K. PERINATAL DEPRESSION AND ASPHYXIA

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PERINATAL DEPRESSION AND ASPHYXIA

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DEFINITIONS AND SIGNIFICANCE

Asphyxia literally means "no pulse," which implies depression of heart action and collapse of the circulation. However, a broader definition of asphyxia includes respiratory dysfunction and impaired gas exchange. Both aspects of the condition lead to (1) *hypoxia*, or reduced availability of oxygen, (2) *anoxia*, or total lack of oxygen, and (3) *hypercarbia*, or inability to adequately eliminate carbon dioxide. Perinatal asphyxia is the occurrence of hypoxia or anoxia and hypercarbia during labor, delivery or the immediate newborn period resulting from inadequate perfusion or gas exchange through the maternal, placental, fetal, or neonatal circulations. Common usage of the term "perinatal asphyxia" frequently makes it synonymous with fetal distress, whereas "neonatal asphyxia" (or asphyxia neonatorum) more specifically relates to hypoxia or anoxia and hypercarbia in the newborn infant. From a clinical standpoint, the initial most striking feature of neonatal asphyxia is delayed onset of breathing at birth, followed by difficulty in making all of the physiologic transitions from intrauterine to extrauterine life (see below).

Further illustrating the distinction yet interconnection between the cardiovascular and respiratory aspects of asphyxia are the two following categories of hypoxia that can occur during asphyxia:

- *Anoxic hypoxia*, signifying low oxygen tension in the blood, whether due to low oxygen concentrations in the environment or some problem with gas exchange at the maternal lung, placenta, or neonatal lung level, and
- *Ischemic (stagnant) hypoxia*, signifying poor tissue perfusion, and resulting in reduced oxygen delivery to the tissues and accumulation of waste products.

After prematurity and birth defects, perinatal asphyxia represents the next most frequent cause of morbidity and mortality arising from the birth experience. If allowed to occur during delivery of the premature or defective infant, perinatal asphyxia will greatly influence the outcome of these groups of patients as well. Of critical importance is the realization that the vast majority of injury and death due to perinatal asphyxia can be avoided through anticipation, preventative measures taken, or timely resuscitation (see section on Resuscitation of the Asphyxiated Newborn).

ANTICIPATION AND PREVENTION

Anticipation of perinatal depression and eventual asphyxia allows time to make preparations to handle the emergency and for early intervention when countermeasures can be less invasive or extensive and are more likely to be effective. The required personnel can be called in, the appropriate equipment and supplies assembled, and action assignments made in advance. Early interventions following precise awareness of when hypoxic-ischemic injury is imminent are key for prevention of morbidity and mortality in this situation.

Causes of perinatal depression and/or asphyxia that can be largely anticipated or quickly identified are listed in Table 1. These result in inadequate blood flow (on either side of the placenta for the fetus, and in the systemic or pulmonary circulation of the newborn) or insufficient gas exchange (through the lungs of the mother or placenta for the fetus, and through the lungs or in the tissues of the newborn).

PATHOPHYSIOLOGIC MECHANISMS

It helps to think of asphyxiating processes as falling into one of two categories:

- *Mechanical problems*, such as maternal vascular disease affecting blood flow to and through the placenta, or cord accidents during labor and delivery, or airway obstruction in the newborn due to meconium aspiration, and
- *Metabolic problems*, such as hypoxemia with associated acidosis and hyperkalemia (see below); CNS depression of the mother, fetus, or newborn due to drugs; or blood sugar (and other metabolic)

abnormalities associated with maternal diabetes (see section on Maternal Diabetes and the Infant of the Diabetic Mother).

Table 1. Causes of Perinatal Depression and/or Asphyxia

Maternal Causes

Reduced oxygen content of the blood flowing to the placenta:

- Maternal hyperemia due to cyanotic heart disease, heart failure, or severe lung disease (either acute, as in pneumonia, or chronic, as in COPD).
- Anemia (HgB, 10 g/dl or Hct, 30%).
- Abnormal hemoglobin or reduced oxygen binding in hemoglobin, as in methemoglobinemia or high carboxyhemoglobin level associated with heavy smoking (see section on Maternal Smoking).

Reduced blood flow to the placenta:

- Maternal cardiac insufficiency.
- Vascular disease, such as lupus, advanced diabetes, preeclampsia.
- Hypotension due to hypotensive agents, hyperventilation, or regional anesthesia received or experienced during labor or delivery.
- Compression of the aorta and vena cava by the uterus.
- Prolonged or tetanic contractions of the uterus, for example, by excessive use of Pitocin.

Placental or Cord Causes

Impaired perfusion or diffusion:

- Placental insufficiency due to vascular disease, infarcts, edema, inflammation, postdatism, etc.
- Partial or total placental separation or abruption.
- Placenta previa.
- True knot in the cord.
- Cord prolapsed and compression.
- Entangled cord.

Neonatal Causes

Depression of the respiratory center of the neonate:

- Passage of depressant drugs across the placenta.
- Congenital malformations of the brain involving the respiratory centers or exerting pressure on brainstem.
- Intracranial hemorrhage or cerebral contusion (e.g. due to birth trauma) resulting in increased intracranial pressures affecting the respiratory centers.

Restriction of lung expansion in the neonate:

- Hypoplastic lungs associated with oligohydramnios (as in Potter's syndrome or chronic leakage of amniotic fluid), diaphragmatic hernia, asphyxiating thoracic dystrophy, congenital hydrops (with pleural effusions or massive ascites restricting lung expansion or descent on the diaphragm).
- External restriction of lung expansion associated with pulmonary interstitial emphysema or lung fibrosis (e.g. bronchopulmonary dysplasia).

Obstruction of airflow into the neonatal lungs:

- Meconium aspiration.
- Congenital malformations of the upper airway (e.g. choanal atresia, laryngeal web, bronchial cyst).
- Tracheal malacia.

Reduction of blood flow through the neonatal lungs:

- Congenital heart disease with right outflow obstruction such as pulmonary stenosis or atresia.
- Persistent fetal circulation or pulmonary vascular obstructive disease.

Table 1 Continued:

Labor and delivery factors that may predispose to or be indicative of perinatal asphyxia include the following:

- Prolonged labor especially prolonged 2nd stage.
- Cord prolapse or entanglement.
- Excessive vaginal bleeding (e.g. placenta previa, abruptio placenta).
- Meconium staining of the amniotic fluid (see section on Postdatism).
- Abnormal presentation (e.g. occiput posterior, breech, etc.).
- Abnormal fetal heart tone patterns (see section on Intrapartum Fetal Monitoring).
- Cesarean delivery before a gestational age of 37 weeks.

Groups of infants predisposed to neonatal asphyxia (or anticipated to be at high risk for the condition) include the following:

- Preterm infants, especially twins or those born by cesarean delivery.
- Growth restricted infants (see sections on Intrauterine Growth Restriction and Small For Gestational Age Infant).
- Postterm pregnancies (see section on Postdatism).
- Multiple births (twins, triplets, etc.).
- Large for gestational age (LGA) infants with prolonged labor or difficult, traumatic delivery.
- Infants with birth defects (see section on Birth Defects).

For the fetus and newborn, the two basic problems associated with asphyxia are its effects on blood flow distribution to the various organs of the body and its effects on cellular integrity. Asphyxia causes "centralization" of the circulation, which results in increased or preferential blood flow to crucial organs such as the heart and brain (supplied by preductal branches off the aorta) and decreased blood flow to the less-essential organs such as the intestines, liver, kidneys and lungs. The lung may indeed be unessential for immediate survival of the newborn. Any organ deprived of blood flow may later pay a price for this centralization of the circulation in the form of hypoxic-ischemic damage and dysfunction (see below). Even in the "protected" organs there may be tissue damage in so-called "watershed" areas, i.e., those regions situated at the extreme end of arterial blood supply. This explains the development of papillary muscle necrosis in the heart and parasaggital damage to the cerebral cortex in cases of severe perinatal asphyxia.

Asphyxia impacts on cellular integrity by compromising cell membrane function and the cell's ability to maintain concentration gradients for key substances by active transport into or out of the cell. As a result, sodium ions intrude into the cell, while potassium and calcium ions and protein tend to leak out. This accounts for much of the cellular and organ dysfunction or destruction seen after asphyxia, clinically presenting as post-asphyxic complications (see below).

The physiologic processes involved in normal transition from intrauterine to extrauterine life are strongly influenced by asphyxiating events. These processes normally begin before the fetus is born at term but rarely occur at or shortly after birth. Although all major organ systems are involved, the focus is on the lungs, heart, and circulation. The more important of these processes, the factors most responsible for their happening, and the effects of perinatal asphyxia upon them are listed in Table 2.

A number of the pathophysiologic mechanisms involved with perinatal asphyxia represent "vicious circles" or self-perpetuating, ever-worsening situations:

- Perinatal asphyxia results in pulmonary vasoconstriction → alveolar hypoperfusion → deficient supply of nutrients to the alveolar cells → reduced metabolism and surfactant synthesis → surfactant deficiency and alveolar atelectasis → reduced alveolar gas exchange further hypoxemia and acidosis → more pulmonary vasoconstriction, etc., etc.

- Pulmonary vasoconstriction means also increased pulmonary vascular resistance → increased right-to-left shunting through the foramen ovale and ductus arteriosis → venous admixture, with systemic hypoxemia and acidosis → further pulmonary vasoconstriction, etc., etc.
- Delayed onset of respirations due to the CNS depression associated with asphyxia → reduced placental transfusion at birth → hypovolemia and hypotension reduced perfusion even of the brain → more CNS and respiratory depression, etc., etc.
- Reduced contractility of the heart resulting from hypoxia and acidosis → lower cardiac output and distal tissue perfusion tissue hypoxia and acidosis → further reduced contractility of the heart, etc. etc.

The challenge of resuscitation is to reverse these spiraling events (see section on Resuscitation of the Asphyxiated Newborn and Management of Post-Asphyxic Compilations). It is known from clinical experience that the sooner any of these vicious circles can be interrupted the easier it is to reverse them into an ever-improving cycle of events.

DIAGNOSTIC CONSIDERATIONS

The two principal means of detecting acute fetal distress (or perinatal asphyxia) during labor and delivery are (1) observation of amniotic fluid for passage of meconium, and (2) manual or electronic external or internal fetal heart rate (FHR) monitoring.

Meconium staining of the amniotic fluid and its consequences and management are discussed in detail in the section on Posdatism. It is helpful to differentiate between early or late, and light or heavy passage of meconium in the amniotic fluid since management and prognosis varies somewhat accordingly:

- *Early* meconium is that which is noted at the time of rupture of the membranes prior to entering into active labor.
- *Late* meconium is that which is passed during the 2^{nd} stage of labor after clear fluid was previously noted.
- *Light* meconium is signified by a small quantity giving only a tinge of discoloration to the amniotic fluid.
- *Heavy* meconium is loosely defined as being in large quantity and having a green color with thick consistency.

Obviously, late heavy meconium can do the most damage and carries with it the worst prognosis since it is still thick and clumpy and can more seriously block airways.

When one confronts a truly high-risk situation for fetal distress and perinatal asphyxia, electronic fetal heart rate (FHR) monitoring becomes absolutely essential since it provides moment-to-moment or “real time” information. Once the membranes are ruptured, internal (direct scalp attachment) FHR monitoring should be considered to obtain more reliable tracings. When used in conjunction with internal uterine pressure monitoring with a fluid-filled catheter attached to a transducer, one has all that is needed to assess the condition of the fetus while being stressed by uterine contractions of known duration and intensity.

(See chapter on Fetal Monitoring for a complete description of the use and interpretation of electronic fetal heart rate monitoring for antepartum and intrapartum assessment of the fetal condition.)

Other means of intrapartum assessment of perinatal asphyxia include (1) fetal scalp pH measurement, (2) transcutaneous (scalp) PO_2 monitoring, and (3) fetal electroencephalogram (EEG) monitoring. Fetal scalp blood sampling of pH is discussed briefly in the section on Fetal Monitoring. It is always used as an adjunct to internal electronic FHR monitoring and internal uterine pressure monitoring, helping to establish significance of some questionable FHR patterns while in the process of making a decision as to the safest route and time of delivery. The last two mentioned monitoring modalities have found little clinical application up to the present time.

Table 2. Physiologic Processes Involved in the Transition from Intrauterine to Extrauterine Life, factors that Normally Facilitate these Processes, and the Adverse Effects of Perinatal Asphyxia.

Transitional Processes	Facilitating Factors	Effects of Perinatal Asphyxia
4) Initiation of effective and rhythmic breathing.	Normal alteration in blood gas tensions associated with hyper-carbia when the nervous system is intact stimulates onset of respirations.	CNS (and respiratory center) depression. Severe hypoxia and hypercarbia depress nervous system function, resulting in reduced respiratory drive and irregularities of breathing.
5) Expansion of the lungs with air, and clearing of fetal lung fluid.	Initial strong gasps at birth. Sudden increase in flow of pulmonary blood, which with its higher oncotic pressure attracts more water into the vascular space and carries it out to the kidneys for excretion.	Premature gasping can result in aspiration. Continuing high pulmonary vascular resistance subsequent to perinatal asphyxia disallows increased pulmonary blood flow. Hypoxic damage to pulmonary capillaries leads to leaking of water back out into the tissues. Post-asphyxic heart failure leads to pulmonary edema.
6) Establishment of residual volume of air in the lungs that remains through end-expiration.	Presence of surfactant to stabilize the alveolar air-fluid interface.	Surfactant production inhibited during situations of hypoxia, acidosis, and low pulmonary blood flow.
1) Rapid decrease in pulmonary vascular resistance which allows for a quick rise in blood flow through the lungs (the new “gas exchanger” having replaced the placenta).	Rise in alveolar oxygen tension associated with air breathing; Physical expansion of the lung itself drops pulmonary vascular resistance; Rise in pH (with fall in PCO_2) drops pulmonary vascular resistance.	Delayed on onset adequate air breathing leaves alveolar PO_2 low. Poor initial expansion of the lungs and collapse at end-expiration for lack of surfactant. Development of metabolic and respiratory acidosis increases pulmonary vascular resistance and decreases pulmonary blood flow.
1) Closure of the intracardiac and extracardiac shunts (i.e., the foramen ovale [FA] and the ductus arteriosis [PDA] respectively) so as to redirect total right-heart blood to the lungs.	The sudden increase in pulmonary blood flow and return of blood to the left atrium raises its pressure and functionally closes the FA. The drop in pulm., artery pressure (with sudden decrease in pulmonary vascular resistance) and rise in systemic arterial pressure (once low-resistance placenta is removed from the circulation) allows L->R shunting through the PDA. The high O_2 content of blood from aorta going L->R through the PDA triggers Kinin system and prostaglandins to close the ductus.	Persistently high pulmonary vascular resistance and low pulmonary blood flow keeps pressure in right atrium higher than in the left, so the foramen ovale remains open and continues to shunt blood R->L through it. Vasomotor instability, poor cardiac contractility, and low circulating blood volume secondary to asphyxia reduces systemic pressure while keeping pulmonary artery pressure high; thus, blood does not shunt L->R through the ductus shortly after birth to stimulate its closure.

Acute assessment of the presence and severity of perinatal asphyxia at the birth should include the following clinical and laboratory techniques:

1. ***The Apgar scoring system***
   Five areas of vital functioning of the newborn baby are assessed at 1, 5, and sometimes 10 minutes of age:
   - *A*ppearance or color.
   - *P*ulse or heart rate.
   - *G*rimace or reflect response.
   - *A*ctivity level or muscle tone.
   - *R*espiratory effort.

   Each area is assigned a score of 0 to 2 points according to the signs or findings listed in Table 3.

Table 3. Scoring the 5 Areas of the Apgar Scoring System

	Explanations of Scores to be Given		
Sign or Area to be Scored	0	1	2
A Appearance or color entire body	Cyanotic/pale but extremities cyanotic	Body pink	Completely pink
P Pulse or heart rate	Absent	<100/m	>100/min
G Grimace or reflex response	No response	Grimace upon suctioning	Gag, cough, cry or Sneeze when suctioned
A Activity level or muscle tone	Flaccid, limp	Some flexion of extremities	Active motion
R Respiratory effort	Absent	Slow, irregular	Vigorous crying or breathing regularly

Apgar scores are rated as follows:

- 8-10 indicates no asphyxia
- 5-7 mild asphyxia
- 3-4 moderate asphyxia
- 0-2 severe asphyxia

The **1-minute Apgar score** helps identify babies requiring immediate resuscitation and suggests a graded response (i.e., the lower the score the quicker and more intense the resuscitation required). The **5- and 10-minute Apgar scores** indicate how well the infant responded to resuscitation and have been shown to correlate with ultimate outcome (see below).

1. ***Distinguishing between primary vs. secondary apnea*** (or “blue” from “white” asphyxia)
   Primary apnea is the period of nonbreathing that sets in approximately 1 minute after onset of acute, total asphyxia. It implies hypoxemia but still compensated circulation, thus, the “blue” appearance. Diagnostic characteristics of blue asphyxia include the following:

- Some muscle tone exists or there is some spontaneous activity.
- Although the patient is not breathing, he or she is still more than 5 minutes away from sustaining brain damage from the asphyxia.

Secondary (or terminal) apnea is the period of nonbreathing following the "last gasp" or last effort the baby will ever make to breathe unless he or she is resuscitated. It begins approximately 8-10 minutes after onset of acute, total asphyxia. It implies circulatory collapse and shock, giving the baby a pale appearance; thus the terminology of "pallid" or "white" asphyxia. Diagnostic characteristics of white asphyxia include the following:

- Heart beat less than ½ normal rate (i.e., $\leq$60/min) and falling.
- Pulses are no longer palpable and blood pressure is falling rapidly, the patient is in shock.
- Muscle tone is now gone; the patient is flaccid.
- The patient is at least 7 or more minutes into total acute asphyxia, and is either in, or only 2-3 minutes away from, brain damage.

2. Retrospective blood gas analysis

By knowing approximately the speed at which blood gases change during acute total asphyxia, one can project back what values were likely to have been present at a prior time (making a number of questionable assumptions along the way). Blood gas values change in total asphyxia as follows:

- PO_2 falls to near zero within 5 minutes
- PCO_2 rises at a rate of approx. 8 mmHg per minute
- pH falls at a rate of 0.04 units per minute
- HCO_3 falls nearly 2 mEq/liter per minute

A persistent metabolic acidosis after ventilation has been compensated (i.e., PCO_2 is back to normal range) indicates severe prior tissue hypoxia/ischemia resulting from centralization of the circulation and shifting to anaerobic metabolism in those tissues less well perfused. Such patients are at extremely high-risk for developing post-asphyxic complications (see below).

3. ***Response to resuscitative efforts***

The improvement (or lack thereof) in Apgar scores from 1 to 5 (and on to 10 minutes) is a valuable indicator of the degree of prior asphyxia suffered by the depressed newborn. Five-minute Apgar scores that remain depressed have been shown to correlate with later adverse outcome.

Of perhaps even greater importance is the demonstrated linear relationship between duration of previous asphyxia and the time interval before recovery of respiratory function of the baby after instituting resuscitation. That is to say, the time that elapses between instituting effective resuscitation (i.e., manual ventilation) and when the infant takes his first spontaneous gasp or goes on to establish rhythmic breathing directly correlates with the duration of prior total asphyxia (measured in animal models from the time of last gasp or onset of terminal apnea). For example, if the baby does not take his first gasp until 5 minutes after instituting your cardiopulmonary resuscitation, you can conclude that he or she was approximately 10 minutes into total asphyxia or secondary apnea at the time you started resuscitation. This brings the child to the lower limits of the time period in which brain damage is beginning to occur. If it was 10 minutes until the first gasp, there was approximately 12-1/2 minutes of prior total asphyxia which brings one into the area of probable brain damage occurring. Beyond 15 minutes until the first gasp (or 30 minutes until spontaneous rhythmic respirations are established on the part of the baby) brings one into the area of inevitable brain damage resulting from the prior asphyxia.

1. ***Occurrence of post-asphyxic complications***

The development of any of the major short term complications discussed below indicates severe degree of prior asphyxia and necessitates both acute treatment (see section on Resuscitation of the Asphyxiated Newborn and Management of Post-Asphyxic Complications) and follow-up examinations of these infants to rule out long-term complications or permanent sequelae.

1. Other biochemical tests to define the severity of asphyxia

None of the following tests can be considered applicable for use in primary care units but are of great theoretical interest for further defining the degree of antepartum-intrapartum fetal distress and neonatal hypoxic-asphyxic damage:

- Serum lactate levels, elevated after significant hypoxia.
- Cathecholamine levels, elevated in the stressed neonate.
- Triglyceride levels, elevated after antepartum-intrapartum fetal distress.
- Hypoxanthine levels, elevated due to asphyxic inhibitation of the xanathine oxidase enzyme system. Subsequent decrease of the once-elevated levels of hypoxathine is quite constant at 10 u Mol/liter/hour, so one can project back and estimate the level at the time of the insult and thereby quantify the severity of the asphyxic tissue damage.
- Serum creatine phosphokinase levels, with specific focus on the myocardinal isoenzyme CPK_2 fraction which is elevated in cases of asphyxia severe enough to result in myocardial dysfunction and temporary tricuspid insufficiency (see below).

POST-ASPHYXIC COMPLICATIONS

The list of acute post-asphyxic complications that require immediate attention in the newborn period (and often necessitate referral to a regional newborn intensive care center) is quite long and can involve every major organ system in the body:

4. Metabolic complications

- Lactic acidosis, as a by-product of anaerobic metabolism.
- Hypoglycemia, due to depletion of glycogen stores and depression of gluconeogenesis.
- Hypocalcemia, as a rebound complication of corrected metabolic acidosis (especially severe if buffer such as bicarbonate has been given).
- Hyponatremia, due to intracellular intrusion, dilutional effect, and later loss through the urine from insufficient kidneys.
- Hyperkalemia, due to leakage from the cells and later retention if there is renal failure.

5. Cardiovascular complications

- Cardiogenic shock and heart failure, evidenced by systemic hypotension, decreased peripheral perfusion (producing mottled skin color, delayed capillary filling and reduced peripheral skin temperature), cardiomegaly on x-ray, tricuspid insufficiency murmur (associated with papillary muscle necrosis), gallop rhythm, and elevated CVP.
- Patient ductus arteriosus and open foramen ovale (see Table 2).

Persistent fetal circulation (PFC), due to open shunts, high pulmonary vascular resistance, and higher pulmonary than systemic circuit pressures. If fetal distress was chronic, there may be pulmonary arteriolar medical hypertrophy and active vasoconstriction as well.

1. Renal complications

- Acute tubular necrosis (and possibly cortical necrosis as well), evidenced by oliguria or temporary anuria, rising BUN and creatinine levels (i.e., above 15 mg/dl and 1.0 mg/dl respectively), blood and protein spillage in the urine, and inability to dilute or concentrate the urine.
- Renal vein thrombosis (rare), evidenced by an enlarging flank mass, grossly bloody urine, and falling hematocrit.

1. Gastrointestinal complications

- Feeding intolerance as well as poor suck and swallow.
- Increased risk for developing necrotizing entero-colitis if enteral feedings are attempted too soon.
- Centrolobular hepatic necrosis and obstructive jaundice, with high direct bilirubin and gamma GT.

1. *Hematologic complications*

- Polycythemia and hyperviscosity syndrome in cases of chronic fetal distress.
- Coagulopathy with or without disseminated intravascular coagulation (DIC), as evidenced by prolonged PT and PTT, reduced fibrinogen level (less than 100 mg/dl), thrombocytopenia (less than 125,000/mm3), and presence of fibrin split products.

1. CNS complications

- Cerebral edema, evidenced by bulging fontanel, early onset seizures and depressed regulatory functions (i.e., apnea, hypothermia, poor vasomotor control).
- Subependymal or intraventricular hemorrhage in prematures; subdural, cerebellar or cerebral cortical hemorrhages in term infants.
- Inappropriate ADH secretion, evidenced by hyponatremia, serum hypo-osmolarity, high urine specific gravity (i.e., greater than 1015), and high urine sodium concentration (in spite of serum hyponatremia).

MANAGEMENT OF POSTASPHYXIC COMPLICATIONS

Management of Metabolic Complications

The management of postasphyxic metabolic complications requires close monitoring of electrolyte, glucose, calcium, and pH levels in the blood. Any baby requiring umbilical vessel catheterization and drug therapy in the delivery room should be continued on an infusion of D10W running at about 3 ml/Kg/hour or 75 ml/Kg/day. Sodium bicarbonate is given to correct metabolic acidosis in amounts specified in Table 2. If the amount required for acidosis correction is less than 3 mEq/Kg/day, NaCl should be added to the IV solution by the second day so as to provide a total sodium intake of 3 mEq/Kg/day.

Wait until the baby urinates before adding potassium to the IV. The usual amount of K^+ needed is 2 mEq/Kg/day. Any infant acidotic enough to receive bicarbonate will need double-maintenance calcium or 400 mg/Kg/day of 10% calcium gluconate in the I.V. infusion. Otherwise, 200 mg/Kg/day or approximately 1 mEq Calcium Gluconate per 100 mL of I.V. fluid will usually suffice.

Post-asphyxic hypoglycemia can be monitored by frequent bG Chemstrip or Dextrostix determinations of serum glucose, and can usually be managed by increasing the D10W IV rate temporarily to 5 ml/Kg/hour after a 5 mL bolus of the same solution. However, in asphyxiated IDM or SGA infants, considerably more glucose intake may be required. This can be provided as an infusion of D15W through an UAC, or up to D20W through an UVC with tip positioned above the diaphragm. These infants require management in a regional intensive care unit.

Management of Cardiopulmonary Complications

Post-asphyxic hypotension or shock is managed by blood volume expansion with human salt-poor albumin as an emergency measure in the delivery room, and then with transfusions of packed RBC's and/or fresh frozen plasma (FFP) according to hematocrit values (i.e., PRBC's if Hct < 45%, and FFP if Hct > 45%) in the post-delivery period. Unless there has been severe intrapartum hemorrhage, single transfusion amounts should not exceed 10-15 ml/Kg infused over a period of 2 to 4 hours. If these measures fail to keep systolic blood pressure above 50-55 mmHg, or mean blood pressure above 35 mmH, initiate a continuous drip of Dopamine, starting at 5 mg/Kg/minute and increasing as necessary. CVP monitoring is helpful. All such patients obviously belong in a newborn intensive care center.

To avoid or blunt the problem of persistent fetal circulation (PFC), liberal enrichment of the ambient oxygen concentration is advised. In term infants there is no risk of developing RLF even if 100% oxygen is used for sustained periods of time. Free water (crystalloid IV solution) intake must be restricted to 40-60 mL/Kg/day for the first day, especially in the premature, asphyxiated infant, if later problems with a significant ductus are to be avoided.

Management of meconium aspiration is discussed in the section on Postdatism. Shock lung and accentuated RDS are managed with various forms of distending airway pressure and surfactant replacement therapy in a newborn ICU.

Management of Renal Complications

Initial fluid restriction in the range of 40-70 cc/Kg/day is crucial until the renal status can be clarified. Close monitoring of urinary output, urine spillage of protein, blood, and bicarbonate (i.e., urine pH > 6.0), and creatinine levels as well as electrolytes provides such clarification. After a few days of oliguria or

anuria, the baby usually enters a diuretic phase, requiring increased fluid intake and higher quantities of electrolyte supplements. Any infant with urine output of less than 1 ml/Kg/hour over a 24 hour period or a creatinine value rising above 1.2 mg/dL belongs in a newborn ICU.

Renal vein thrombosis is now managed conservatively, i.e., the kidney left in place unless hypertension develops. Inappropriate ADH secretion is a possibility after severe birth asphyxia, and this is handled by temporarily curtailing free water intake even more severely.

Management of Gastrointestinal Complications

The more severely a baby is asphyxiated, the longer the required "wait period" before instituting enteral feedings. Hypoglycemia is not an excuse to start early enteral feedings if the baby was significantly asphyxiated. Rather, the problem of hypoglycemia is managed in this setting by IV therapy. The risk for developing necrotizing enterocolitis (NEC) is very real in the severely asphyxiated newborn, and especially in the premature baby. Waiting as long as 5-6 days may be required before one can safely start low volume gavage feedings of low-lactose formula, or go to direct breast feedings.

Management of Hematologic Complications

Polycythemia in the asphyxiated infant may contribute to heart failure, PFC, venous thrombosis (of the saggital sinus or other cerebral veins as well as the renal veins), and development of NEC. If the central Hct is 70% or above, or if the infant is symptomatic, a reduction transfusion using between 50 and 100 ml of FFP for exchange is indicated.

Observing for petechiae and unexpected bleeding from puncture sites, as well as monitoring platelet counts, are good ways to pick up early DIC. Heparinization may be tried early; otherwise treatment is one of replacing clotting factors with FFP and platelet infusions. These babies are best managed by neonatologists in tertiary-level care units.

Management of CNS Complications

Post-asphyxic cerebral edema can be minimized by rigidly restricting free water intake, i.e., to less than 60 ml/Kg/day. Lasix diuretic (1 mg/Kg/dose) may be of help here also. Seizures are treated with phenobarbital as the first-line drug, and adding Dilantin if necessary. Loading doses are 10-20 mg/Kg for both phenobarbital and Dilantin, whereas maintenance dose is 5 mg/Kg/day and 3-5 mg/Kg/day respectively. All infants with the post-asphyxic neonatal neurological syndrome (see section on Perinatal Asphyxia and Post-Asphyxic Complications) should be transferred to a regional newborn center for further diagnostic work-up and integration into a comprehensive follow-up program.

ULTIMATE OUTCOME

In cases of very severe birth asphyxia as defined as stillbirth (i.e., 1-minute Apgar score of zero) or failure of the infant to establish spontaneous breathing within 20 minutes of birth (all with Apgar scores of 1 or 2 at 1 minute of age), approximately 50% will die in the immediate newborn period. Death within the first year of life after severe perinatal asphyxia has been shown to correlate directly with the duration of persistently low Apgar scores. For instance, mortality is about 20% in term infants with 10-minute Apgar scores of 0-3, and it climbs to about 60% if the score remains that low at 20 minutes of age.

Among survivors of severe perinatal asphyxia, long term sequelae frequently encountered include the following:

- Cerebral palsy of either the athetoid or spastic (diplegia, hemiplegia or quadriplegia) type
- Seizure disorder
- Mental retardation
- Deafness
- Visual impairment
- Learning or behavioral disorders

Factors known to be associated with the above-listed sequelae include the following:

- Low 5, 10, 15 and 20-minute Apgar scores, with the percentages of damaged survivors increasing with the duration of low scores.
- Perinatal asphyxia associated with prolonged fetal stress factors such as (1) maternal preeclampsia, hypertension, or heart disease, (2) prolonged labor, and (3) anything that leads to fetal growth restriction or the SGA infant (see section on IUGR and SGA).
- Persistent abnormal neurologic signs in the neonatal period (i.e., "the post-asphyxic neonatal neurological syndrome") including (1) sucking, swallowing, feeding difficulties necessitating tube feeding, (2) apneic or cyanotic spells, (3) seizures that are difficult to control, (4) high-pitched or cerebral cry, and (5) hypotonia and apathy followed later with hyperexcitability and hypertonia. Persistence of these signs beyond 1-2 weeks signifies high likelihood of lasting serious neurologic sequelae.
- CAT scans showing cerebral atrophy, porencephalic cysts or watershed infarcts carry with them a very poor prognosis. Failure of head growth or excessive head growth may accompany these findings.

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