often require volume replacement to maintain and/or restore adequate tissue perfusion. Inflammation develops in underperfused areas because of activation of the inflammatory process.[26] Inflammatory mediators are released and damage the vascular endothelium, which can result in large fluid shifts into the interstitial space causing severe hypovolemia. This decrease in intravascular volume will exacerbate shock if volume is not replaced. The amount and type of fluid used for volume replacement depends on the cause of volume depletion.

Volume expansion is accomplished with colloid, crystalloid, or various blood products in the event of hemorrhage. Crystalloids are inexpensive solutions of water with electrolytes added to approximate the mineral and electrolyte content of human plasma. They increase osmotic pressure. Normal saline and lactated ringers are 2 examples of crystalloid solutions used for volume expansion. Colloid solutions are similar to crystalloids in that they also contain minerals and electrolytes. The major difference is that colloids increase oncotic pressure and do not easily cross semipermeable membranes and therefore may remain in the intravascular space longer than crystalloids.[26] The colloid most commonly used for volume expansion is 5% albumin. Bolus doses (usually 10–20 mL/kg/dose) of colloids or crystalloids are used for volume expansion to treat shock.[27] However, there is a lack of consensus in the literature regarding which product is most effective at maintaining normal blood pressure.

The controversy over colloid vs. crystalloid to treat hypotension has existed for decades. A major concern is that using large volumes of crystalloids may cause the patient to develop pulmonary edema. One randomized trial compared normal saline to 5% albumin in the treatment of 41 neonates with hypotension.[28] The researchers found that both products were equally effective in restoring normal blood pressure. Neonates in both groups had similar increases in mean arterial pressure with 17/20 neonates in the saline group and 17/21 neonates in the albumin group having a sustained mean arterial pressure for a minimum of 30 minutes after treatment.[28] Lynch et al[27] conducted a similar comparison, using a sufficiently powered and blinded design. These investigators found a significant difference between the 2 groups in the percentage of neonates becoming normotensive after 1 fluid bolus (57% in the

albumin group and 32% in the saline group, $P < .05$); the duration of normotension after the second fluid bolus (15.2 ± 11 hours in the albumin group and 9.5 ± 10.5 hours in the saline group, $P < .05$); and the percentage of neonates requiring dopamine infusion (24.5% in the albumin group and 44.2% in the saline group, $P < .05$).[27]

In clinical practice, crystalloids have been used more extensively because they are inexpensive. In addition, there may be less fluid retention and the incidence of adverse effects (eg, intraventricular hemorrhage and infection transmission) may be lower with normal saline.[27,28] Alternatively, albumin may be more effective for volume replacement as it is less likely to leak into the interstitial space due to the large size of the albumin molecule.[26,28] Other reported advantages of albumin are the ability to use smaller volumes to achieve desired effects, more effective volume expansion and lower incidence of pulmonary edema.[29] These data illustrate the ongoing lack of clear evidence to support choosing one product over the other for volume replacement. Despite the ongoing controversy, providers must focus on the more important issue of treating shock in a timely, appropriate manner that is tailored to individual patient needs.

Pharmacologic therapies

A brief overview of the indications and uses of pharmacologic agents for the treatment of shock follows. A detailed discussion of the indications, mechanisms of action, and side effects of the pharmacologic therapies below is beyond the scope of this article. The reader is referred to recent publications for more in-depth discussions of these drug therapies.[9,29–31]

INOTROPES

Inotropic drugs increase cardiac output by increasing heart rate and/or myocardial contractility.[32] Use of inotropes is indicated when myocardial contractility remains compromised despite adequate volume replacement.[9] Medications in this group include dopamine, dobutamine, epinephrine, and norepinephrine. However, these drugs may not always be appropriate in treating shock because some of them increase systemic blood pressure by inducing vasoconstriction and that may be counterproductive if the aim of treatment is to improve tissue perfusion. For example, dopamine may increase blood pressure via vasoconstriction but a concurrent decrease in left ventricular output and superior vena cava flow without improvement in cardiac contractility has been demonstrated, thus diminishing the desired effect of improved tissue perfusion.[33–37] Therefore, when using inotopic drugs, it is prudent to be cognizant of the therapeutic endpoints desired. These endpoints include improved capillary refill time less than 2 seconds, equivalent and normal upper and lower extremity pulses, urine output more than 1 mL/kg/hour, and improved acid–base balance.[38]

GLUCOCORTICOIDS

Steroids are often used to treat shock when volume expansion and inotropes are ineffective; however, long-term clinical outcome data are lacking. Steroids raise blood pressure and improve tissue perfusion by increasing receptor sensitivity to endogenous catecholamines and blunting the inflammatory response.[31] Hydrocortisone and dexamethasone are the steroids most often used. Members of the Surviving Sepsis Campaign recommend using hydrocortisone for managing shock in children.[19] However, there is neither any specific recommendation for neonates nor any recommendations regarding the use of dexamethasone. Therefore, this discussion will focus on the use of hydrocortisone for the management of shock.

Hydrocortisone is lifesaving when adrenal insufficiency is suspected as the cause of catecholamine-resistant hypotension.[39] One randomized trial of 48, critically- ill, very low-birth-weight neonates found that neonates treated with low-dose hydrocortisone had higher mean arterial blood pressures and required significantly less vasopressor support and volume expanders.[40] The dose of hydrocortisone ranged from the "stress-dose" used in adrenal insufficiency of 1–2 mg/kg to the empirical shock dose of 50 mg/kg.[38]

There is a lack of consensus regarding what cortisol level is diagnostic of adrenal insufficiency in neonates. Langer et al[29] published a summary of studies on adrenal stimulation testing in critically ill neonates. Cortisol levels indicative of adrenal insufficiency ranged between less than 15 μg/dL (basal cortisol) to greater than 17 μg/dL after a cortisol stimulation test. In addition, the variability of basal and peak serum cortisol levels during the first 2 weeks of life makes it difficult to establish normal ranges.[41] More study of the use of hydrocortisone for the treatment of shock in neonates is needed specifically in the areas of efficacy, dose-response, and long-term outcomes.

NEWER THERAPIES

Newer therapies for the treatment of shock include the use of milrinone, vasopressin, and strict glycemic

control.[32] Each of these therapies will be briefly described.

Milrinone, a phosphodiesterase type III (PDE III) inhibitor, acts by inhibiting cyclic AMP degradation in the cardiac myocytes leading to increased cardiac contractility and cardiac output.[32,42] Reported uses of milrinone include administration to term infants and pediatric patients to improve cardiac function after cardiac surgery, and for treatment of septic shock in children.[43] However, there are limited data regarding the use of milrinone for treatment of shock in preterm infants. In an open-label pharmacokinetic study, premature neonates at risk for low superior vena cava flow were treated with different doses of milrinone.[42] The investigators found that neonates ($n = 10$) treated with a loading dose of 0.75 μg/kg/min for 3 hours followed by a maintenance dose of 0.2 μg/kg/min of milrinone maintained normal superior vena cava flow and only 3 neonates required treatment of hypotension. Conversely, neonates treated with 0.25 μg/kg/min ($n = 8$) and 0.5 μg/kg/min ($n = 11$) were observed to have low SVC flow and/or hypotension necessitating treatment with inotropes or hydrocortisone.[42] Although these findings are encouraging, caution must be used when considering milrinone to treat shock. Milrinone causes vasodilation due to its effects on the smooth muscle cells and neonates may need volume expansion or inotropic support during the therapy. Milrinone is primarily excreted in the urine, and if a neonate in shock demonstrates signs of renal compromise, toxicity may occur.[32] It may have a role in the treatment of shock with low cardiac output, although more study in the preterm neonate is needed.

Vasopressin is a naturally occurring hormone synthesized in the hypothalamus and stored in the posterior pituitary gland.[32,44] Endogenous arginine-vasopressin (AVP) is released from the hypothalamus in response to low blood pressure, decreased blood volume, and increased plasma osmolality.[32] Septic patients have lower plasma levels of vasopressin and are less sensitive to catecholamines. Consequently, they are prone to vasodilation and severe hypotension that may progress to catecholamine-refractory shock.[45]

Arginine-vasopressin and terlipressin (TP) are 2 forms of vasopressin that are indicated for rescue therapy in neonates and pediatric patients to treat catecholamine-refractory shock.[32,45] A study by Meyer et al[45] summarized the literature (17 studies) regarding the use of AVP and TP to treat catecholamine-refractory shock. The studies included patients from 23 weeks' gestation to 19 years old. Investigators in 8 studies used AVP and in 9 studies used TP. All researchers used either AVP or TP as rescue therapy for catecholamine-refractory shock. The administered dosage of vasopressin varied greatly among the studies. One hundred percent of the studies reviewed reported an increase in arterial pressure within 1 hour after administration, regardless of the medication given. Reports of decreased heart rate and increased urine output associated with the increased arterial pressure was not consistent across studies, but those findings were not based on the drug used. In the majority of the studies (76%), researchers noted a significant reduction in the need for inotropic medications. Mortality was high but the statistical significance of that finding could not be determined because of the heterogeneous study population. Survival rates may have been low due to the grave condition prior to drug administration.[45]

In a case series report of 6 extremely low-birth-weight neonates weighing less than 900 g with shock and acute renal failure unresponsive to catecholamines, volume, and hydrocortisone, rescue vasopressin was used.[46] The neonates' mean arterial blood pressure and urine output increased 2 hours after vasopressin administration, and serum lactate decreased in 2 of the 6 neonates with septic shock. Four of the neonates died, likely because of the severity of their underlying illnesses.[46]

In summary, the meta-analysis conducted by Meyer et al did not demonstrate a clear advantage of one drug over the other.[45] In the extremely low-birth-weight neonate, vasopressin did not appear to improve the outcome.[46] In addition, the appropriate time to begin therapy and start dose to use in neonates remains unclear. Finally, additional research is still needed to determine the safety and efficacy of AVP and TP use in neonates and children. Until that time, AVP and TP should be used only as a last resort to treat catecholamine refractory shock.[45]

A seminal work demonstrated that strict glycemic control significantly decreased mortality and morbidity in adult surgical patients with organ failure in the intensive care unit.[47] In one descriptive study of pediatric patients in septic shock, a glucose level of 178 mg/dL or more was associated with a 2.59 increased risk of mortality.[48] Other researchers noted a similar outcome in extremely low-birth-weight-infants who had glucose levels greater than 150 mg/dL.[49] Kashyap and Polin[50] conducted a prospective trial with 359 very low-birth-weight-infants to determine whether early insulin infusions to control glucose impacted morbidity and mortality. Although there was better control of hyperglycemia in the treatment group, neonates in that

group also experienced higher mortality.[50] The study was discontinued earlier than planned because of a higher incidence of cerebral ventricular dilatation and parenchymal lesions on cranial ultrasounds of neonates in the treatment group. These reports are encouraging, but the use of strict glycemic control in the preterm neonate presents many challenges. First, hypoglycemia is a far greater risk with the preterm neonate and has devastating effects. Second, the use of a continuous insulin infusion diminishes that amount of nutrients administered to the neonate and requires frequent blood sampling for glucose measurement. Until these types of issues are resolved, strict glycemic control in the treatment of neonates with sepsis, SIRS, and shock is not yet standard of care in the neonatal intensive care unit.

CURRENT RESEARCH

Research is ongoing to promote an in-depth understanding of the pathogenesis of shock. While much is known about the various types of shock, there is little understanding of the mechanisms that lead to the refractory hypotension and multiple organ dysfunction syndrome (MODS) that are responsible for significant morbidity and mortality in patients with anaphylactic and septic shock.[51,52] Identification of those mechanisms may facilitate discovery of specific treatments aimed at preventing those problems, thereby decreasing morbidity and mortality due to shock.

Recent studies found that production of nitric oxide (NO) is upregulated during the inflammatory process and may be the cause of refractory hypotension and MODS.[51–53] NO is an endogenous vasodilator that is produced in vascular endothelial cells and is involved in regulating vascular tone.[51–53] Nitric oxide stimulates production of cyclic guanosine monophosphate in vascular smooth muscle cells that causes smooth muscle relaxation.[54] A physiologic level of NO production is needed to relax the smooth muscles to ensure adequate blood flow for tissue perfusion. Endothelial nitric oxide synthase and inducible nitric oxide synthase are 2 types of NO enzymes that regulate NO production. When inflammation occurs, production of those enzymes increases, which causes a concomitant increase in production of NO. Excessive NO production causes widespread vasodilation and resistance to vasopressin, which leads to inadequate perfusion that may be the cause of cardiovascular collapse in septic and anaphylactic shock.[51,55]

The protein C (PC) pathway is one of the main pathways responsible for controlling the body's response to inflammation.[55] It diminishes the inflammatory response by interfering with metabolic processes that promote inflammation including migration of tumor necrosis factor alpha, migration of macrophages, and leukocyte adhesion to selectin.[55] Inflammation, if left untreated, causes PC levels to decline because of increased consumption and degradation, vascular leakage, and decreased hepatic synthesis. Low PC levels have been correlated with poorer outcome in pediatric patients with septic shock. PC replacement has been shown to improve patient outcome in adults, but results of current studies in children are inconsistent,[55] so PC replacement cannot be recommended for routine treatment of shock in pediatric patients.

CONCLUSION

The complex syndrome of shock may be due to cardiogenic, hypovolemic, and distributive or vasogenic causes and, if left untreated, results in cell death due to lack of nutrients and inadequate removal of cellular waste. An overview of the causes of shock, classification of shock, and the management and goals of treatment were presented with newer treatments described. For the neonatal nurse, the definition of shock in the neonate remains elusive because of the confounding difficulty in defining hypotension and ascertaining oxygen delivery adequacy in the hypotensive neonate. Blood pressure norms are needed for neonates of various gestational ages and noninvasive measures of oxygen delivery are needed to differentiate between the hypotensive neonate, the hypotensive neonate in shock, and the normotensive neonate in shock. The goal of treating the patient in shock is to eliminate the cause of shock; however, supportive therapy with volume replacement, inotropes, and glucocorticoids is necessary until adequate tissue perfusion is restored. Knowledge gleaned from recent research on the pathogenesis of shock is leading to the development of specific therapies to manage the devastating effects of widespread vasodilation and MODS that occurs in some types of shock. That knowledge is not yet applicable to humans because the subjects in most of those studies were mice. More research is needed in human subjects, establishing safety and efficacy of these new therapies before adopting them as standard treatment in clinical settings.

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