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## Multiorgan System Failure from Perinatal Asphyxia

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Perinatal asphyxia is one of the most devastating complications associated with the process of birth. Medical complications that arise from this condition affect not only the brain, but also many other organ systems critical for the maintenance of life. An increased understanding of the multifactorial nature of this disease will help all health care workers to improve care for patients with this condition.

Perinatal asphyxia or perinatal depression is a condition due to lack of oxygen resulting in impending or actual cessation of life around the time of birth. It is a common disorder with an incidence of 2-4 per 1000 term newborns. Both short and long-term outcomes for this disorder are very poor. Infants who present with hypoxic-ischemic encephalopathy secondary to perinatal asphyxia have a very high mortality with 15%-20% of these infants dying during the newborn period. Out of the survivors, over 25% have permanent severe neurological deficits.

The definition of perinatal asphyxia is complex and requires that all of the following criteria be met (AAP/ACOG Guidelines for Perinatal Care). 1) Presence of metabolic or mixed acidosis with a pH < 7.00 in the umbilical artery. 2) An Apgar score of 3 or less for longer than 5 minutes. 3) The presence of neurologic sequelae such as seizures, coma or hypotonia in the immediate neonatal period. 4) Multisystem organ dysfunction in one or more of the following systems: cardiovascular, gastrointestinal, hematologic, pulmonary, or renal.

There are numerous risk factors that allow a health care worker to anticipate the possibility of the delivery of an asphyxiated or depressed newborn. However, not all infants with these risk factors are depressed at birth. Still, there is an increased association of these factors with the need for neonatal resuscitation at birth. Some of the major antepartum factors associated with this risk include: maternal age > 35 yrs, maternal diabetes, pregnancy-induced hypertension, fetal anemia, bleeding in the 2<sup>nd</sup> or 3<sup>rd</sup> trimester, polyhydramnios, oligohydramnios, premature rupture of membranes, intra-uterine

infection, post-dates gestation, multiple gestation, small for gestational age or intrauterine growth restriction, maternal substance abuse, fetal malformations, decreased fetal activity and no prenatal care. Some of the major intrapartum factors associated with this risk include: emergency cesarean section, breech presentation, premature labor, prolonged rupture of membranes > 24 hrs, intrauterine infection, precipitous labor, prolonged labor > 24 hrs, prolonged 2<sup>nd</sup> stage of labor > 2 hrs, non-reassuring fetal heart rate patterns, general anesthesia, maternal analgesia with narcotics within 4 hrs of delivery, meconium stained amniotic fluid, prolapsed cord, placenta previa and abruptio placentae.

Multisystem organ dysfunction occurs from the lack of blood flow to the kidneys, liver and gastrointestinal tract in an initial attempt to preserve cerebral and cardiac blood flow. As this "dive reflex" begins to fail the cerebral and cardiac systems soon become affected. Organ failure ensues from the lack of oxygen delivery to the tissues as a consequence of hypoxemia—not enough oxygen in the blood or from ischemia—inadequate delivery of oxygenated blood to the tissues from low cardiac output or anemia. Multiple organ systems are affected by perinatal asphyxia with 82% of neonates incurring injury to one or more organs. These include the brain (72%), kidneys (42%), lungs (26%), heart (29%), bone marrow (<20%), bowel (29%), and liver (<20%).

### Brain—Hypoxic Ischemic Encephalopathy (HIE)

Hypoxic ischemic encephalopathy is the neurologic injury that results from the lack of oxygen delivery to the brain. HIE presents with the following clinical signs: apnea, seizures, jittery or hyper-alert behavior, hypotonia, lethargy, obtunded or comatose state, and loss of cranial nerve function including an absent suck, swallow or gag. The patient can also present with hypotension from an intracranial hemorrhage or hypertension from cerebral edema or seizures.

Evaluating the severity of the neurologic insult from hypoxic ischemic encephalopathy with the criteria from Sarnat is a very useful tool for prognosis. In the Sarnat Stages, a poor outcome is defined as mental retardation, cerebral palsy, chronic seizures, or death.

Sarnat Stages of HIE (*Arch Neurol* 33:696, 1976)

- Stage 1 (Mild)
  - Hyper-alert, irritable, jittery, lasts < 24 hours
  - normal EEG: < 1% poor outcome
- Stage 2 (Moderate)
  - lethargic, obtunded, hypotonic with flexion
  - seizures variable - multifocal on EEG
  - lasts > 24 hours: 20 - 40% poor outcome
- Stage 3 (Severe)
  - comatose, stuporous, flaccid, seizures
  - decorticate or decerebrate posturing, absent suck
  - EEG - periodic discharges or isopotential
  - lasts > 5 days: 100% poor outcome

The initial stabilization of an infant with HIE from perinatal asphyxia includes the following steps. Maintain normal ventilation. It is important to avoid low PaCO<sub>2</sub> secondary to further risk of cerebral ischemia from decreased cerebral blood flow. Diagnose and treat seizures. An EEG can help to guide diagnosis, therapy and prognosis. Ativan, phenobarbital and phenytoin should be considered for treatment of seizures, always watching closely for apnea as a side effect of therapy. Maintain normal glucose levels. Hypoglycemia can cause neurologic injury and hyperglycemia can worsen neurologic outcomes after HIE. Maintain normal blood pressure to ensure adequate cerebral blood flow. Obtain head imaging studies (head ultrasound, CT scan or MRI) to rule out intracranial hemorrhage, to detect cerebral edema or ischemia and to establish a baseline for long-term follow-up.

### Treatment of Perinatal Asphyxia

There have been many therapies used to treat perinatal asphyxia, but few have been successful at preventing neurologic injury. Trials focused on reducing cerebral edema through the use of diuretics (furosemide or mannitol) or steroids were not successful. The use of a drug-induced coma with barbiturates to reduce metabolic demand has also failed except for one small study with high-dose phenobarbital that demonstrated more normal neurological outcomes, 10/15 vs 3/16 controls, but this study has never been replicated. Because of the lack of success of pharmacotherapy in treating this condition the use of hypothermia has been recently reexamined.

### Hypothermia for the Treatment of Perinatal Asphyxia

Hypothermia with cooling of the body to 27°C in a cold-water bath as a treatment for perinatal asphyxia was reported to improve survival with normal outcomes in a series of cases from the 1950's and 1960's. However, enthusiasm for hypothermia as a therapy was abandoned after widespread dissemination of the results of a controlled trial of hypothermic room temperature incubators (28.9°C) vs normothermic incubators (31.7°C) in premature infants which indicated decreased survival.

In the 1980's, hypothermia during cardiac surgery was shown to be beneficial. Systemic cooling down to 16°-24°C in older infants was found to protect the brain from ischemic injury for up to 90 minutes during cardiopulmonary bypass. These studies led to increased animal research using hypothermia to prevent neuronal injury. Multiple studies showed that selective cooling of the brain by 6°C in neonatal rats, newborn pigs, and fetal sheep reduce neuronal loss and neurological injury. The above studies led to a reevaluation of the neuroprotective effects of hypothermia.

In 2002 trials of therapeutic hypothermia (32-34°C) for cardiac arrest after ventricular fibrillation were shown to significantly improve survival and neurological outcome in adults. However, neonatal trials of hypothermia for perinatal asphyxia have not been as clear. In 2004 the first multicenter randomized controlled trial of selective head cooling for perinatal asphyxia was reported. This study enrolled 234 infants within 6 hours of birth with an umbilical artery pH < 7.1 or Apgar score < 6<sup>5</sup> with HIE. The brain was cooled by circulating water at 10°C through coils of tubing in a head cap for 72 hours leading to a drop in rectal temperature to 34.5°C. There was no difference found in the incidence of death or severe disability. However, when subcategorized by severity of EEG before entry, the intermediate severity group did show a significant benefit from cooling, with adverse outcomes reduced from 66% to 48%, and neuromotor disability from 28% to 12%. There were no adverse effects seen from cooling to this level.

In 2004 a second multicenter randomized controlled trial of hypothermia for perinatal asphyxia was reported, except in this trial whole body cooling (33.5°C for 72 hours) instead of selective brain cooling was used. This study enrolled 208 infants within 6 hours of birth with an umbilical artery pH < 7.0, base deficit > 16 or HIE. There was no difference in mortality or adverse events between groups and the neurodevelopmental outcomes have not yet been reported. A consensus has not yet been reached regarding the use of hypothermia for perinatal asphyxia and thus the use of brain cooling for this condition remains experimental.

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## Renal Complications Associated with Perinatal Asphyxia

The kidney is the second major organ after the brain that is most commonly affected by perinatal asphyxia. Newborns who suffer from perinatal asphyxia often develop oliguria and acute renal failure from acute tubular necrosis (ATN). Anticipation of acute renal failure after perinatal asphyxia has occurred is critical to the prevention of complications such as hyponatremia from fluid overload. Fluid intake and output need to be strictly monitored (consider the use of a urinary catheter) and follow electrolytes closely watching for hyponatremia or hyperkalemia.

Therapy for acute renal failure involves volume resuscitation with normal saline to restore blood pressure and adequate circulating volume, then fluid restriction to avoid fluid overload. Restricting to 50-60 cc/kg/day of D10W with 1/2 NS allows adequate glucose intake with an appropriate sodium intake of 4 Meq/kg/day. Potassium intake should be restricted or avoided until normal urine output returns. Kayexalate should be used early for hyperkalemia. Low dose dopamine should be considered in an attempt to improve renal blood flow. Anticipate the possibility of gross hematuria from ATN and consider a renal ultrasound to rule out renal vein thrombosis. Follow BUN, Cr and gentamicin levels closely. Acute renal failure from perinatal asphyxia tends to be transient with recovery usually within a week.

## Pulmonary Complications Associated with Perinatal Asphyxia

The most serious pulmonary complication associated with asphyxia is the development of persistent pulmonary hypertension of the newborn also known as persistent fetal circulation (PFC). Pulmonary hypertension is caused by a hyper-reactive labile pulmonary vascular bed, which easily undergoes vasoconstriction. Pulmonary vasoconstriction causes a return to fetal circulation with right to left shunting through either the ductus arteriosus or the foramen ovale leading to inadequate pulmonary blood flow. The end result is a newborn with severe cyanosis and life-threatening hypoxic respiratory failure.

Newborns with perinatal asphyxia have a very reactive pulmonary vasculature so to minimize their risk of PFC it is important to keep them adequately oxygenated (saturation > 95% or PaO<sub>2</sub> 70-150 mm Hg). Acidosis also leads to pulmonary vasoconstriction so treat both respiratory and metabolic acidosis and keep the pH and PaCO<sub>2</sub> within normal limits. Infants with PFC have labile oxygenation so it is important to minimize any excess environmental stimulation including noise, light and rough handling. Sepsis can lead to both perinatal asphyxia and PFC, so it is important to always

consider this possibility and start asphyxiated patients on antibiotics when indicated.

If pulmonary hypertension worsens and does not respond to standard therapies inhaled nitric oxide (NO) should be considered. The major concern with using inhaled NO as a pulmonary vasodilator for PFC is that the risk for NO failure, requiring rescue by ECMO is 38%. Furthermore, the abrupt stopping of NO can often lead to a life-threatening deterioration with worsening oxygenation from increased pulmonary arterial pressure. Thus, if ECMO is not available, having the ability to transport the patient while still on inhaled NO to an ECMO center becomes critical!

## Cardiac Complications Associated with Perinatal Asphyxia

The heart can be affected in numerous ways from ischemic injury associated with perinatal asphyxia. Hypotension is often the first manifestation of cardiac dysfunction due to poor contractility. Cardiogenic shock or heart failure can result in pulmonary edema, which is often worsened from concurrent fluid overload associated with renal failure. Rhythm abnormalities can occur. An EKG and especially an ECHO are very useful for diagnosis of many of the above problems. Hypotension can also result from asphyxia causing capillary leakage, which in turn leads to inadequate intravascular volume.

Treatment of hypotension depends on the cause. Volume resuscitation with normal saline should be given if preload or intravascular volume is inadequate. Inotropic agents such as dopamine, dobutamine or milrinone should be started if cardiac function is poor. The use of stress doses of hydrocortisone should also be considered for the treatment of hypotension associated with asphyxia, especially in patients who have a poor response to inotropic agents.

## Hematologic Complications Associated with Perinatal Asphyxia

Bleeding abnormalities often occur after perinatal asphyxia. Thrombocytopenia can result from either reduced platelet production or increased consumption and the remaining platelets may have poor function. Bone marrow suppression can occur from asphyxia with decreased production of red blood cells and platelets. Perinatal asphyxia can lead to a chain of events from severe acidosis, hypoxia, or endothelial damage to consumption of coagulation factors resulting in diffuse intravascular coagulation (DIC).

Not only is there increased consumption of clotting factors with asphyxia, but decreased production as well from liver dysfunction and bone marrow suppression. The end result is a prolonged PT and PTT, decreased

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levels of fibrinogen and low platelets. Together these clotting abnormalities often lead to severe bleeding complications such as pulmonary hemorrhage or intracranial hemorrhage or can result in either hematuria or hematochezia. Neutropenia can be present secondary to sepsis that may have precipitated the asphyxia or from bone marrow suppression. Anemia is often present from blood loss associated with the etiology of the perinatal asphyxia such as abruption, fetal-maternal hemorrhage or intracranial hemorrhage.

It is important to monitor for and anticipate the possibility of bleeding disorders associated with asphyxia. Treatment involves the use of blood products such as fresh frozen plasma, cryoprecipitate or even activated Factor VII for severe cases of DIC. Platelet transfusions are often needed when there is bleeding in the presence of thrombocytopenia (platelet count < 50,000-100,000). In an emergency it may be necessary to give uncross-matched O negative blood to prevent cardiovascular collapse from an acute hemorrhage.

### **Gastrointestinal Complications Associated with Perinatal Asphyxia**

Ischemic injury can lead to both hepatic and intestinal dysfunction. Liver injury can be detected through abnormal liver function tests such as the ALT. Synthetic damage can be directly assessed by serum albumin levels and indirectly by coagulation factors. Bilirubin levels both total and direct can be elevated and an elevated GGT level also points to cholestatic injury.

There is an increased risk of necrotizing enterocolitis (NEC) from a lack of gut perfusion from perinatal asphyxia. NEC is often manifested by abdominal distention and tenderness along with hematochezia (grossly bloody stools). To minimize this risk, it is important to keep patients with significant asphyxia, NPO for at least 48-72 hours. Furthermore when feeds are initiated, advance slowly and observe for signs of feeding intolerance.

### **Metabolic Complications Associated with Perinatal Asphyxia**

Significant metabolic derangements will occur in patients suffering from perinatal asphyxia. Thermoregulation can be impaired in these patients leading to problems in maintaining a stable core temperature. A major hallmark of hypoxic-ischemic injury is the pres-

ence of a lactic acidosis from the lack of oxygen delivery to the tissues. An elevated lactate can be a marker of tissue ischemia and trends in lactate levels can be useful in interpreting the patient's response to therapy. It is important to correct both the initial cause of the hypoxia-ischemia as well the subsequent metabolic acidosis. A prolonged acidosis can lead to a negative feedback loop with poor cardiac function causing poor perfusion, resulting in more tissue ischemia from inadequate oxygen delivery leading to a worsening metabolic acidosis, again causing poor cardiac function until death. Thus, it is important to break this cycle of poor cardiac output. A metabolic acidosis can also worsen pulmonary hypertension, which can lead to increased hypoxia and poor oxygenation, which can set up another cycle of inadequate oxygen delivery worsening the acidosis, which in turn increases pulmonary hypertension which caused the hypoxia and so forth. Thus, it is important to break the cycles of acidosis that worsen both cardiac output and pulmonary hypertension.

Hypoglycemia is a very common finding in patients suffering from perinatal asphyxia and it should be anticipated. This is a significant emergency and needs to be quickly treated with an IV push of 2 cc/kg of D10W followed by a maintenance glucose infusion of 5 mg/kg/min of dextrose. At the same time, avoid hyperglycemia, which has been shown to worsen hypoxic-ischemic brain damage. The possibility of hypocalcemia should be considered, especially if either hypotension or arrhythmias occur. One of the most common complications from asphyxia is hyponatremia from acute renal failure in the face of fluid overload from normal maintenance fluids. Again, fluid restriction (50-60 cc/kg/day) needs to be implemented for patients with perinatal asphyxia to minimize the development of hyponatremia.

### **Conclusion**

Perinatal asphyxia is the end result of a significant degree of global hypoxia-ischemia during the time of birth. Lack of oxygen delivery from this episode often leads to multiorgan failure. A multisystem approach to the management of perinatal asphyxia will help to minimize the high morbidity and mortality associated with this devastating condition.

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