Shock and Hypotension in the Newborn

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Background: Shock is a complex clinical syndrome caused by an acute failure of circulatory function and is characterized by inadequate tissue and organ perfusion. When this occurs, inadequate amounts of oxygen and nutrient substrate are delivered to body tissues, and removal of metabolic waste products is inadequate. This results in cellular dysfunction, which may eventually lead to cell death. Failure of perfusion may involve isolated organs or the entire organism. Hypotension (ie, lower than expected blood pressure) frequently, but not always, accompanies shock.

Pathophysiology: Maintenance of adequate tissue perfusion depends on a combination of 3 major factors: (1) cardiac output; (2) integrity and maintenance of vasomotor tone of local vascular beds, including arterial, venous, and capillary; and (3) the ability of the blood to carry out its necessary delivery of metabolic substrates and removal of metabolic wastes.

Cardiac output is the product of heart rate and stroke volume. Neonatal cardiac output is more dependent upon heart rate than stroke volume; therefore, both very high (>160/min) and very low (<120/min) heart rates are likely to compromise cardiac output if prolonged, although not all infants with subnormal heart rates have impaired perfusion. At higher rates, ventricular filling time and end-diastolic volume are diminished, and myocardial oxygen consumption is increased. Because myocardial perfusion itself occurs during diastole, further increases in heart rate may produce undesirable cardiac ischemia and ventricular dysfunction. Stroke volume, the other major determinant of cardiac output, is influenced by 3 factors, which are preload, afterload, and myocardial contractility.

- Preload corresponds to the myocardial end-diastolic fiber length and is determined by the amount of blood filling the ventricles during diastole. Increases in preload increase stroke volume up to a maximum value, beyond which stroke volume falls according to the Starling Law.
- Afterload is the force that the myocardium generates during ejection against systemic and pulmonary vascular resistances (for the left and right ventricles, respectively). Reductions in afterload increase stroke volume if other variables remain constant.
- Contractility is a semiquantitative measure of ventricular function. An increase in contractility produces an increase in stroke volume if preload and afterload are unchanged.

- Clinically significant alterations in preload, afterload, and contractility may be achieved by the use of vasoactive pharmacologic agents, administration of inotropic agents, or changes in blood volume.

Blood flow to tissues and organs is influenced by their vascular beds, which are under the control of central and local vasoregulation, also referred to as autoregulation. This provides different organs with the ability to maintain internal blood flow over a wide range of arterial blood pressure fluctuations. When autoregulation is lost, blood flow becomes pressure passive, and this may lead to ischemic or hemorrhagic consequences. The biochemical mediators of vasomotor tone for each vascular bed are different, and their complex interactions are not yet fully understood.

The ability of the blood to impart delivery of oxygen and nutrients and to remove metabolic excretory products is largely determined by adequate lung ventilation and perfusion, oxygen-carrying capacity, and oxygen extraction by the tissues. Although each gram of hemoglobin can bind 1.36 mL of oxygen, fetal hemoglobin binds oxygen more tightly than adult hemoglobin and thus has a relatively reduced oxygen-unloading capacity at the tissue level. This results in a leftward shift of the oxygen-hemoglobin dissociation curve. Other factors that may also cause a significant leftward shift of this curve frequently accompany shock and include hypothermia and hypocarbia. Under these circumstances, oxygen extraction by tissues may be inappropriate despite adequate oxygen delivery.

Inadequate tissue perfusion may result from defects of the pump (cardiogenic), inadequate blood volume (hypovolemic), abnormalities within the vascular beds (distributive), flow restriction (obstructive), or inadequate oxygen-releasing capacity (dissociative). These are summarized in History .

Hypotension refers to a blood pressure that is lower than the expected reference range. Although normal physiologic range for the blood pressure, defined by the presence of normal organ blood flow, is not well studied in the newborn population, in clinical practice, the reference range blood pressure limits are defined as the gestational and postnatal age–dependent blood pressure values between the fifth (or 10th) and 95th (or 90th) percentiles. Usually, mean blood pressure rather than systolic pressure is used when judging the normality of data obtained from the indwelling arterial line because it is thought to be free of the artifact caused by resonance, thrombi, and air bubbles, but this may not always be true. Based on these data, the statistically defined lower limits of mean blood pressure during the first day of life are approximately numerically similar to the gestational age of the infant. However, by the third day of life, most preterm infants, even with 24-26 weeks' gestation, have a mean blood pressure of 30 mm Hg or greater.

A linear relationship exists between blood pressure and both gestational age or birthweight and postnatal age; however, only preliminary data are available on the gestational and postnatal age–dependent organ blood flow autoregulatory range and on the relation between blood pressure and systemic blood flow, cardiac output, and neonatal mortality and morbidity. Oxygen delivery to the tissues is influenced by cardiac output and blood flow more so than blood pressure, and, hence, values of blood pressure that are statistically abnormal are not necessarily pathologic. This is true for systolic, diastolic, and mean arterial blood pressures. Similarly, hypotension is not synonymous with shock, but it may be associated with the later stages of shock.

Frequency:

- In the US: The true frequency of neonatal shock is unknown because it is primarily a clinical syndrome.

Mortality/Morbidity: Shock remains a major cause of neonatal morbidity and mortality. Because shock is an accompaniment of other primary conditions, specific figures are unavailable. Morbidity as a consequence of end-organ injury and dysfunction is similar.

Race: No predilection based on race exists.

Sex: No predilection based on sex exists.

History: Many conditions and pathophysiologic disturbances are associated with shock and hypotension.

- Causes of neonatal shock include the following:

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    - Hypovolemic shock is caused by acute blood loss or fluid/electrolyte losses.
    - Distributive shock is caused by sepsis, vasodilators, myocardial depression, or endothelial injury.
    - Cardiogenic shock is caused by cardiomyopathy, heart failure, arrhythmias, or myocardial ischemia.
    - Obstructive shock is caused by tension pneumothorax or cardiac tamponade.
    - Dissociative shock is caused by profound anemia or methemoglobinemia.

- Risk factors for neonatal shock include the following:

    - Umbilical cord accident

    - Placental abnormalities

    - Fetal/neonatal hemolysis

    - Fetal/neonatal hemorrhage

    - Maternal infection

    - Maternal anesthesia/hypotension

    - Intrauterine and/or intrapartum asphyxia

    - Neonatal sepsis

    - Pulmonary air leak syndromes

    - Lung overdistension during positive pressure ventilation

    - Cardiac arrhythmias

Physical: Clinical manifestations of hypotension include prolonged capillary refill time, tachycardia, mottling of the skin, cool extremities, and decreased urine output. Give attention to heart sounds, peripheral pulses, and breath sounds.

The physical examination should carefully assess these factors, as well as accurately assess blood pressure. Measurement of neonatal blood pressure can be completed directly through invasive techniques or indirectly through noninvasive techniques. Invasive methods include direct manometry using an arterial catheter or use of an in-line pressure transducer and continuous monitor. Noninvasive methods include manual oscillometric techniques and automated Doppler techniques. A good correlation exists between mean pressures with some variability between systolic and diastolic pressures.

Causes: Shock is a progressive disorder, but it can generally be divided into 3 phases: compensated, uncompensated, and irreversible. Each phase has characteristic clinicopathologic manifestations and

outcomes, but, in the neonatal setting, distinguishing them may be impossible. Initiate aggressive treatment in all cases where shock is suspected.

- Compensated: In compensated shock, perfusion to vital organs, such as the brain, heart, and adrenal glands, is preserved by sympathetic reflexes, which increase systemic arterial resistance. Derangement of vital signs, such as heart rate, respiratory rate, blood pressure, and temperature, is absent or minimal. Increased secretion of angiotensin and vasopressin allows the kidneys to conserve water and salt, the release of catecholamines enhances myocardial contractility, and decreased spontaneous activity reduces oxygen consumption. Clinical signs at this time include pallor, tachycardia, cool peripheral skin, and prolonged capillary refill time. As these homeostatic mechanisms are exhausted or become inadequate to meet the metabolic demands of the tissues, the uncompensated stage ensues.

- Uncompensated

  - During uncompensated shock, delivery of oxygen and nutrients to tissues becomes marginal or insufficient to meet demands. Anaerobic metabolism becomes the major source of energy production, and production of lactic acid is excessive, which leads to systemic metabolic acidosis. Acidosis reduces myocardial contractility and impairs its response to catecholamines. Numerous chemical mediators, enzymes, and other substances are released, including histamine, cytokines (especially tumor necrosis factor and interleukin-1), xanthine oxidase (which generates oxygen free radicals), platelet-aggregating factor, and bacterial toxins in the case of septic shock. This cascade of metabolic changes further reduces tissue perfusion and oxidative phosphorylation.

  - A further result of anaerobic metabolism is the failure of the energy-dependent sodium-potassium pump, which maintains the normal homeostatic environment in which cells function. The integrity of the capillary endothelium is disrupted, and plasma proteins leak, with the resultant loss of oncotic pressure and intravascular fluids in the extravascular space.

  - Sluggish flow of blood and chemical changes in small blood vessels lead to platelet adhesion and activation of the coagulation cascade, which may eventually produce a bleeding tendency and further blood volume depletion. Clinically, patients with uncompensated shock present with falling blood pressure, very prolonged capillary refill time, tachycardia, cold skin, rapid breathing (to compensate for the metabolic acidosis), and reduced or absent urine output. If effective intervention is not promptly instituted, progression to irreversible shock follows.

- Irreversible: A diagnosis of irreversible shock is actually retrospective. Major vital organs, such as the heart and brain, are so extensively damaged that death occurs despite adequate restoration of the circulation. Early recognition and effective treatment of shock are crucial.

Lab Studies:

- Take the opportunity to sample blood for hematocrit, electrolytes, blood culture, and glucose as soon as vascular access is obtained.

- Among laboratory investigations, supportive data include metabolic acidosis in the face of reasonable oxygenation on an arterial blood specimen.

- Mixed venous blood gases may be more helpful because this reflects oxygen extraction and waste products at the tissue level, compared to arterial blood, which reflects lung function and the composition of blood before it is delivered to the tissues.

- Comparison of simultaneous arterial and mixed venous blood gas determinations may be more useful in assessing cardiac output, tissue oxygenation, and acid-base balance.

- The value of capillary blood gas determinations is severely limited because they may only reflect diminished perfusion to the periphery and not reflect central perfusion.

- Elevated plasma lactate with a normal pyruvate also suggests anaerobic metabolism triggered by tissue hypoxia-ischemia.

- Specific studies must be performed to rule out both the causes (eg, sepsis, cardiac lesions, anemia) as well as the sequelae (eg, renal, hepatic, endocrine) of shock.

Imaging Studies:

- Echocardiography and Doppler flow velocimetry may provide semiquantitative and semiqualitative noninvasive analysis of myocardial function.

- Automated Doppler provides blood pressure readings through a noninvasive method.

Other Tests:

- Manual oscillometric techniques for noninvasive blood pressure testing

Procedures:

- Infant blood pressure testing through invasive methods includes direct manometry using an arterial catheter or use of an in-line pressure transducer and continuous monitor.

Medical Care: Once shock is suspected in a newborn, appropriate supportive measures must be instituted as soon as possible. These include securing the airway and assuring its patency, providing supplemental oxygen and positive-pressure ventilation, achieving intravascular or intraosseous access, and infusing 20 mL/kg of colloid or crystalloid. Use of crystalloid or colloid solutions is appropriate, unless the source of hypovolemia has been hemorrhage, in which case whole or reconstituted blood is more appropriate.

Take the opportunity to sample blood for hematocrit, electrolytes, blood culture, and glucose as soon as vascular access is obtained. At this stage, attempt to determine the type of shock, eg, hypovolemic, cardiogenic, or maldistributive, because each requires a different therapeutic approach. In any neonate who is hypotensively compromised, the authors encourage the early use of a bladder catheter because hourly urine output is one of the few objective methods of evaluating specific organ failure and perfusion and it prevents the assumption that low urine output (which often happens in babies receiving narcotics) is always a problem.

Hypovolemic shock is the most common cause of shock in infancy, and the key to successful resuscitation is early recognition and controlled volume expansion with the appropriate fluid. (The Table below lists agents commonly used in the treatment of neonatal shock.) The estimated blood volume of a newborn is 80-85 mL/kg of body weight. Clinical signs of hypovolemic shock depend on the degree of intravascular volume depletion, which is estimated to be 25% in compensated shock, 25-40% in uncompensated shock, and over 40% in irreversible shock. Initial resuscitation with 20 mL/kg of volume expansion should replace a quarter of the blood volume. If circulatory insufficiency persists, this dose should be repeated.

Once half of the blood volume has been replaced, further volume infusion should be titrated against central venous pressure (CVP), if possible, measured through an appropriately placed umbilical venous or other central catheter. This requires careful interpretation because of inherent technical difficulties. In the

absence of CVP, titration against clinical parameters should be completed. Use of crystalloid or colloid solutions is appropriate, unless the source of hypovolemia has been hemorrhage, in which case whole or reconstituted blood is more appropriate. If blood is needed in an emergent situation, type-specific or type O (Rh negative) blood can be administered. Frequent and careful monitoring of the infant's vital signs with repeated assessment and reexamination are mandatory.

Cardiogenic shock usually occurs following severe intrapartum asphyxia, structural heart disease, or arrhythmias. Global myocardial ischemia reduces contractility and causes papillary muscle dysfunction with secondary tricuspid valvular insufficiency. Clinical findings suggestive of cardiogenic shock include peripheral edema, hepatomegaly, cardiomegaly, and a heart murmur suggestive of tricuspid regurgitation. Inotropic agents, with or without peripheral vasodilators, are warranted in most circumstances. Structural heart disease or arrhythmia often requires specific pharmacologic or surgical therapy. Excessive volume expansion may be potentially harmful.

The most common form of maldistributive shock in the newborn is septic shock, and it is a source of considerable mortality and morbidity. In sepsis, cardiac output may be normal or even elevated, but it still may be too small to deliver sufficient oxygen to the tissues because of the abnormal distribution of blood in the microcirculation, which leads to decreased tissue perfusion. In septic shock, cardiac function may be depressed (the left ventricle is usually affected more than the right). The early compensated phase of septic shock is characterized by an increased cardiac output, decreased systemic vascular resistance, warm extremities, and a widened pulse pressure. If effective therapy is not provided, cardiovascular performance deteriorates and cardiac output falls. Even with normal or increased cardiac output, shock develops. The normal relationship between cardiac output and systemic vascular resistance breaks down, and hypotension may persist as a result of decreased vascular resistance.

Newborns, who have little cardiac reserve, often present with hypotension and a picture of cardiovascular collapse. These critically ill infants are a diagnostic and therapeutic challenge, and sepsis must be presumed and treated as quickly as possible. Survival from septic shock depends upon maintenance of a hyperdynamic circulatory state. In the early phase, volume expansion with agents that are likely to remain within the intravascular space is needed, whereas inotropic agents with or without peripheral vasodilators may be indicated later. In early-onset neonatal sepsis, ampicillin and either gentamicin or cefotaxime are the antimicrobials of choice until a specific infectious agent is identified.

During and following restoration of circulation, varying degrees of organ damage may remain and should be actively sought out and managed. For example, acute tubular necrosis may be a sequela of uncompensated shock. Once hemodynamic parameters have improved, consider fluid administration according to urine output and renal function as assessed by serum creatinine and electrolytes and blood urea nitrogen concentrations.

Despite adequate volume restoration, myocardial contractility may still be a problem as a consequence of the prior poor myocardial perfusion, in which case inotropic agents and intensive monitoring may need to be continued. During the process of shock, production of chemical mediators may initiate disseminated intravascular coagulopathy (DIC), which requires careful monitoring of coagulation profiles and management with fresh frozen plasma, platelets, and/or cryoprecipitate. The liver and bowel may be damaged by shock, leading to gastrointestinal bleeding and increasing the risk for necrotizing enterocolitis, particularly in the premature infant. However, the extent of irreversible brain damage is probably most anxiously monitored following shock because the brain is so sensitive to hypoxic-ischemic injury once compensation fails.

In circumstances where volume expansion and vasoactive/inotropic agents have been unsuccessful, glucocorticoids, such as dexamethasone or hydrocortisone, have been shown to be effective. The findings that steroids rapidly up-regulate cardiovascular adrenergic receptor expression and serve as hormone replacement therapy in cases of adrenal insufficiency explain their effectiveness in stabilizing the

cardiovascular status and decreasing the requirement for pressure support in the critically ill newborn with volume- and pressure-resistant hypotension.

Surgical Care: Structural heart disease or arrhythmias often require specific pharmacologic or surgical therapy. The liver and bowel may be damaged by shock, leading to gastrointestinal bleeding and increasing the risk for necrotizing enterocolitis, particularly in the premature infant.

Consultations: Depending upon the type of shock, potential consultants might include the following pediatric subspecialists: neonatologist, cardiologist, nephrologist, infectious disease specialist, and hematologist.

Diet: Infants in shock should not be fed, and feedings should not be resumed until gastrointestinal function has recovered. Initiate total parenteral nutrition as soon as possible.

Drug Category:

1) Adrenergic agonists -- Cardiovascular performance deteriorates and cardiac output falls if effective therapy is not administered. These agents improve the hemodynamic status by increasing myocardial contractility and heart rate, resulting in increased cardiac output. They also increase peripheral resistance by causing vasoconstriction. Increased cardiac output and increased peripheral resistance lead to increased blood pressure.

2) Volume expanders -- Use of crystalloid or colloid solutions is appropriate, unless the source of hypovolemia is hemorrhage, in which case whole or reconstituted blood is more appropriate.

3) Antimicrobials -- In early-onset neonatal sepsis, ampicillin and either gentamicin or cefotaxime are the antimicrobials of choice, until a specific infectious agent is identified.

Further Inpatient Care:

- Infants recovering from neonatal shock are at risk for multiple sequelae and should be intensively screened for neurodevelopmental abnormalities, using brain imaging and brainstem audiometric evoked responses. Other tests are determined by the clinical course and complications.

Further Outpatient Care:

- Outpatient care should include neurodevelopmental follow-up testing and other studies as indicated by the neonatal course.

Transfer:

- Infants presenting with evidence of shock should be transferred immediately to a full-service neonatal intensive care unit with adequate support, personnel, and expertise.

Deterrence/Prevention:

- Early recognition and treatment is essential to maximizing outcome in neonatal shock.

Complications:

- Complications of neonatal shock are related to both the underlying cause (eg, sepsis, heart disease) and the injury sustained during the period of inadequate tissue perfusion. Frequent sequelae include pulmonary, renal, endocrine, gastrointestinal, and neurologic dysfunction.

Prognosis:

- Prognosis following neonatal shock is also related to both the underlying cause (eg, sepsis, heart disease) and the injuries sustained during the period of inadequate perfusion.

Patient Education:

- Parents should be informed of the risk for neurodevelopmental handicaps as well as the need for intensive follow-up care of both medical and neurologic problems.

Medical/Legal Pitfalls:

- The major medicolegal pitfall is delayed diagnosis and treatment, leading to permanent neurologic sequelae such as cerebral palsy, epilepsy, and mental retardation.

- Another potential pitfall is the misclassification of shock and subsequent inappropriate treatment.

- Failure to transfer an affected infant to a level III neonatal intensive care unit in a timely manner is another pitfall.

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