Annie J. Rohan, MSN, RNC, NNP/PNP, and
Sergio G. Golombek, MD, MPH, FAAP

CE

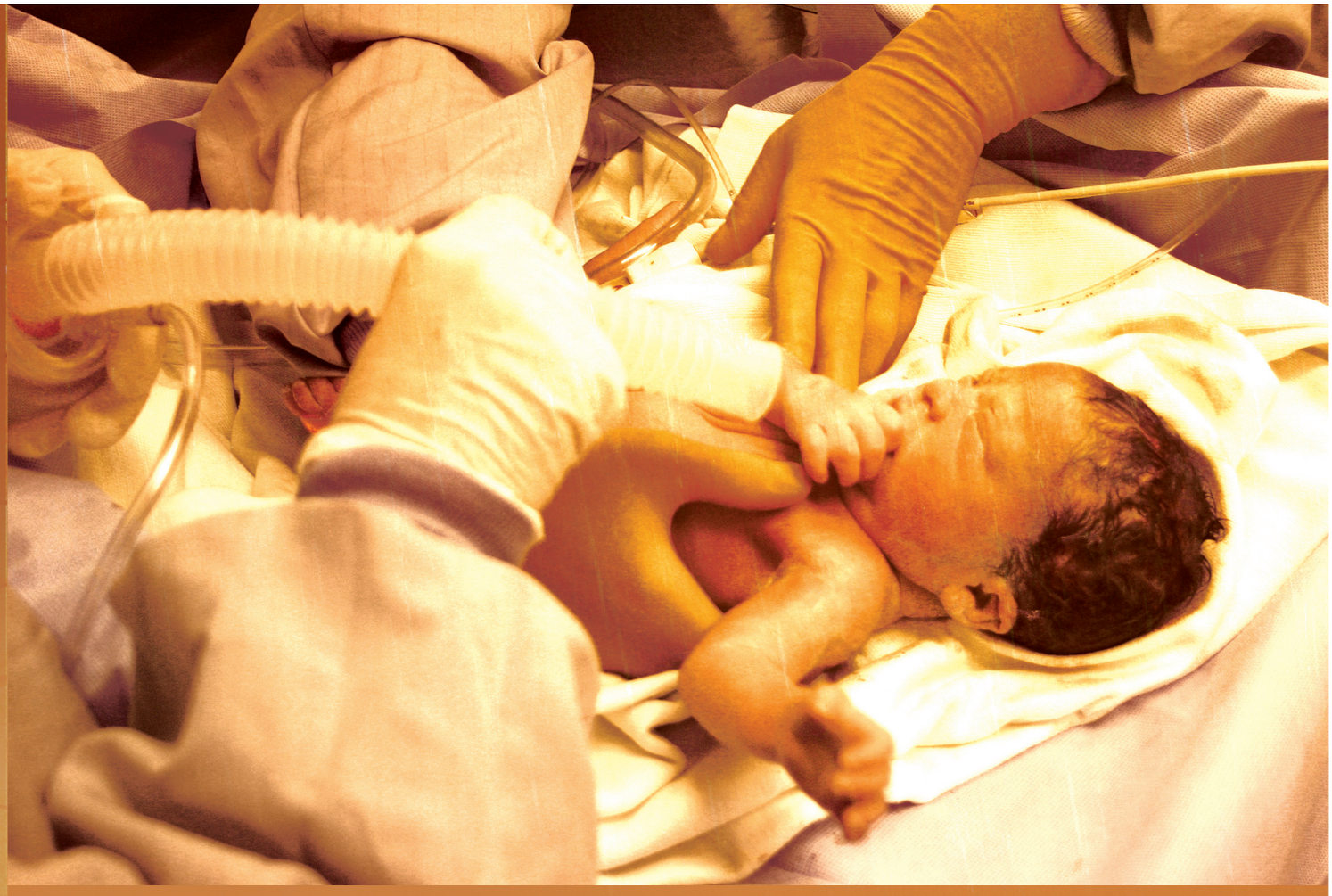
HYPOXIA IN THE Term Newborn:

PART THREE—SEPSIS AND HYPOTENSION, NEUROLOGIC, METABOLIC AND HEMATOLOGIC DISORDERS

ABSTRACT

Causes of hypoxia and cyanosis in the term newborn can be found within all physiologic systems and take the form of hundreds of specific diagnoses. In the first and second parts of this series, a wide range of cardiac and pulmonary causes for newborn hypoxia and cyanosis have been examined. Because they are familiar, cardiac and pulmonary diagnoses often represent our reactionary opinions—the options that we first entertain even before a proper systematic approach to the infant has been taken. In this final of a three part series, neurologic, hematologic and metabolic disorders are explored as a cause for abnormal oxygenation, as well as sepsis and hypotension. It is within these final categories that we find many of the obscure possibilities for neonatal hypoxia—the diagnoses that often require rigorous testing, or more sophisticated laboratory interpretation. Without consideration of these elusive entities, however, appropriate treatment and referral will be unnecessarily delayed.

Key Words: Hypoxia; Metabolic; Neurologic; Newborn.



Newborn care providers need to meet the familiar challenge of evaluating hypoxia in the term infant. The first article in this three-part series (Rohan & Golombek, 2009a) discussed cardiopulmonary adaptation of the term newborn, definitions and features of neonatal hypoxia, cardiac causes for hypoxia in the newborn, and neonatal pulmonary hypertension. The second article (Rohan & Golombek, 2009b) described primary pulmonary disease, airway obstruction, and lung or airway compression as a cause for impaired oxygenation. In this final part, neuromuscular, metabolic disorders, and hematologic disorders will be explored as causes for hypoxia in the term infant, as well as sepsis and hypotension.

Central Nervous System/ Neuromuscular Diseases

Central nervous system (CNS) disorders and neuromuscular diseases can cause altered control of respiration and result in hypoxia in the term neonate.This compromised neurologic control of respiration can be a result of a congenital neurologic disorder, due to seizures or CNS infection, or as a result of neurologic injury. A summary of these neurologic causes can be found in Table 1.

Congenital Neurologic Disorder

Congenital neurologic disorders as a cause of hypoxia in the term newborn infant are infrequent, and should be suspected when neurologic examination is abnormal without a perinatal course suggesting neurologic injury. In addition, history may suggest isolated lack of movement on sonographic examination or reveal breech presentation secondary to the fetus' limited ability to shift in utero.

Almost any condition that affects the central or peripheral nervous system of the newborn can be expressed with a reduction in tone, and can thus impact respiration. Respiratory failure, hypoxia, and cyanosis caused by significant muscle weakness may be due to abnormalities of the nervous system, irregularity of the muscles, and sometimes concomitant deformity of the chest wall.

When tone impacts the infant's ability to sustain adequate ventilatory function, ventilatory assistance with continuous positive airway pressure or intermittent positive pressure ventilation may be required until a definitive diagnosis and treatment plan is established. Because of the rarity of these disorders, however, when hypoventilation is a presenting feature, it is prudent for the on-call practitioner to consider the possibilities of infection or metabolic derangement, and arrange an appropriate chemistry panel, metabolic support, cultures, and antibiotics pending more extensive neurologic investigation (Castrodale, 2003).

Seizures

When apnea presents in the term infant, without other signs of respiratory distress, one must consider seizures as an

Table 1. Neurologic Conditions That Can Cause Respiratory Failure, Hypoxia, and Cyanosis

	CONGENITAL NEUROLOGIC DISORDERS	SEIZURES	NEUROLOGIC INJURY	CNS INFECTION
Mechanism of hypoxia	**Reduction of tone: decreased respiratory effort**	**Epileptiform activity: apnea**	**Increased ICP, Impaired circulation brain structures: multifaceted effect on respiratory control, can cause seizures/apnea**	**Can cause reduction in tone, seizures, increased ICP, apnea**
Examples	**Congenital hydrocephalus** **Werdnig-Hoffman disease** **Neurologic malformations (i.e., Chiari malformation)** **Spinal muscle atrophy** **Dejerine-Sottas disease** **Muscular dystrophy** **Charcot Marie tooth disease** **Neurogenic arthrogryposis** **Phrenic nerve paralysis** **Congenital myasthenia** **Congenital myopathies** **Congenital neuropathies** **CNS malignancies**	**Seizures resulting from congenital neurologic disorder or genetic syndrome** **Seizures resulting from CNS injury** **Seizures resulting from infection** **Seizures resulting from metabolic derrangement**	**Hypoxic-ischemic encephalopathy** **Intraventricular hemorrhage** **Subdural hemorrhage** **Subarachnoid hemorrhage** **Hemorrhagic infarction** **Intracerebellar hemorrhage**	**Bacterial Infection: Group B Streptococcus, *Escherichia coli, Listeria monocytogenes*** **Viral infection: *Syphilis toxoplasmosis, Herpes simplex, Rubella, Cytomegalovirus***

CNS = central nervous system. ICP = intracranial pressure.

etiology. Recognition of neonatal seizures is difficult, as generalized clonic jerking is rare. Rather, clinical manifestations are often minimal, with brief periods of posturing or tonic extension, eye deviation, or apnea. Particularly when a seizure presents with apnea, the infant may become hypoxic and cyanotic as a first clinical sign (Volpe, 2001a, 2001b).

Fifty percent of neonatal seizures occur during the first day of life, and 75% by day 3. Adding to diagnostic complexity, the most likely etiology of a neonatal seizure transforms over the first week of life: During the first 48 hours, neurologic injury and hypoglycemia are common culprits; during days 5 to 7, hypocalcemia is seen, and at any time in the first week, infectious and genetic causes can emerge. In almost all cases, evaluation by electroencephalography and anticonvulsant therapy for seizure control is indicated until differential diagnoses are assimilated and eliminated (Volpe, 2001b, pp. 178-214; Painter, 1993).

Neurologic Injury

There are two major categories of neurologic injury that

can be observed in the full-term infant—hypoxic-ischemic encephalopathy (HIE) and intracranial hemorrhage. These injuries can occur separately, or in concert, and often can be suggested by the perinatal history. In most clinically significant cases, the infant exhibits periods of hypoxia and cyanosis, the duration and degree of which is determined by the nature and extent of the injury.

An infant with a history of problems during labor and delivery, with severely depressed level of consciousness and seizures, is likely to have sustained neurologic injury, or "hypoxic-ischemic encephalopathy." Many clinical features of neonatal HIE are nonspecific, but low cord or scalp pH (<7.0), poor Apgar scores (<5 persisting beyond 5 minutes), and early severe metabolic acidosis are common indicators for early transfer to a neonatal intensive care unit (Plessis, 2005). Typically, these infants have a significant degree of ventilatory depression (especially apnea and respiratory failure) and oxygen requirement at delivery that brings urgency to their bedside in the labor and delivery suite. More subtle cases, however, where blood gas testing is absent and Apgar scoring is overly zealous, may transfer to the newborn nursery with "cyanosis" as the first sign (Figueroa et al., 2005; Volpe, 2001a, pp. 331-394).

Intracranial hemorrhage in the full term infant occurs much less commonly than in the preterm infant, being seen with clinical symptoms in fewer than one in 100 births (Schwartz, Ahmann, Dykes, & Brann, 1993). These hemorrhages can be intraventricular, subarachnoid, subdural, or intracerebellar in origin. All, however, commonly present with ventilatory disturbance and hypoxia from a varying level of neurologic depression or disruption.

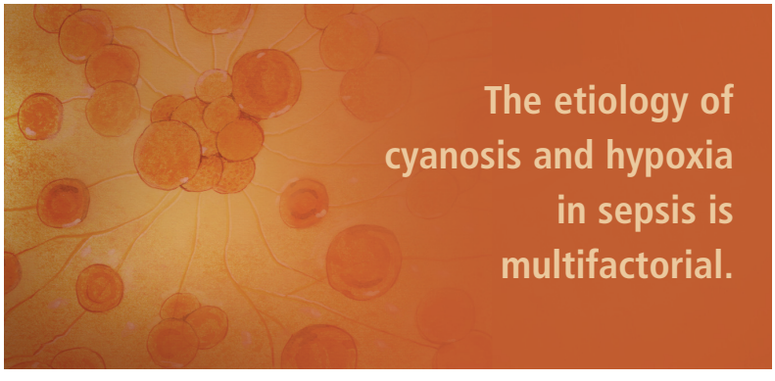
Intraventricular hemorrhage (IVH) in the full-term infant most commonly originates from the choroid plexus. Many of these infants have evidence of intrapartum asphyxia. There is a possibility that IVH in the term infant is clinically silent and underdiagnosed, and is the cause of later deficits or hydrocephalus. Where symptoms exist, seizures are common. Ultrasonographic or CT imaging provides rapid and accurate diagnosis.

Significant subarachnoid hemorrhage can occur with intrapartum hypoxia, or can result from delivery trauma alone. It can be isolated or related to subdural bleeding and cerebral contusion, depending on the degree of trauma. Presentation is highly variable but generally includes periods of alternating CNS depression and irritability, and seizures, all commonly with ventilatory disturbance and hypoxia. Diagnosis often occurs when a lumbar puncture is performed as a more complete evaluation for suspected sepsis or meningitis, and demonstrates the presence of red blood cells. When subarachnoid hemorrhage is associated with other signs of physical injury caused by difficult delivery often with mid or high forceps application, outcome is frequently poor (Schwartz et al., 1993).

Clinically significant subdural hemorrhage, which is also commonly associated with instrumented or difficult breech deliveries, has become a rarer disorder of the newborn (Hofmeyr & Hannah, 2003). Such events produce excessive molding of the infant's skull or excessive extension of the infant's neck, with relatively sudden tearing of venous channels over the hemispheres, or of the venous sinus. In association with ventilatory disturbance, early manifestations of significant subdural hemorrhage usually include signs of increased intracranial pressure, seizures, anemia, and jaundice, and physical examination may reveal a bulging fontanelle and other neurologic deficits. CT scanning is a more reliable method of diagnosis over cranial ultrasound.

Sepsis and Hypotension

Outside of primary pulmonary disease, perhaps the next most common abnormality presenting with hypoxia in the term newborn is sepsis. The clinical signs of neonatal sepsis are nonspecific and often camouflaged or associated with other neonatal diseases such as respiratory distress syndrome, metabolic disorders, intracranial hemorrhage, and asphyxia. As such, infection is considered and empirically treated with nearly all unexpected events of hypoxia in the term newborn. Eighty-five percent of newborns with early-onset infection present within 24 hours, 5% present at 24 to 48 hours, and a smaller percentage of patients present between 48 hours and 6 days of life (Anderson-Berry & Belig, 2006).



The newborn sepsis syndrome is associated with acquisition of microorganisms from the mother. Transplacental infection or an ascending infection from the cervix may be caused by organisms that colonize in the mother's genitourinary tract, with acquisition of the microbe by passage through a colonized birth canal at delivery. The microorganisms

Table 2. Risk Factors for the Development of Neonatal Sepsis in the Term Newborn

MATERNAL FACTORS	INTRAPARTUM FACTORS	NEONATAL FACTORS
Low parity	Increased duration of internal monitoring	Low Apgar score (<6 at 1 or 5 minutes)
Recent urinary tract infection	Increased duration of ruptured membranes	Low birth weight
Poor prenatal care	Increased number of vaginal examinations	36 to 37 weeks
Low socioeconomic status	Greater duration of labor	Asphyxia
Substance abuse	Maternal fever >38° C	
	Chorioamnionitis	
	Difficult delivery	
	Meconium staining	

most commonly associated with early-onset infection include group B *Streptococcus* (GBS), *Escherichia coli*, *Haemophilus influenzae*, and *Listeria monocytogenes* (Anderson-Berry & Belig, 2006).

Risk factors implicated in neonatal sepsis reflect stress on the fetus during the intrapartum period, as well as the problematical uterine environment surrounding the fetus before delivery (Soper, 1989). Factors associated with early-onset neonatal sepsis are summarized in Table 2.

The etiology of cyanosis and hypoxia in sepsis, with or without CNS infection, is multifactorial. While apnea is a hallmark of seizure as a result of CNS infection, apnea with resultant intermittent hypoxia is also common in both CNS and non-CNS infections without seizure, as is hypotonia, hypoventilation, and cardiovascular instability.

An early phase of the cardiovascular instability ("shock") of sepsis is typically a compensated phase, characterized by pulmonary hypertension, decreased cardiac output, and hypoxemia. Vital organ function is maintained by compensatory mechanisms that keep organ blood flow primarily to the heart, brain, and adrenal glands, and away from the "nonvital" organs (the "diving seal reflex"). Without recognition and treatment, the infant may later manifest with hypotension, pallor, poor capillary perfusion, and edema, as there is failure of the compensatory mechanisms. It is at this point that the infant manifests with hypoxia and cyanosis. These late signs of shock are indicative of severe compromise and are highly associated with long-term morbidity (Noori, Friedlich, & Seri, 2004; Seri & Evans, 2001).

Hypotension and shock secondary to sepsis and other causes—cardiogenic, neurogenic, hypovolemic—all present with a similar cascade of events, and in all cases, the underlying cause must be addressed while treatment is given to support the infants' circulation and blood pressure (Stebor, 2005; Vanhaesebrouck, 1987). If treatment is delayed, or the condition is prone to rapid deterioration, such as in fulminant sepsis, myocarditis, or asphyxia with multiorgan failure, neonatal shock will enter a final and irreversible phase, in which cellular damage leading to complete organ failure dominates the clinical picture, and death occurs invariably (Figueroa et al., 2005).

Given the nonspecific nature of the signs of infection, providing treatment for suspected neonatal sepsis, while excluding other disease processes, is prudent. Treatment with appropriate broad-spectrum antibiotics is standard at the time of suspicion and prior to laboratory confirmation of infection. Supportive care may include supplemental oxygen administration or mechanical ventilation, intravenous fluids, inotropic agents for hypotension, and nitric oxide for infection-associated pulmonary hypertension. The mortality from infections has decreased over time with more aggressive intrapartum administration of antibiotics to high-risk women and advances in neonatal intensive care.

Hematologic Disorders

Another category of disorders with a possible manifestation as hypoxia in the term newborn are hematologic disorders, although these are significantly less common. As with many

other body systems in the neonate, the hematologic system is immature at birth. As a result, newborns may be at an increased risk for various problems. Bleeding disorders in an infant can be viewed in two categories: inherited or acquired. Inherited disorders include factor deficiencies such as hemophilia, von Willebrand disease, and both autoimmune and alloimmune thrombocytopenias. The most commonly acquired disorders are vitamin K deficiency and disseminated intravascular coagulation (DIC) secondary to some underlying cause.

DIC is a disorder of hemostasis that may occur in the neonatal period as a complication of various other disease processes. Its effects on the newborn—typically an otherwise sick infant—can be particularly devastating. The clinical manifestations of DIC and their time of onset can be variable. The infant will first show signs of the underlying disease process and then may progress to subtle clues or major signs of DIC. Bleeding is typically an initial presentation. An infant who continues to bleed after lab draws or venipuncture should raise suspicion. Hemorrhage can range from oozing of a wound to frank blood in the mouth, nose, or orogastric or endotracheal tube indicating a major gastrointestinal or pulmonary bleed, the latter almost always associated with some degree of hypotension or shock.

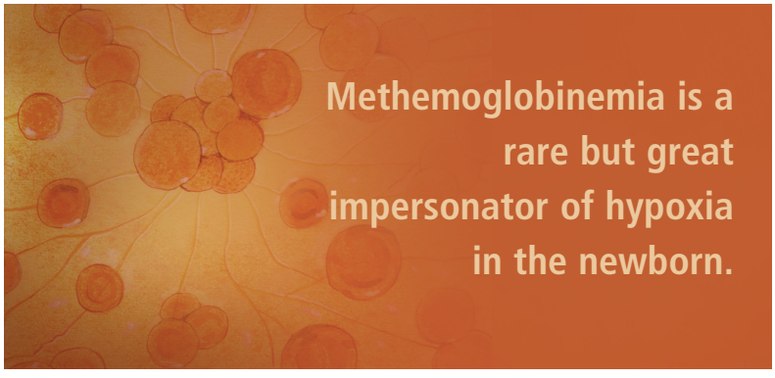
Hematologic disorders—whether inborn or acquired—may present as well with petechiae, purpura, ecchymoses, or hematomas. Ischemic damage related to thrombosis could manifest as cyanosis, as well as specific organ failure, depending on the site of the clot. As previously noted, hematologic disorders can also present with internal hemorrhage—especially intracranial hemorrhage. Significant internal hemorrhage is often marked by a sudden deterioration, hypovolemia, hypotension, cardiovascular instability, and resultant hypoxia. While the internal hemorrhage may not always be initially evident to the clinician, signs and symptoms will indicate shock with red blood count or platelet abnormalities.

Methemoglobinemia is the rare but great impersonator in the evaluation of cyanosis of the newborn, and worth mentioning at this juncture. Methemoglobinemia causes reduced blood-oxygen carrying capacity due to abnormal hemoglobin or enzyme deficiency. Examination generally reveals a markedly cyanotic infant without respiratory distress, who has an arterial PaO_2 that is normal, although the infant will have low oxygen saturation values. Arterial blood obtained from such an infant is often described as "chocolate" in color. In the general population, methemoglobinemia is caused by ingestion of toxic agents such as nitrites, but in the term newborn, methemoglobinemia instead is related to congenital absence of methemoglobin reductase.

Metabolic Abnormalities

The clinical symptoms of metabolic disorders in the neonate, including those of drug withdrawal, are nonspecific and usually not possible to distinguish from other disorders without laboratory testing. Nearly all of these disorders, however, can present with apnea and hypoxic episodes in the term newborn, and as such, need to be considered by the clinician when called to evaluate an infant who has cyanosis or suboptimal oxygen saturation findings.

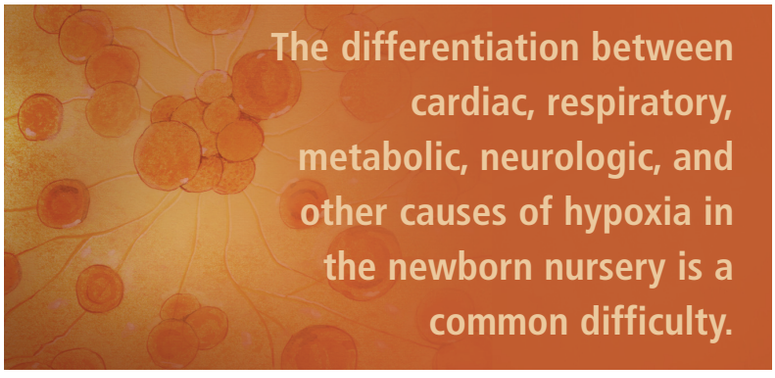
The effect of maternal substance abuse during pregnancy on a neonate's behavior and adaptation has long been acknowledged. Well-recognized signs of withdrawal include clonus, high-pitched and excessive crying, and diarrhea, but also can include hypoxia secondary to metabolic derangement, apnea, or nasal congestion. There is also evidence that neurological alterations occur during withdrawal that prevent normal autonomic functions. Newborns, in particular, depend on their reflexive suck and swallow ability, which may be affected significantly by intrauterine drug exposure. As such, poor feeding, unto itself, can start a cascade of other diagnoses. The vasoconstrictive properties of cocaine have also been implicated as a cause for intrauterine hypoxia with poor fetal growth and persistent pulmonary hypertension (Bauer, 2005; Levy & Koren, 1990).



Electrolyte derangements, most commonly hypoglycemia but also abnormalities of calcium, phosphorus, magnesium, and potassium, can cause an array of nonspecific clinical symptoms in the neonate, with hypoxia common to all. The occurrence of these symptoms is different in individual infants and there is a lack of a universal threshold below or above which symptoms can be expected. Cardiac rhythm disorders are also found as potassium and calcium become increasingly out of range, and

hypoxemia secondary to impaired cardiac output can be observed in these cases. Hypermagnesemia—usually secondary to maternal administration of magnesium—can result in hypoventilation or apnea in the newborn, with resultant hypoxia and cyanosis.

Diagnosis of electrolyte derangement is made by blood chemistry evaluation, and treatment often involves replacing or withholding the offending electrolyte. In many cases, the metabolic derangement is part of a larger syndrome, such as hypoglycemia in Beckwith-Wiedemann syndrome and in the infant of a diabetic mother, or in the case of hypocalcemia in hypoparathyroidism and in DiGeorge syndrome.



Other metabolic disorders, although rare, have been implicated in hypoxia and include:

- mitochondrial disorders
- inborn errors of metabolism
- peroxisomal disorders (adrenoleukodystrophy, cerebrohepatorenal syndrome)
- acid maltase deficiency (Pompe disease)
- phosphofructokinase deficiency
- phosphorylase deficiency
- carnitine deficiency.

The workup and treatment for these listed disorders is complex and generally requires the consultation of a genetic or metabolic specialist.

Management

In summary, treatment of the hypoxic infant depends on accurate diagnosis. Initially, however, respiratory support with oxygen, CPAP (continuous positive airway pressure), or mechanical ventilation is indicated in most cases. In congenital heart disease, medication used to maintain the patency of the PDA (patent ductus arteriosus) may be necessary to maintain tissue perfusion until surgical correction can be achieved. In PPHN (persistent pulmonary hypertension), the goal of the therapy is to lower the pulmonary-to-systemic vascular resistance ratio and thus reduce shunting. ECMO (extracorporeal membrane oxygenation) and has been used with success, while supportive measures are in place, and newer medical therapies such as inhaled nitric oxide are now improving upon those successes (Golombek, 2000; Verklan, 2006; Williams, 2004).

Given the often vague signs of neonatal infection, which includes hypoxia of various etiologies, evaluating for suspected sepsis while excluding other disease processes, is uniformly prudent for the clinician. Treatment with appropriate broad-spectrum antibiotics is standard at the time of suspicion and prior to laboratory confirmation of infection.

Where cyanosis is secondary to poor cardiovascular function in any form of shock, volume expanders and inotropic agents are important at maintaining adequate tissue oxygenation. Red blood cell transfusion to support oxygen-carrying capacity and metabolic and electrolyte management to optimize cardiac function are fundamental.

For emergency conditions, such as pneumothorax, evacuation by the bedside clinician is often warranted, even before specialized neonatal care. Obstructive lesions may also require urgent bedside palliation prior to definitive treatment (i.e., oral airway for choanal atresia or Pierre Robin Sequence, tracheal intubation, and gastrointestinal evacuation for diaphragmatic hernia).

Where gastroesophageal reflux is identified, medical management with H_2 blockers is often effective, as well as other pharmacologic remedies and formula thickening, for the management of events that cause hypoxia.

Unusual conditions, such as methemoglobinemia, are treated more uniquely under the guidance of subspecialists, and after further targeted diagnostic tests are interpreted. Similarly, the treatment of hypoventilation as a function of metabolic or neuromuscular disorder, while initially supported by oxygen administration and ventilation, may require more specialized therapies.

Outcomes

During normal development, cardiovascular and circulatory functions progress from fetal life through transition at birth, and the fetus and newborn are clearly able to thrive despite their "hypoxic" environment. Moreover, due to adaptive responses of the cardiovascular, metabolic and endocrine systems, relatively severe intrauterine stress may be tolerated and still permit the fetus to have relatively normal growth and development. However, hypoxic stress in utero—both acute and chronic—can be severe enough to cause compromised circulation, organ dysfunction, and threaten survival—or intact survival. At the time of transition to extrauterine life, signs of a depressed circulatory system from in-utero hypoxia may become suddenly apparent because of the increased metabolic demands at birth, and

Table 3. Differentiating Between the Many Etiologies for Newborn Hypoxia: Typical History and Clinical Findings

CATEGORY	PREGNANCY HISTORY	LABOR AND DELIVERY HISTORY	RESPIRATORY SIGNS	PHYSICAL EXAM	RADIOLOGICAL AND LAB DATA
Congenital cardiac defects and disease	May have abnormal fetal echocardiogram, maternal diabetes	Unremarkable	None or mild	Significant murmur	Low PaO_2 despite high supplemental oxygen, abnormal cardiac silhouette on X-ray
Pulmonary hypertension (usually associated with a second category)	Often unremarkable	Often with evidence fetal stress/distress	Mild to severe respiratory distress	Variable, depending on associated category	Low PaO_2 despite supplemental oxygen
Primary pulmonary disease	Often unremarkable, sometimes gestational diabetes	Often unremarkable, but may have evidence fetal stress/distress, history cesarean birth, or delivery at 36-37 weeks	Mild to severe respiratory distress	Often unremarkable	Abnormal bilateral lung fields on X-ray
Airway obstruction	May have abnormal fetal sonogram	Unremarkable	Moderate to severe respiratory distress	Notable or palpable obstruction	Abnormal neck/chest X-ray or CT
Extrinsic compression of the lungs	May have abnormal fetal sonogram	Unremarkable	Moderate to severe respiratory distress	Chest asymmetry	Lesion on chest X-ray or CT
Central nervous system/ neuromuscular diseases—congenital disorder	May have abnormal fetal sonogram, may have evidence abnormal fetal movement	Malpresentation common	Apnea	Hypotonia seizures,	Abnormal CT, EEG, or nerve/muscle studies
Central nervous system/ neuromuscular diseases—injury	Often unremarkable, sometimes LGA	Often with evidence fetal stress/distress	Apnea	CNS depression or irritability, seizures, increased ICP, anemia	Abnormal head CT
Sepsis and hypotension	Often unremarkable, may have history UTI, poor prenatal care	Often with evidence fetal stress/distress	Apnea, mild to severe respiratory distress	Hypotension, poor perfusion, hypotonia	Abnormal CBC, elevated CRP

CNS = central nervous system. CT = computed tomography. CRP = C-reactive protein.

(*continued*)

Table 3. Differentiating Between the Many Etiologies for Newborn Hypoxia: Typical History and Clinical Findings (*continued*)

CATEGORY	PREGNANCY HISTORY	LABOR AND DELIVERY HISTORY	RESPIRATORY SIGNS	PHYSICAL EXAM	RADIOLOGICAL AND LAB DATA
Hematologic disorders—inherited and acquired (acquired disorders usually associated with a second category)	Unremarkable, or may have family history	Often unremarkable if inherited disorder	None, or mild if developing hypovolemia	Petechiae, purpura, ecchymoses, hematomas, prolonged bleeding with heelstick	Abnormal clotting studies, anemia
Metabolic abnormalities	Often unremarkable, but may have family history of metabolic disorder, or may have history of drug use	Unremarkable	Apnea (associated with seizures)	Hypotonia, tremors	Metabolic acidosis, electrolyte abnormalities, positive toxicology screen

loss of placental gas exchange (Anderson, Kleinman, Lister, & Talner, 2004).

Acute Hypoxia

Acute hypoxemia produces various circulatory adaptations in the fetus that enhances fetal survival, including the development of bradycardia, hypertension, redistribution of blood flow toward the brain, myocardium and adrenals, and depression of fetal breathing and skeletal muscle activity. The fetal heart also has a greater capacity for anaerobic metabolism than the adult heart (Jensen, 1991; Philipps, 2004).

Ischemia is a reduction of blood flow to an organ that either causes hypoxia by compromising oxygen and substrate delivery to an organ, or is caused by hypoxia when increasing hypoxic acidosis has a depressant effect on cardiovascular function. While in theory, the diving seal reflex maintains blood flow to vital organs during an acute hypoxic event, in practice, any organ system may become compromised after insult because of ischemia (Anderson et al., 2004; Jensen, 1991).

The neonatal brain is in some ways more resistant to acute hypoxia than the brain of an older child or adult. Nevertheless, hypoxia occurring in the fetus or newborn is a major cause of acute mortality and chronic neurologic disability in survivors. The outcome of infants sustaining cerebral hypoxia and ischemia is influenced by many factors, including the duration and severity of the event, and associated infectious, traumatic, or metabolic (especially hypoglycemic) derangements (Bloom, 2006).

At some point, repetitive episodes of severe hypoxia cause global neuronal, cortical, midbrain, and cerebellar damage, even to the "spared" CNS. Damage is typically to the watershed areas of the cerebral cortex, an event closely correlated to cerebral palsy and developmental disabilities in later life. The human fetus may experience these episodes during a high-risk pregnancy, well before birth, with recovery of biochemical markers of distress, such as metabolic acidosis (Bloom, 2006).

If myocardial contractility is impaired following severe or sustained hypoxia, the resultant reduction in cardiac output may further compromise cerebral blood flow and other organ perfusion. Again, depending on degree of insult, this can be associated with acute myocardial dilatation and resultant tricuspid regurgitation, myocardial ischemia, and hypotension. Such hypotension is usually resistant to volume resuscitation—dopamine has been shown to be more effective in restoring blood pressure in these infants.

Renal impairment is commonly reported following hypoxic-ischemic insult at birth. Again, depending on degree of insult, impairment can take the form of mild oliguria with minor electrolyte abnormality and minimally elevated creatinine, to full-blown renal failure requiring dialysis.

Elevated liver enzymes are also common following acute hypoxia, but irreversible liver damage is very rare. Liver enzymes levels are often telling in identifying the existence of a perinatal insult. Similarly, coagulation impairment should also be anticipated in severely affected newborns; however, treatment is supportive and resolution is the norm.

The full-term infant, while more likely to survive a severe hypoxic-ischemic insult at birth than a preterm infant (approximately 70% vs. 30%), is also more likely to have significant long-term morbidity than the preterm counterpart (Gressens & Huppi, 2006).

Chronic Hypoxia

Fetal cardiovascular and endocrine response may be altered not only in acute hypoxia but also in chronic hypoxia. This is important because recurrence of mild hypoxic insults may not be infrequent in human pregnancies, where blood flow to the placenta, uterus, and fetus is repeatedly compromised by many physiologic and environmental influences. In states of considerable chronic hypoxia, such as may occur in a variety of clinical situations, fetal growth retardation is not uncommon. Depression of growth factors during hypoxic states has an important protective effect by conserving fetal substrate for energy as opposed to growth needs (Noori et al., 2004; Seri & Evans, 2001).

Summary

Possibly the most common approach for the pediatric clinician involves the evaluation of the hypoxic infant during this transitional period. Differentiating between the many etiologies for newborn hypoxia is undoubtedly an incredible challenge for the pediatric specialist in the newborn nursery. While there are several common causes for newborn cyanosis—primary pulmonary disease and sepsis—a myriad of disorders spanning all organ systems exist as possibilities. It was the intention of this series to supply the practitioner with a basic knowledge of the breadth of these possibilities, as well as a systematic approach to the assessment of these term newborns to assure accurate diagnosis, treatment, and referral.

A summary of these categories of disorders, along with characteristic history and typical physical, laboratory, and radiologic findings can be found in Table 3. ✣

Annie J. Rohan is a Senior Nurse Practitioner, Stony Brook Hospital, Stony Brook, New York, and Jonas Nursing Scholar, Columbia University School of Nursing, PhD Program, New York, NY. She can be reached via e-mail at ajr73@columbia.edu

Sergio G. Golombek is an Associate Professor of Pediatrics and Clinical Public Health, New York Medical College, New York, NY, and an Attending Neonatologist, Maria Fareri Children's Hospital of Westchester Medical Center, Valhalla, New York.

The authors have disclosed that they have no financial relationships related to this article.

References

Anderson, P., Kleinman, C., Lister, G., & Talner, N. (2004). Cardiovascular function during development and response to hypoxia. In: R. Polin, W. Fox, & S. Abman (Eds.), *Fetal and neonatal physiology* (pp. 635-669). Philadelphia, PA: Saunders.

Anderson-Berry, A. L., & Belig, L. L. (2006). *Neonatal sepsis.* Retrieved May 28, 2009, from www.emedicine.com/ped/topic2630.htm

Bauer, C. R. (2005). Acute neonatal effects of cocaine exposure during pregnancy. *Archives of Pediatric and Adolescent Medicine, 159*, 824-834.

Bloom, R. (2006). Resuscitation of the newborn. In: A. A. Fanaroff, & R. J. Martin (Eds.), *Neonatal-Perinatal Medicine* (pp. 483–511). St Louis, MO: Mosby.

Castrodale, V. (2003). The hypotonic infant: Case study of central core disease. *Neonatal Network, 22*, 53-59.

Figueroa, R., Khabbaz, A., & Quirk, G. (2005). Identification and management of the fetus at risk for acidosis. In: A. Spitzer (Ed.), *Intensive Care of the Fetus and Neonate* (pp. 91-110). Philadelphia, PA: Mosby.

Golombek, S. G. (2000). The use of inhaled nitric oxide in newborn medicine. *Heart Disease, 2*, 342-347.

Gressens, P., & Huppi, P. S. (2006). The central nervous system: Hypoxic ischemic encephalopathy. In: R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Neonatal-perinatal medicine.* St Louis, MO: Mosby.

Hofmeyr, G. J., & Hannah, M. E. (2003). Planned caesarean section for term breech delivery. *Cochrane Database Review*, 3, CD000166.

Jensen, A. (1991). Effects of reducing uterine blood flow on fetal blood flow distribution and oxygen delivery. *Journal of Developmental Physiology, 15*, 309.

Levy, K., & Koren, G. (1990). Obstetric and neonatal effects of drug abuse. *Emergency Medicine Clinics of North America, 8*, 633.

Noori, S., Friedlich, P., & Seri, I. (2004). Pathophysiology of shock in the fetus and newborn. In R. Polin, W. Fox, & S. Abman (Eds.), *Fetal and neonatal physiology* (pp. 772-781). Philadelphia, PA: Saunders.

Painter, M. J., & Gaus, L. M. (1993). Neonatal seizures. In: K. M. Pellock, & E. C. Myer (Eds.), *Neurologic emergencies in infancy and childhood* (pp. 24-41). Boston: Butterworth-Heinemann.

Philipps, A. (2004). Oxygen consumption and general carbohydrate metabolism of the fetus. In R. Polin, W. Fox & S. Abman (Eds.), *Fetal and neonatal physiology* (pp. 465-478). Philadelphia, PA: Saunders.

Plessis, A. J. (2005). Perinatal asphyxia and hypoxic-ischemic brain injury. In A. Spitzer (Ed.), *Intensive care of the fetus and neonate* (pp. 775-802). Philadelphia, PA: Mosby.

Rohan, A., & Golombek, S. (2009a). Hypoxia in the term neonate: Part 1. *MCN: The American Journal of Maternal Child Nursing*, 34 (2).

Rohan, A., & Golombek, S. (2009b). Hypoxia in the term neonate: Part 2. *MCN: The American Journal of Maternal Child Nursing*, 34 (3).

Schwartz, J. F., Ahmann, P. A., Dykes, F. D., & Brann, A. F. (1993). Neonatal intracranial hemorrhage and hypoxia. In: K. M. Pellock, E. C. Myer (Eds.), *Neurologic Emergencies in Infancy and Childhood* (pp. 1-23). Boston: Butterworth-Heinemann.

Seri, I., & Evans, J. (2001). Controversies in the diagnosis and management of hypotension in the newborn infant. *Current Opinions in Pediatrics, 13*, 116.

Soper, D. E., Mayhall, C. G., & Dalton, H. P. (1989). Risk factors for intraamniotic infection: A prospective epidemiologic study. *American Journal of Obstetrics and Gynecology, 161*, 562.

Stebor, A. (2005). Basic principles of noninvasive blood pressure measurement in newborns. *Advances in Neonatal Care, 5*(5), 252-261.

Vanhaesebrouck, P. (1987). Tight nuchal cord and neonatal hypovolemic shock. *Archives of Diseases in Children, 62*, 1276.

Verklan, M. T. (2006). Persistent pulmonary hypertension of the newborn: Not a honeymoon anymore. *Journal of Neonatal and Perinatal Nursing, 20*, 98-112.

Volpe, J. J. (2001a). Hypoxic-ischemic encephalopathy: Clinical aspects. In: Neurology of the newborn (pp. 331-394). Philadelphia, PA: Saunders.

Volpe, J. J. (2001b). Neonatal seizures. In: *Neurology of the newborn* (pp. 178-214). Philadelphia, PA: Saunders.

Williams, L. J., Shaffer, T. H., & Greenspan, J. S. (2004). Inhaled nitric oxide therapy in the near-term or term neonate with hypoxic respiratory failure. *Neonatal Network, 23*, 5-13.