Oral Feeding Readiness in the Neonatal Intensive Care Unit

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Abstract

Oral feeding is a complex sensorimotor process that is influenced by many variables, making the introduction and management of oral feeding a challenge for many health care providers. Feeding practice guided by tradition or a trial-and-error approach may be inconsistent and has the potential to delay the progression of oral feeding skills. Oral feeding initiation and management should be based on careful, individualized assessment of the NICU infant and requires an understanding of neonatal physiology and neurodevelopment. The purpose of this article is to help the health care provider with this complex process by (a) defining oral feeding readiness, (b) describing the importance of oral feeding in the NICU and the physiology of feeding, and (c) providing a review of the literature regarding the transition from gavage to oral feeding in the NICU.

Oral feeding by breast or bottle is the first developmental milestone infants must achieve and is a necessary accomplishment for discharge from the neonatal intensive care unit (NICU). Often regarded as an innate skill, oral feeding is actually a very complex sensorimotor process that is influenced by many variables, both physiologic and environmental.[1,2] This complexity makes the introduction and management of oral feeding in the NICU a challenge for many health care providers.

Feeding practices vary among health care providers, and the process lacks consistency in many NICUs. Practice is often guided by tradition or by trial-and-error approach rather than the most current evidence.[3–6]

The purpose of this article is to: (a) define oral feeding readiness; (b) describe the importance of oral feeding in the NICU and the physiology involved with feeding; and (c) provide a review of the literature regarding the transition from gavage to oral feeding in the NICU.

DEFINITION OF ORAL FEEDING READINESS

Oral feeding readiness can be defined in two different contexts: (a) when an infant is ready to initiate oral feeding attempts for the first time, and (b) when an infant is ready to participate in a specific feeding event. The first definition describes when an infant, who has been exclusively receiving feedings by gavage tube, is ready to be introduced to oral feedings by breast or bottle. Oral feeding readiness in this context is usually determined by the infant's maturational state.[7] Most health care providers also take the infant's postconceptional age (PCA) and size into consideration prior to the introduction of oral feeding. Oral feeding readiness also refers to an infant's readiness to participate in a specific feeding event. Criteria used to determine this state of readiness include an infant's level of alertness, physiologic status, and display of hunger cues.[8]

The goal for infants is to safely make the transition to complete oral feeding and become a successful feeder prior to discharge. Successful feeding can be defined as the ability to take the prescribed volume in an appropriate time period while maintaining cardiorespiratory stability. The infant should be able to do this while maintaining their own temperature in a neutral thermal environment and maintaining appropriate weight gain.[9] Safe and successful feeding implies that the infant is at minimal risk for aspiration and has demonstrated coordination of sucking, swallowing, and breathing.[10]

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Importance of Oral Feeding in the Neonatal Intensive Care Unit

Improved technology has made it possible to increase the survival rate of infants born extremely premature and with complex medical diagnoses such as congenital heart disease and chromosomal anomalies. This has led increased morbidities, longer lengths of stay, and continued rising health care costs, making a timely discharge from the NICU a major focus of health care providers and third-party payers. Successful oral feeding is just one NICU discharge criterion and is often the last that infants achieve. Consequently, successful transition to oral feeding plays a critical role in determining discharge readiness from the NICU.

The American Academy of Pediatrics (AAP) Committee on Fetus and Newborn acknowledged that the decision to discharge a high-risk infant is a complex one that is based primarily on an infant's medical status, but it is also influenced by other factors that include (a) pressure to contain hospital costs by shortening length of stay, and (b) pressure from parents to discharge an infant even if the infant is not physiologically ready.[11] If discharged prior to achieving physiologic readiness, an infant may be placed at increased risk for rehospitalization.

If the introduction of oral feeding and the transition process is not approached carefully, an infant may require prolonged gavage tube feeding. This experience can be traumatic for both the infant and their family. Dodrill and colleagues found that even healthy preterm infants can be at risk for long-term altered oral sensitivity, facial defensiveness, and oral feeding delays if they receive >3 weeks of nasogastric (NG) feeding compared to preterm infants who received <2 weeks of NG feeding.[12] Consequences of long-term gavage tube feeding include esophageal inflammation, pharyngeal desensitization, and an increased risk for gastroesophageal reflux (GER). Gastroesophageal reflux impacts oral feeding and may be demonstrated by emesis, food refusal, arching of the back during feedings, a hypersensitive gag reflex, dysphagia, coughing, and choking. Gastroesophageal reflux may also lead to laryngeal and pharyngeal edema, increasing the risk of aspiration. Feeding problems left unresolved at the time of discharge may persist into early childhood and present as oral feeding aversion and other long-term feeding issues, which include tactile sensitivity, selective eating, and failure to thrive.[10,13,14]

The importance of oral feeding to the family should not be overlooked. Feeding, whether by breast or bottle, allows a mother to bond and form an attachment with her infant. Silberstien and colleagues found that infants with less intact neurobehavioral functioning had difficulties with the transition to oral feeding, having a negative impact on mother–infant relationships.[15] Problems with oral feeding potentially prolong an infant's hospital stay which then becomes an emotional, psychological, and financial burden for the entire family.[8,13,16,17]

PHYSIOLOGY OF FEEDING

Successful oral feeding is a complex physiologic process that is dependent on the coordination of sucking, swallowing, and breathing. In utero studies have shown that the sucking reflex begins as early as 15 weeks gestation.[18–20] Swallowing begins by 15 weeks gestation and occurs consistently by 22–24 weeks gestation.[2,21] Fetal breathing is first noted around ten weeks gestation.[20] Despite these reflexes being present in utero, it remains unclear as to what is the optimal time to introduce oral feedings in the NICU.

Health care providers generally agree that premature infants develop the ability to coordinate sucking, swallowing, and breathing and are ready to begin oral feedings between 32 and 34 weeks gestation.[3,10,21–24] Researchers have noted that infants may be able to obtain suck-swallow-breathe coordination as early as 28 weeks but may lack the physiologic stability to feed successfully at that gestation.[25–28] Rogers and Arvedson examined the neurobiology and physiology of feeding, and their work illustrates the complexity of the feeding process and the maturation that must occur for premature infants to orally feed.[2]

Development of Sucking, Swallowing, and Breathing Coordination

Lau and colleagues identified five primary stages of sucking development in the preterm newborn, beginning with no suction and arrhythmic expression and advancing to a rhythmic, well-defined suction and expression.[26] During this process, an infant's suck becomes more rhythmic and he develops sucking bursts. The sucking bursts become more prolonged and have increased amplitude as an infant matures. In the final stage of sucking development, suction amplitude increases to the point that it resembles the suck of a full-term infant. Lau and colleagues found that oral motor skills advance with increasing PCA but that there was a wide variation in feeding skills between subjects at any given PCA.[26] There was no correlation found between level of feeding skills and an infant's gestational age (GA) at birth. The exact etiology as to why some infant's oral feeding skills advanced faster than others remained unclear. It should be noted that the population of infants they studied consisted of relatively healthy preterm infants.

Amaizu and colleagues confirmed that the development of oral feeding skills mature at different rates in different infants.[24] Unlike Lau and colleagues, they did find that GA at birth has an impact on the development of feeding skills. When they stratified their data between 26/27 and 28/29 weeks GA at birth, they found that those born earlier had more difficulty with feeding coordination when oral attempts were initiated. By the time the 26/27 weeks group reached 6–8 bottle feedings per day, their feeding skills were similar to that of the 28/29 week group. Both groups began oral attempts at 33–34 weeks PCA and reached full oral feedings by 38 weeks PCA.

Gewolb and colleagues studied the developmental patterns of rhythmic suck and swallow in 20 healthy preterm infants using intranipple and pharyngeal pressure recordings. They

noted that swallow rhythm is established as early as 32 weeks PCA, and the stability of the swallow rhythm did not improve between 32 and 40 weeks postmenstrual age (PMA).[18] The maturation of sucking and swallowing of preterm and full-term infants can be summarized as increased sucking and swallowing rates, longer sucking bursts, and larger volumes per suck as PCA increases. After 34 weeks PCA, sucking patterns are well-defined and coordinated with swallowing at a 1:1 ratio.

Two components of suck, expression and suction, play an important role in the suck-swallow-breathe relationship.[25] Expression is the positive pressure that results from the squeezing of the nipple between the hard palate and the tongue leading to the expression of milk. Suction is the negative pressure inside the oral cavity during feeding. Preterm infants initially demonstrate more expression than suction, and this is coordinated with swallow. As preterm infants mature, alternating suction and expression are demonstrated with improved coordination occurring with swallowing.[18]

Coordination of the swallow with breathing must occur during a safe phase of the respiratory cycle to prevent aspiration.[10] The safest time to swallow is when there is no airflow, either at the beginning or end of inspiration or expiration.[29] The coordination of breathing and swallowing matures significantly between 34 and 42 weeks PCA.[2] Full-term and preterm infants demonstrate decreased minute ventilation, respiratory rate, and tidal volume during oral feeding in the initial weeks of learning to feed. These physiologic changes disappear shortly after birth in full-term infants, unless they have been neurologically compromised. These physiologic differences may persist in preterm infants as they continue to mature developmentally. Apnea related to swallowing can be seen during this maturational phase but decreases with increasing PCA. These physiologic differences also help explain why preterm infants are at a higher risk for aspiration.[29]

The link between neurologic maturation and the coordination of sucking, swallowing, and breathing has been studied.[10,18,29] It has been hypothesized that suck-swallow coordination does not develop simultaneously with swallow-breathe coordination. Instead, this coordination develops in a caudocephalad manner within the brainstem. Gewolb and colleagues found that the maturation of the swallowing rhythm occurred before the maturation of the sucking rhythm, which would support this hypothesis.[18] The work done by Lau and colleagues implies that stable suck-swallow-coordination has been achieved by preterm infants by the time oral feedings are introduced.[29] Stable swallow-breathe coordination evolves more slowly and continues to become more coordinated as the preterm infant matures.

Enhancing the Maturation of Feeding Skills

Researchers have looked at the correlation between maturation of feeding skills and increasing PCA versus feeding experience. Gewolb and colleagues found that feeding skills did not improve with increased feeding experience. However, the majority of evidence suggests otherwise.[18] Amaizu and colleagues studied 16 infants born between 26 and 29 weeks gestation and found that "training" or feeding experience did enhance the development of oral feeding skills when nonnutritive stimulation (NNS) was offered prior to the introduction of oral feeding.[24] Pickler and Crosson found that preterm infants with more feeding experience contributed to shorter transition times to full oral feeding regardless of the severity of illness of the infant.[30] The Neonatal Cochrane Review identified numerous studies regarding the use of NNS and concluded that this practice does aid in the transition from gavage to oral feeding.[31] It is believed that NNS facilitates the development of sucking behavior as well as digestion, which improves the tolerance of enteral feeding.

Poore and colleagues found that the use of orocutaneous therapy speeds up the transition to oral feedings.[21] Orocutaneous stimulation is provided to preterm infants by a biomedical device called the NTrainer. The NTrainer sends pneumatic pulses through a silicone pacifier for three minute intervals mimicking an appropriate nonnutritive sucking pattern, which differs from a nutritive sucking pattern. The impact of this therapy on nonnutritive sucking patterns has not been studied, but a correlation between this therapy and improved oral feeding was noted. Orocutaneous stimulation is thought to enhance the development of central pattern generators (CPGs), which are neural networks within the brainstem that control swallowing and breathing.[10]

Assessment of Oral Feeding Readiness

Breton and Steinwender posed an interesting question: "Is sucking and feeding developmentally programmed in infants?"[20] If this was the case, then the introduction of oral feeding would simply involve waiting until an infant reached the appropriate maturational stage and displayed specific feeding readiness cues. As described earlier, oral feeding is a complex physiologic and neurobehavioral process where multiple internal and external variables come into play. This makes the determination of oral feeding readiness that much more complicated.

Howe and colleagues conducted a literature review and identified seven neonatal feeding assessment tools (Table 1).[32] The psychometric properties of these tools were evaluated, and none were found to have been empirically validated. More well-designed studies are needed to evaluate the validity, reliability, and responsiveness of these instruments for use in the NICU. Additionally, there are some limitations of the tools currently available: (a) not all were designed to score both bottle and breastfeeding readiness; (b) not all were designed to score both term and premature infants; and (c) most were not designed for use by the average caregiver in the clinical setting and require a training course.

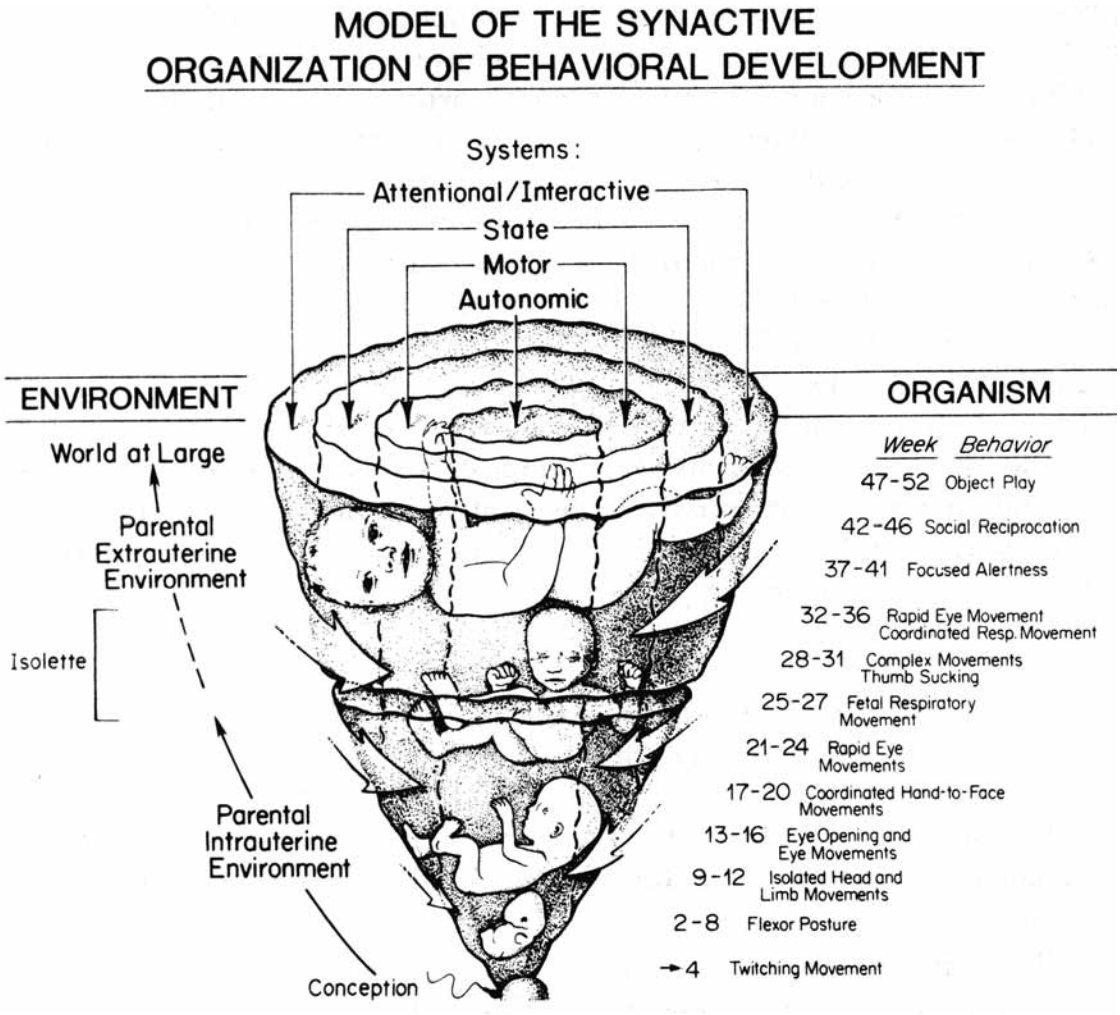
Until a valid and reliable assessment tool can be identified, the decision to initiate oral feeding is often a subjective one made by the health care provider. The synactive theory of neonatal behavioral organization developed by Heidelise Als (Figure 1) provides an understanding of the neurodevelopment of preterm infants and can help guide health care

TABLE 1 ■ Neonatal Feeding Assessment Tools

Tool	Mode of Feeding	Target Age Group	Number of Scoring Items	Person Scoring
Early feeding skills (EFS)[45]	Bottle	Preterm	36	Trained professionals
Infant Breastfeeding Assessment Tool (IBFAT)[46]	Breast	Term	6	Mother or professionals
LATCH[47]	Breast	Preterm/term	5	Postnatal caregiver (original version) or mother (revised version)
Mother–Baby Assessment (MBA)[48]	Breast	Term	10	Nurse
Neonatal Oral-Motor Assessment Scale (NOMAS)[49]	Breast/bottle	Preterm/term	28	Trained professionals
Preterm Infant Breastfeeding Behavior Scale (PIBBS)[50]	Breast	Preterm	6	Professionals and mothers
Systematic Assessment of the Infant at Breast (SAIB)[51]	Breast	Term	18	Nurses and mother

Note: Adapted from Howe TH, Lin KC, Fu CP, Su CT, Hsieh CL. A review of psychometric properties of feeding assessment tools used in neonates. *J Obstet Gynecol Neonatal Nurs*, 2008;37(3):338–349.

FIGURE 1 ■ Als' synactive model of neonatal behavioral organization.



Note: Adapted from Als H. Toward a synactive theory of development: promise for the assessment and support of infant individuality. *Infant Ment Health J.* 1982;3(4):229–243. Copyright by The Michigan Association for Infant Mental Health. Reprinted with permission.

providers in their decision making regarding oral feeding readiness. This theory proposes that preterm infants interact with and adapt to their environment through the integrated activity of four hierarchical subsystems: autonomic, motor, behavioral, and attention/interaction. An infant strives for an organized state through self-regulation, which is achieved when a stable relationship exists between the subsystems and the environment. Caregivers can help the preterm infant become organized and achieve self-regulation by providing individualized care based on infant behaviors.[7,8,14,33–35]

Preterm infants mature in each of the subsystems in a sequential fashion. An infant must first obtain stability of the autonomic and motor subsystems before he can move on to the higher level tasks, such as oral feeding.[14] Oral feeding can stress the autonomic subsystem of the preterm infant, causing a disorganized state (Table 2). If an infant cannot self-regulate and remain in an organized state then he will have difficulty in feeding.[7,8]

TABLE 2 ■ Signs of Disorganized State Behavior

Autonomic and visceral stress signals	• Seizures • Respiratory pauses • Tachypnea • Color changes (mottled, webbed, cyanotic, grey, flushed) • Gagging • Gasping • Spitting up • Hiccoughing • Straining as if or actually producing bowel movement • Tremoring and startling • Twitching • Coughing • Sneezing • Yawning • Sighing
Motoric stress signals	• Flaccidity (trunk, extremities, facial) • Hypertonicity (legs, arms, trunk, finger splaying, facial grimacing, tongue extensions, hand on face, high guard arm, fisting, fetal tuck) • Frantic/diffuse activity
Behavior state-related stress signals	• Diffuse sleep/awake states with whimpering sounds, facial twitches, smiling • Eye floating • Strained fussing or crying • Staring • Gaze aversion • Panicked or worried alertness • Glassy-eyed, strained alertness • Rapid-state oscillations • Irritability and diffuse arousal • Crying

Note: Adapted from Als H. Toward a synactive theory of development: promise for the assessment and support of infant individuality. *Infant Ment Health J.* 1982;3(4):229–243.

Once an infant achieves autonomic control, he must achieve motor control. The motor subsystem includes muscle tone, posture, body movements, and facial movements. If an infant has poor motor control, he will move into a disorganized state (see Table 2) and will have difficulty with oral feeding as well as unnecessary energy expenditure.[7,8,14]

The behavioral state system indicates the infant's level of alertness. This covers a wide range of behavior states, from sleep state to full arousal with crying. A preterm infant must be able to transition through these states and achieve a quiet alert or active alert state for successful oral feeding to occur. This state may be very brief in preterm infants caused by their immature central nervous system.[7,8,14]

The final subsystem of attention/interaction is the most complex because it requires an infant to be alert and interact with the environment. Alertness is an organized state of behavior where an infant is most able to interact with the environment. This is the most optimal state for oral feeding and essential for feeding success.[14]

At any given point, if balance between the infant's subsystem and environment is not achieved, disorganized behavior may be demonstrated by the preterm infant. The NICU environment, with its excessive light, noise, multiple caregivers, and inconsistent care can overwhelm a preterm infant leading to a disorganized state. Signs of disorganized behavior (see Table 2) indicate stress and that the infant is not ready for oral feeding. The NICU nurse and parents of the hospitalized infant are often the first to recognize these signs of a disorganized state.

With the lack of a valid and reliable tool to determine feeding readiness, it is up to the health care provider to decide when to initiate oral feeding. There are specific variables to consider that determine an infant's maturational state and influence oral feeding readiness: (a) GA at birth; (b) PCA at the time oral feedings are being considered; (c) severity of illness; (d) respiratory and cardiovascular stability (i.e., need for oxygen support, apnea, bradycardia); (e) motor stability (tone, posture, quality of movement); (f) sucking, swallowing, and breathing coordination; (g) ability to maintain temperature in an open environment; (h) ability to maintain alertness; (i) demonstration of hunger cues; and (j) tolerance of enteral feedings, which indicates overall physical well-being.[8,33,36,37] The health care provider should perform individual assessments, evaluating each of these variables, to determine an infant's maturational state and if the highest hierarchical subsystem has been reached. Careful consideration prior to initiation of oral feeding will give each infant the greatest chance to achieve feeding success.

It is obvious that the more premature an infant is at birth, the longer it will take him to reach the maturational state required to orally feed. However, there is still controversy over the appropriate PCA to begin oral feeding, which is why it should not be the sole deciding factor. Based on the

understanding of physiology and information in the literature, it is clear that feeding readiness is specific to individual infants. Preterm infants of the same PCA will demonstrate feeding readiness at different times, and their feeding skill development will also progress at individual rates. The PCA at which infants make the successful transition to full oral feeding will also vary depending on individual infant circumstances and severity of illness. It is important to note that not all preterm infants will achieve this milestone by 36–38 weeks gestation.

TRANSITION FROM GAVAGE TO ORAL FEEDING FOR THE HEALTHY PRETERM INFANT

On average, the transition from gavage to oral feeding has been found to take 10–14 days for healthy preterm infants.[7,33,38] Eichenwald and colleagues suggested that variation in NICU care practices may delay the identification of mature feeding behavior, leading to the delay of the initiation of oral feeding and lengthening of hospital stay.[5] Several researchers have focused on the development of oral feeding protocols or pathways to guide the transition process and improve the consistency of care. However, little evidence is available to support the benefits of these protocols.

Kirk and colleagues studied 51 preterm infants to determine if the use of a nursing-driven, cue-based clinical pathway for oral feeding initiation and advancement would result in the achievement of earlier full oral feeding.[39] The control group had oral feedings managed by physician order, and the study group had oral feedings managed by nursing staff using the clinical pathway. Study infants reached full oral feeding six days earlier than infants in the control group. Limitations of this study were lack of randomization, small sample size, and the fact that strict compliance to the pathway was not measured. This study was designed to assess the oral feeding management of a broader group of premature infants and was not designed to specifically look at infants with specific morbidities.

McCain and colleagues studied 81 preterm infants to determine if a semidemand feeding protocol (based on infant cues) would allow infants to achieve full oral feeding earlier than those receiving standard care (gradual increase of oral attempts).[6] The semidemand method was noted to shorten the time to full oral feedings by five days. The authors noted that both groups had appropriate weight gain during the transition period. Infants with congenital anomalies, gastrointestinal conditions, neurologic diagnoses, or Grade III or IV intraventricular hemorrhage were excluded from the study.

Simpson and colleagues studied 29 preterm infants (<30 weeks GA) to determine if the early introduction of oral feeding would shorten the transition time to full oral feeding.[19] Infants were randomized to the experimental group (initiated oral feeding 48 hours after reaching full enteral feeding by gavage tube) and to the control group (oral feeding managed by the physician). The protocol established for the experimental group eliminated the bias placed on weight and PCA criteria typically used for initiating oral feeding and provided guidelines for advancing oral feeding. Infants in the experimental group were introduced to oral feedings about 2.6 weeks sooner (32.4 weeks PMA ± 1.0) than their control group counterparts (34.3 weeks PMA ± 0.9). The experimental group achieved full oral feeding at an earlier PCA (34.5 weeks PMA ± 1.6) and had a shorter transition time to full oral feedings by almost 12 days. Weight gain and discharge weights were similar for both groups. This study found no correlation between the time it took to achieve full oral feeding and discharge home; however, the experimental group was discharged ten days earlier than the control group. It should be noted that this study design only addressed oral feeding of the healthy premature infant.

Drenckpohl and colleagues compared the clinical outcomes of two different oral feeding protocols. This was a retrospective study that included 200 preterm infants born at <34 weeks GA. The control group included infants transitioned to full oral feeding with a protocol based on established feeding times. The intervention group was transitioned using a protocol based on infant feeding cues. It was noted that infants following the cue-based protocol began oral feedings one week earlier than the control group. There was no statistical significance between the groups regarding (a) when oral feedings were initiated, (b) weight status during hospitalization and at time of discharge, (c) feeding therapy consultations, and (d) length of stay. Limitations of this study were that it was retrospective and that the subjects were relatively healthy preterm infants.[40]

Premji and colleagues described the Calgary Health Region Neonatal Oral Feeding Protocol (CHRNOFP), which was developed by an interdisciplinary team in Canada.[34] This evidence-based, nursing-driven protocol was the result of a quality improvement initiative that began with the revelation that NICUs across Calgary provided inconsistent and often contradictory strategies for the initiation and management of oral feeding. Als' synactive theory of development provided the theoretical framework for the protocol. The authors acknowledged that feeding is a social interaction between caregiver and infant, and a huge emphasis was placed on nurse–infant and mother–infant interactions.[41] Other premises of the protocol included (a) strong communication between caregivers and families to promote consistency and continuity of feeding practices, and (b) the quality of the feeding experience is more important than the quantity consumed by the infant. The protocol consisted of five stages beginning with the preoral stimulation stage. In this stage, an attempt was made to minimize negative oral stimulation. This is followed by a nonnutritive sucking (NNS) stage, where NNS was actively offered to infants. There were three phases of nutritive sucking: minimal, moderate, and full oral feeding. The minimal intake phase focused on making the feeding experience as positive as possible, focusing more on

the quality of the feed than the quantity taken. The moderate intake phase involves the infant taking 10–80 percent of his daily enteral feeding orally. Full oral feeding is indicated by the infant taking >80 percent of his daily feeding volume and focuses on preparing the family for discharge. In 2006, the CHRNOFP Committee evaluated the use of the oral feeding protocol in the five participating units at four hospital sites. Pretest and posttest questionnaires were used to examine nurse and physician awareness of the protocol's basic premises. Poor response rates for the survey portion of the evaluation (32 percent pre and 13 percent post for registered nurses; 89 percent pre and 0 percent post for physicians) made it difficult for inferences to be made. The protocol was found to provide practical information pertaining to feeding strategies; however, these strategies were inconsistently used in clinical practice.[42]

Shaker and Woida described a protocol for initiating and advancing oral feedings for three distinct groups of patients: the healthy preterm infant, preterm infants with a complicated medical course, and sick term infants.[43] Infants are assigned a Neonatal Medical Index (NMI) score, developed by Korner and colleagues in 1993, to determine the severity level of their illness.[44] This score determines which path is taken along the feeding protocol. The protocols are nursing-driven and cue-based for all three groups of infants. The protocols for the preterm infant with medical complications and the sick term infant prompt early involvement by a feeding specialist.

The evidence presented here demonstrates a common theme. Feeding practice should be based on the most current evidence, and health care providers should strive to provide consistent care. Decisions regarding feeding readiness should be based on careful, individualized assessment of infants, looking for signs of stability or stress. Care-giving interventions should be individualized and be based on cues given by the infant. This individualized, developmentally supportive approach also encourages parent participation and support so that they are able to feed their infant competently and confidently. Nursing staff have the most interaction with NICU infants and families and are in the best position to guide the transition from gavage to oral feeding.[16]

SUMMARY

The initiation of oral feeding should be undertaken after careful, individualized assessment of the NICU infant, keeping multiple factors in mind. The decision to initiate oral feeding should not be solely based on an infant's PCA. Feeding initiation and management should be done consistently and ideally based on nursing observation of individual infant feeding readiness behaviors. The health care provider should remember that feeding skills develop and mature at different rates in individual infants. Infants of the same GA at birth or PCA may not reach full oral feeding in the same time interval. The health care provider should expect the feeding skills of infants to mature at their own pace and to be influenced by their severity of illness. It should be expected that extremely premature infants or those with a higher degree of morbidity will take longer to transition to full oral feeding and may not reach full oral feeding by 36–40 weeks PCA.

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Case Reports of Congenital Central Hypoventilation Syndrome

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Abstract

Congenital central hypoventilation syndrome (CCHS), which occurs in less than 1 in every 50,000 infants and children, is a rare syndrome first noted in literature by Mellins in 1970. Congenital central hypoventilation syndrome is a condition in which the patient loses the drive to breathe during deep sleep and can mimic many diseases. Until recently, CCHS has largely been a diagnosis of exclusion; fortunately, there is now a genetic test available to confirm the diagnosis.

The purpose of this article is to discuss the steps taken to confirm the diagnosis of CCHS. In addition to the history of the disease and clinical manifestations, genetics and prognosis of children with CCHS will be discussed. Two cases are presented for illustration of hospital course and preparation for discharge.

Congenital central hypoventilation syndrome (CCHS), once known as Ondine's curse, is a rare syndrome characterized by the inability to respond to hypercapnia and hypoxemia while asleep. Congenital central hypoventilation syndrome affects nearly 1 in 50,000 infants and children.[1] As of 2008, there were an estimated 500 cases of CCHS in the United States and Europe.[2] Infants diagnosed with CCHS are usually full term with uneventful pregnancies and deliveries. These infants require assisted ventilation, especially at rest, in the absence of lung disease, infection, or lung anomaly of any sort. Despite the rarity of this disorder, a significant amount of research has been conducted and has shown this to be an autonomic nervous system dysfunction or dysregulation. The central chemoreceptors seem to fail; however, the peripheral chemoreceptors remain active.[3] Congenital central hypoventilation syndrome has been shown to result from mutations in the *PHOX2B* gene, which is a gene located on chromosome 4p12.[3] A diagnostic genetic test is now available to detect these mutations.

In this article the history, genetics, pathophysiology, clinical presentation, diagnosis, management, and prognosis of CCHS will be discussed. In addition, two confirmed cases of CCHS that occurred in the same facility will be presented. The first case took much longer to diagnose because of the rare nature of the disorder. Many other differential diagnoses were considered prior to testing for the *PHOX2B* gene.

The second case was diagnosed more readily by including the evaluation for the *PHOX2B* gene with the other diagnostic testing done in the first week of admission. The purpose of this case review is to assist others in the early detection of the syndrome, resulting in more timely intervention and education for the caregivers and family members.

HISTORY

In 1970, CCHS was first reported in an article by Mellins.[4] Since then, CCHS has been known by several other names including central hypoventilation syndrome, alveolar hypoventilation, central apnea syndrome, and Ondine's curse.[5] When combined with Hirschsprung's disease, it is referred to as Haddad syndrome.[6] The name *Ondine's curse* comes from German folklore in which the nymph Ondine falls in love with a mortal. The mortal is then unfaithful to Ondine. Ondine's father, the nymph king, placed a curse on the mortal requiring that the mortal remember to perform all bodily functions including breathing. When the mortal falls asleep, he "forgets" to breathe and he dies.[3]

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GENETICS

For many years, researchers suspected CCHS was caused by a genetic defect. In 2003–2004, researchers found *PHOX2B* as the "disease-defining gene."[7] *PHOX2B* is located on the chromosome 4p12 and is a key gene in autonomic nervous system development.[7] *PHOX2B* is a transcription factor required for proper migration of neural crest cells and development of autonomic neural crest derivatives such as peripheral chemoreceptors.[8] The majority of CCHS cases have heterozygous polyalanine expansions in the second polyalanine repeat region in exon 3 of the *PHOX2B* gene on chromosome 4p12; a few others have missense, nonsense, or frame shift mutations.[2]

Most cases of CCHS result from spontaneous mutations of the *PHOX2B* gene. However, there is an inherited form of CCHS. This form is autosomal dominant with different types of phenotypic expression.[2] Children who are in the same family can have different/varying degrees of symptoms ranging from none to severe. Some studies have reported CCHS children have a phenotypical face, which is reportedly box-shaped, generally shorter and flatter.[2] These children have decreased upper face height, increased nasal tip protrusion, decreased upper lip height, and decreased nasolabial angle.[13]

The expression of the gene mutation can vary from mild, with the child only needing minimal ventilator support while sleeping, to severe, that is, needing ventilation support regardless of his sleep state.[9] One study has suggested that the length of the *PHOX2B* polyalanine repeat mutation is correlated with the number of autonomic nervous system symptoms.[10] There is also a significant association between the number of repeats in the mutation and the ventilation support which is required.[10] The *PHOX2B* gene is confirmed by testing a blood sample using a polymerase chain reaction (PCR)-based assay.[7] Gene testing is sent as the PCR-based assay to a regional research facility.

Genetic counseling is done with the parents, and they are given the option for further testing because some parents carry the gene and are unaware.[13]

PATHOPHYSIOLOGY

Under normal circumstances, the control of ventilatory function involves several key components, including the central and peripheral nervous system, a patent upper airway, and sufficient strength of the musculoskeletal system. Respiratory drive and minute ventilation are controlled by centers in the midbrain with input from the central and peripheral chemoreceptors.[1]

Although the principal problem in CCHS has not been discovered, histologic and anatomic changes in the peripheral and central nervous system in those areas involved in the central control of respiratory function have been identified.[11] This includes decreased neuronal signaling in the cerebellar region of the brain,[11] changes in the glomus cells in the carotid bodies, nonspecific degenerative changes in the arcuate nucleus of the midbrain, and decreased dense core vesicles, the storage site for neurotransmitters in the peripheral chemoreceptors of the carotid bodies.[1] Research has suggested that CCHS represents a primary physiologic abnormality of integration of chemoreceptor input to central ventilatory controllers, rather than abnormalities in the chemoreceptors themselves.[11]

The symptoms of CCHS are potentiated during deep sleep and nonrapid eye movement (NREM) sleep and are less severe during rapid eye movement (REM) sleep and wakefulness.[12]

Congenital central hypoventilation syndrome represents an extreme form of autonomic nervous system dysfunction/dysregulation.[13] A nonprogressive congenital sleep disorder, CCHS is now considered to be a component of a neurocristopathy or a defect in neural crest cell migration.[1] Because of this association with a neural cell migrational defect, several other diseases are often associated and diagnosed with CCHS. They are Hirschsprung's disease and neural crest tumors such as neuroblastoma, ganglioneuroma, and ganglioneuroblastoma. These tumors can present at any age, but tumor-related deaths are not common.[2] These children with CCHS also can present with other physiologic symptoms of autonomic nervous system dysregulation including cardiovascular symptoms (e.g., decreased heart rate variability and cardiac dysrhythmias), gastrointestinal symptoms (e.g., constipation, dysphasia, or gastric reflux), altered temperature regulation (a lack of fever with infection, altered sweating, low basal body temperature), and altered pain perception.[2] These infants may also have eye abnormalities, which include strabismus, poor papillary response, and convergence insufficiency.[14]

CLINICAL PRESENTATION

The spectrum of the disease has a wide range. Some have only mild hypoventilation during quiet sleep but normal ventilation while awake, whereas others have complete apnea while sleeping and severe hypoventilation while awake.[9]

The majority of CCHS cases are diagnosed in the newborn period. The syndrome can present in several ways. The newborn may become dusky or cyanotic after falling asleep. While asleep there is a simultaneous and progressive rise in PCO_2 and fall in PO_2 without changes in respiratory rate. The baby also fails to arouse in response to these changes.[2] Others present around three months of age with cyanosis, edema, and symptoms of right-sided congestive heart failure related to the persistent undiagnosed hypoxia, which forces the heart to work harder. Lastly, a few will present with life-threatening events of tachycardia, diaphoresis, and cyanosis while the baby is asleep.[2]

DIAGNOSIS

Congenital central hypoventilation syndrome can mimic many diseases, and in the past has primarily been a diagnosis of exclusion.[15] The diagnosis is made when documentation of hypoventilation during sleep occurs in the absence of primary neuromuscular, brain, lung, or cardiac disease.[16] The diagnostic criterion for CCHS includes (a) continual hypoventilation during sleep with a PCO_2 >60 mmHg,

TABLE 1 ■ Differential Diagnoses and Pertinent Tests

Differential Diagnosis	Evaluation
1. Structural abnormalities of brainstem	1. CT or MRI of brain
2. Neuromuscular diseases myotonic dystrophy	2. Polysomnography
3. Cardiovascular disease	3. Pulmonary function testing
4. Primary pulmonary disorders	4. Bronchoscopy
5. Metabolic disease	5. Chest x-ray
6. Trauma delivery, nonaccidental, and so forth	6. Diaphragm ultrasonography or fluoroscopy
7. Asphyxia	7. ECG, echocardiography, holter monitor
8. Infection—respiratory	8. Muscle biopsy
9. Infarction cerebral or cerebellar	9. Rectal biopsy
	10. Genetic testing for *PHOX2B*[1]

(b) the beginning of symptoms during the first year of life, (c) the absence of primary neuromuscular or pulmonary disease, and (d) no cardiac disease.[1] The differential diagnosis list (Table 1) is substantial; therefore, extensive evaluation must be done before the definitive diagnosis can be confirmed. Confirmation of the diagnosis is made with the *PHOX2B* gene testing. The exclusion testing, which is done before the genetic test returns, is beneficial in ruling out other conditions that can be part of the CCHS diagnosis, such as Hirschsprung's disease.

CASE PRESENTATIONS

Baby A was born at 40 weeks gestation to a 19-year-old primigravida who was O+. The mother's rapid plasma reagin (RPR), group β *Streptococcus* infection (GBS) status, hepatitis, and rubella were all satisfactory, and she had no history of smoking, illicit drug use, or alcohol use. Complications of the pregnancy included pregnancy-induced hypertension (PIH), with frequent colds and viruses. Baby A was born via cesarean section caused by the PIH. Membranes were ruptured at delivery and Apgars were 7 and 8, respectively.

Within a few hours of delivery, the baby was intubated and placed on a ventilator for persistent cyanosis and apnea. The baby was transferred to the tertiary facility on day of life (DOL) 3 after several unsuccessful attempts to wean the infant from the ventilator, which resulted in respiratory insufficiency as evidenced by inexplicable, labile carbon dioxide (PCO_2) levels. Prior to transfer, the referring facility drew a blood culture, placed the infant on antibiotics, and performed an echocardiogram and a cranial ultrasound, both of which were normal.

Initial testing at the tertiary facility included an evaluation for sepsis, chest x-ray, abdominal x-ray, an echocardiogram, and magnetic resonance imaging (MRI) of the brain. No abnormalities were appreciated on any of the tests. A pediatric neurology consult was obtained. Per the suggestion of neurology to rule out any possible metabolic disease, metabolic studies, including serum ammonia, carnitine, urine organic, and plasma amino acids were obtained. All of these results were also within normal limits.

On DOL 8 an electroencephalogram (EEG) was obtained because of the patient's persistent apneic episodes despite being assisted on the ventilator. Of note, most apneic spells occurred on low mechanical ventilator breathing rates and when the patient was at rest or sleeping. The EEG showed a normal sleep/wake recording for patient age with no seizure activity identified.

An ear, nose, and throat (ENT) specialist was then consulted on DOL 12. At this time, a second attempt at extubation was made, but the patient continued to have recurrent apneic spells, noted especially during sleep. A flexible bronchoscopy was performed, which showed normal anatomy. Pulmonology was then consulted, recommending a multichannel sleep study and the diagnosis of CCHS as well as *PHOX2B* gene testing. The sleep study showed several apneic and hypoventilation episodes leading to the suggested genetic testing for the *PHOX2B* gene on DOL 17.

Although awaiting the *PHOX2B* results, several unsuccessful attempts were made at weaning the ventilator and extubation. A CO_2 detector proved to be accurate and useful in maintaining normal CO_2 levels. An end tidal CO_2 detector, which is attached to the end of the endotracheal tube, was used to monitor the CO_2 levels continuously. By watching the levels, the practitioners were able to make ventilator changes in a timely manner and keep the CO_2 in a normal range. On DOL 34 the *PHOX2B* test was positive, confirming the diagnosis of CCHS. Further evaluation included echocardiogram to rule out cor pulmonale (normal), holter monitor (normal), and ophthalmic exam (normal). Urine catecholamines and abdominal ultrasonography were done to rule out neuroblastoma. As mentioned in this article earlier, neuroblastomas are a migrational disorder and can accompany CCHS. On DOL 38, a rectal biopsy, circumcision, gastrostomy tube insertion, and tracheotomy were performed. The rectal biopsy was negative for Hirschsprung's disease. Baby A was eventually discharged to a pediatric long-term care facility on continuous ventilation on DOL 89.

Baby B was term gestation and born to a 30-year-old mother who was gravida 3, para 2, A+, RPR nonreactive, hepatitis B negative, and rubella immune. Complications included late prenatal care, polyhydramnios, and PIH. Mom smoked but denied illicit drug use or alcohol use. Baby B was born via repeat cesarean section. Thin meconium was noted at delivery. Initially, Baby B had spontaneous respirations but quickly became apneic, requiring positive pressure ventilation. Apgars were 5 and 6, respectively.

Baby B was intubated and placed on a ventilator for the first 24 hours of life. Over the next several days, the baby was extubated and reintubated (for apnea and high CO_2s) with no obvious lung disease per x-ray. Baby B received dexamethasone for attempts at extubation and also experienced labile PCO_2s (30–120). A cranial ultrasound, an EEG, a renal ultrasound, and a sepsis evaluation were performed, all of which were normal.

Baby B was transferred at four days of age to a tertiary pediatric center because of failure to remain extubated. Initial testing included an echocardiogram, which showed a small patent ductus arteriosus; and an MRI of the brain and an EEG, both of which were normal. Pediatric neurology and pulmonology were consulted on DOL 5, which resulted in recommendations to test for *PHOX2B*, carnitine, ammonia, urine organic acids, lumbar puncture (LP) for CSF and lactate, and further neuromuscular studies. The LP studies were normal, and the spinal muscular atrophy test was negative. All metabolic tests were within normal limits. On DOL 8, a rigid and flexible bronchoscopy were performed by ENT after consultation. The bronchoscopy showed normal structures, copious secretions, and moderate subglottic edema.

During the interim of testing, further unsuccessful attempts at extubating Baby B were made. The *PHOX2B* testing was sent on DOL 9. The results returned 13 days later confirming the diagnosis of CCHS.

Placement of gastrostomy tube and tracheostomy was performed on DOL 25. Teaching for all home care and transition to home ventilator took place over the next few weeks. The baby was discharged home on DOL 113.

MANAGEMENT

Management of CCHS depends primarily on the severity of the syndrome. All individuals need a thorough evaluation by a pediatric pulmonologist. Some patients will require constant-assisted ventilation, whereas others only require ventilation intervention at times of rest or sleep.

Once the diagnostic evaluation is completed and the infant has been evaluated by a pulmonologist, the need for a tracheotomy is determined. A tracheostomy will allow for eventual transition to a home ventilator. Monitoring of sleep/wake cycles and need for ventilatory intervention should be established prior to transition to a home ventilator. This will help define the need for continuous positive pressure or positive pressure assistance just during sleep cycles. The patient is stabilized on a conventional ventilator while hospitalized and then transitioned to a home ventilator for discharge. Once at home, the parents/caregivers must manage these children with extreme vigilance because of their lack of response to hypoxemia and hypercarbia.[15]

Over the first few years of life, some patients improve their independent ventilatory efforts during times of wakefulness. However, caution is required as the child will still not respond to hypoxia in times of sleep because the peripheral autonomic regulation remains unresponsive.[2]

Regardless of the severity of the syndrome, the caregivers must be extremely attentive to any subtle changes as these children may not alter their temperature when infected because of autonomic dysregulation.[2] Because of this unusual clinical feature, sepsis symptoms may be missed until the child is in grave danger.

Long-term multidisciplinary follow-up with these patients is of utmost importance to document proper growth, speech, mental and motor development. Regular follow-up visits with their pediatrician, pulmonologist, and all other specialists involved are imperative.

PROGNOSIS

Earlier diagnosis results in better long-term survival and better outcomes. Mortality can be low with lifelong optimal ventilation. Most deaths are caused by pulmonary infections. Two-thirds to 80 percent of patients are able to breathe on their own while awake after infancy.[2] However, continuing abnormalities in breathing require lifelong ventilatory support.[15] Neurologic complications can include learning disabilities and attention deficit disorder.[17]

Children with CCHS now have prolonged survival and most have a good quality of life. Long-term studies of neurodevelopmental outcomes show a broad range of results. The neurologic status usually correlates to the severity of CCHS.[11] Mortality is most often associated with complications, caused by long-term mechanical ventilation or from bowel involvement.[3] Highly motivated parents play a vital role in providing care to these most complex of patients. No known cure for CCHS exists, and the disorder is lifelong.

SUMMARY

Congenital central hypoventilation syndrome is a complicated syndrome, not only because the road to diagnosis can be quite tedious, but also because the management and subsequent discharge can be quite a challenge. Diagnosis, care, and subsequent discharge home require a multidisciplinary approach as well as patience, persistence, and good outpatient follow-up. Each step is uniquely challenging and involves careful planning and assessment. Because CCHS is a nonprogressive disease, these children can live productive lives with good care and consistent follow-up.

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The Apgar Score: Simple Yet Complex

Lori Rubarth, PhD, NNP-BC

Evaluation of the newborn at birth includes assignment of the Apgar scores at one and five minutes of age. Dr. Virginia Apgar (Figure 1) developed this evaluation procedure in the 1950s, and it has been used routinely for more than a half century. Apgar developed this assessment tool with five objective criteria: (a) heart rate (HR), (b) respiratory effort, (c) reflex irritability, (d) muscle tone, and (e) color (Table 1).[1] Apgar described the criteria, scoring method, and the rationale for each of the five criteria. She stated in her second report that HR and respiratory effort were the most important of the five assessment criteria; that reflex irritability and muscle tone were next in importance; and that color was the least important.[2] She explained that color is dependent on the criteria of HR and respiratory effort. To become pink, an infant needs to be breathing.

PURPOSE OF SCORING

Apgar's initial purpose in the development of the Apgar score was an attempt to predict survival.[1] In studying the relationship between mortality rates and Apgar scores she demonstrated that those infants with low scores (0–2) had higher rates of death (14 percent). Those infants with high scores (7–10) had lower death rates (0.13 percent). Her research showed that infants delivered by cesarean section had lower overall Apgar scores than those delivered vaginally.

Casey, McIntire, and Leveno studied more than 150,000 infants over a 10-year period, evaluating the five-minute Apgar score in relation to mortality within the first month of life.[3] The one-minute Apgar score was found to be less useful in predicting mortality because many infants with low one-minute scores recover quickly by five minutes of age. In looking at the five-minute Apgar score, they found that the mortality rate for preterm infants (26 to 36 weeks gestation) with low Apgar scores (0–3) was 315 deaths per 1,000 infants compared with 5 per 1,000 for preterm infants with high Apgar scores (7–10). The mortality rate for term infants (>37 weeks) with low Apgar scores was 244 per 1,000, whereas the mortality rate for term infants with high Apgar scores was 0.2 per 1,000. They concluded that Apgar's scoring system is still useful in predicting survival at 28 days of life. Butterfield and Covey stated that the Apgar score "reflects the immediate status as well as the prognosis of the newborn infant."[4(p143)]

The Apgar score was not meant as a tool for whether to initiate resuscitation, even though Dr. Apgar stated that "the score was especially useful in judging the need for resuscitative measures, such as respiratory assistance."[2(p1985)] The need for resuscitation often occurs prior to one minute of age.[5] The infant dictates the need for resuscitation, not the Apgar score. The criteria of HR and breathing/respirations are used in both neonatal resuscitation and in the Apgar score.[5] Dr. Apgar was an early advocate for assessment of the infant and stated the importance of assessing the infant's HR and respirations, just as the Neonatal Resuscitation Program (NRP) does today. Even though clinicians do not wait for the results of the Apgar score to decide whether to proceed with resuscitation efforts, the score can be used to compare the results of resuscitative efforts to the initial assessment of the infant. With continued resuscitation, the infant is assessed every five minutes until recovery or death occurs. The Apgar score can show the effects of a well-done resuscitation.[6]

The Apgar score was meant as a consistent way to evaluate and score the condition of infants after birth. It was not meant as a predictor of neurologic outcomes or asphyxia but has been previously misused to predict cerebral palsy.[3,7,8] Nelson and Ellenberg found a high risk of motor impairment associated with prolonged, low Apgar scores (<4 for longer than 10–15 minutes) in term infants. Mainly, Apgar scores have been used to predict survival or mortality.

The Apgar score has been used for many reasons. Clinicians must understand that the Apgar score will increase with successful resuscitation and may be useful for predicting overall survival rates. Primarily, the Apgar score is a quick assessment tool for evaluating the infant at the specific times of one minute and five minutes after birth.

EACH SCORING CRITERIA AND ITS POSSIBLE VARIATIONS

Heart Rate

Heart rate is a very objective measurement and is the easiest criterion to assess in the newborn. There are variations in how the HR is evaluated. The nurse or neonatal nurse practitioner (NNP) must either listen with a stethoscope for a HR or feel for the pulse on the umbilical stump. The HR is usually assessed shortly after birth but needs to be repeated at one minute of age and five minutes of age for the Apgar score. There may be a drop in HR after birth as a result of suctioning, emesis of amniotic fluid, or some other vagal stimulus.

Disclosure

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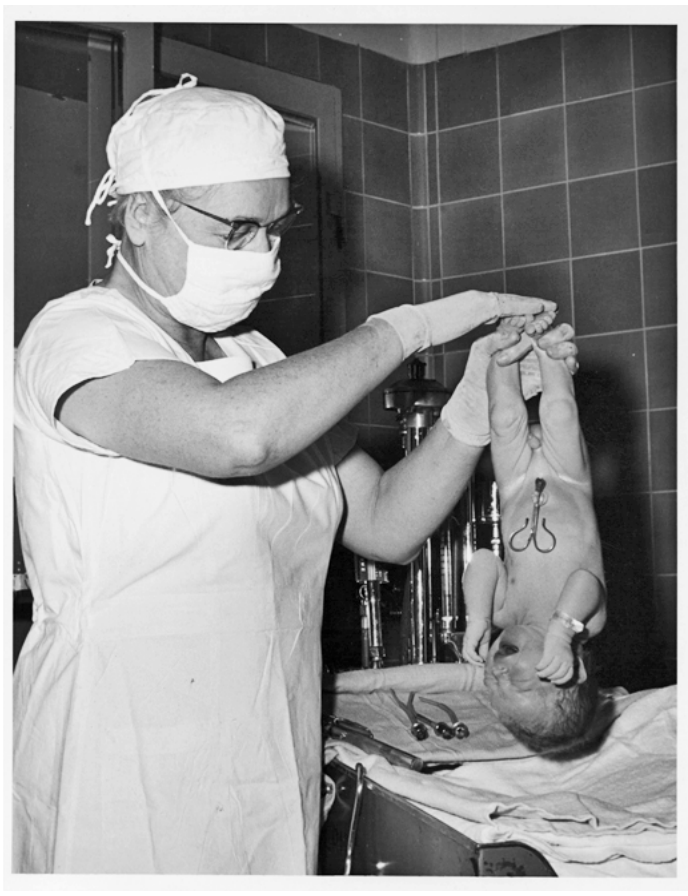
FIGURE 1 ■ Dr. Virginia Apgar evaluating a newborn for reflex irritability.



Source: National Library of Medicine.

Palpation of the HR is done by positioning your fingers at the base of the umbilical stump near the skin or beneath the umbilical cord. As per NRP recommendations, you can palpate for six seconds and multiply by 10 for a quick evaluation.[5]

Most infants born by vaginal delivery with fetal heart tones present will have a pulse or HR after birth. A HR can be so slow that the six-second check does not catch a beat. Before declaring that the HR is absent, it should be checked more thoroughly. In cases where the HR is slow, the nurse or NNP can listen with a stethoscope for one full minute while resuscitation continues. If the HR is not auscultated the baby should be placed on a cardiorespiratory monitor to assess cardiac status. Electrical activity could be present without a forceful contraction and pulse; in this case, chest compressions would still be immediately required.

Infants with no HR score a 0; infants with a HR >100 receive a score of 2, and an infant with any HR between one and 100 will receive a score of 1. One can look at the scoring of HR as absent (0 score) to present or normal (>100), with everything in between as being a score of 1. Following a perinatal insult, the HR is the last to disappear and the first to return with adequate resuscitation.[2]

Respiratory Effort

The respiratory effort criterion focuses on whether or not the baby requires assistance with breathing. Infants who are apneic will receive a 0 score for this criteria and require stimulation or assistance to breathe. Infants who are breathing normally without increased effort or crying will receive a 2 score and nothing needs to be done. Infants who have hypoventilation usually can't ventilate sufficiently to keep their HR above 100.

As with changes in HR between delivery and one minute of life, the infant may cry at delivery but become apneic by one minute of age. This would require the evaluator to score a 0 for one minute of age for respiratory effort. Although unusual, some infants may cry and then go apneic, requiring stimulation, and even bagging to start breathing again.

Infants who are grunting, have nasal flaring, retractions, or are having some types of respiratory distress will still be breathing—although often too fast—and would score a 2. Some evaluators mistakenly give these infants a 1 score because of their respiratory distress. The respiratory effort criterion looks at the infant's breathing or respirations—from none, minimal, some, or good effort—and does not involve the distress that may accompany the respirations. There is a difference between respiratory effort and respiratory distress. As long as the infant is breathing, the infant scores a 2, even

TABLE 1 ■ Apgar Scoring Chart With All Known Variations in Terminology

CRITERIA	SCORE		
	0	1	2
Heart rate	Absent	<100/minute	≥100/minute
Respiratory effort	Absent	~~Irregular Respirations~~ (deleted in 1958 per Dr. Apgar); weak cry; hypoventilation; shallow respirations; slow respirations; gasping	Good cry; good; cry; crying; strong cry; lusty cry; breathing well; good respiratory effort
Reflex irritability	Absent; no response	Grimace; some motion	Cough, sneeze, or cry; active withdrawal (pulls away from foot stimulation)
Muscle tone	Flaccid; limp	Some flexion	Flexion of extremities; resistance of extension; active motion
Color	Blue; pale	Body pink and extremities blue; acrocyanosis	Completely pink

with retractions and grunting. The Apgar score is to reflect the extent of his breathing effort or respirations. In NRP, we state whether the infant is breathing or not. In Apgar scoring, this would be either "No, no breathing—absent" which gives a score of 0 or a "Yes, the infant is breathing—present" which would give him a score of 2. The gasping respirations or weak, poor effort consistent with inadequate ventilation would give the infant a 1 score for respiratory effort. A premature infant may have inadequate ventilation because of a lack of surfactant and may result in a score of 1 based on poor respiratory effort or hypoventilation. Most term infants who are breathing will be receiving a score of 2 for respiratory effort *because they will be breathing well enough to keep their HR above 100.*

Reflex Irritability

Reflex irritability is the infant's response to stimulation. Initially, the stimulation that Apgar recommended was suctioning of the mouth and nares with a catheter.[1] In 1958, Apgar wrote that a change in the reflex stimulation from suctioning to "a brisk tangential slap of the soles of the feet" was simpler to do and more effective for testing this criteria.[2(p1988)] The main objective of reflex irritability is to do something to the infant that would cause the normal infant to become upset or cry. The evaluator either bulb suctions the infant, slaps the feet, or otherwise irritates the infant. Bulb suctioning is also no longer recommended by the NRP. They suggest wiping fluids out of the mouth with a towel and using bulb syringes for known obstruction.[5]

In the past century, infants were hung by their ankles and slapped on their bottoms to stimulate them to cry. Today, we are more cautious and stimulate them to cry by drying them off and vigorously rubbing their back or slapping the soles of their feet. Most infants are crying readily and do not need further stimulation to exhibit this reflex or response. Both muscle tone and reflex irritability tests the neurologic status of the newborn.[5]

Infants who do not respond to stimulation are given a 0 score. Infants who cry are given a 2 score, and infants who only make a facial grimace or respond with "some motion" will receive a 1 score. Again, looking at it from an absent to present perspective can be helpful. Absent is no response, and present is the full-blown crying of a normal, healthy infant. Infants who have a mediocre response will receive the middle score of 1.

Muscle Tone

Muscle tone was described by Apgar as "an easy sign to judge."[1(p261)] Muscle tone is the last criterion to return following a hypoxic insult and successful resuscitation. Hypotonia occurs after the insult caused by ischemia of the nonvital organs. Hypoxia and the resulting ischemia cause a lack of adenosine triphosphate (ATP) for muscle activity.[9] Tone can be decreased for 15 to 20 minutes after a successful resuscitation, with active movement slow to return.

Apgar's theory of ease of measurement would suggest that there should be less variation in the scoring of muscle tone between individual evaluators; however, this does not appear to be the case. In one study of 42 raters viewing a video of a delivery, interrater reliability for muscle tone was quite low at 0.46.[10] The raters were nurses, physicians, and residents in various specialties. A 1.00 reliability rating would be perfectly consistent with each other, and a rating of 0.00 would be no relationship between the raters. These raters were given an Apgar score sheet and asked to score the baby on the video. There were wide variations between the scores assigned among the raters and also when compared with the original score at birth. The original scores given in the delivery room at birth were higher than those given by the raters of the videos. This study showed the difficulty in the consistency of Apgar scoring, especially with the muscle tone criterion.

In rating the muscle tone, a limp or floppy baby with no appreciable muscle tone would score a 0—absent tone. An infant who is actively moving with good flexion would receive a 2 score—present. An infant who is somewhere in between with some tone or some flexion would receive a 1 score.

Color

Color is a more difficult criterion to measure. Unlike HR, color is a subjective measure. Is the baby pink or blue? Totally pink or totally blue may not be difficult to assess, but the infant's color as perceived by the rater may be affected by factors such as the lighting in the room, the infant's race, and differences in hemoglobin levels. In a study by O'Donnell and colleagues, the interrater reliability of color was only 0.30.[10] This very low reliability among the raters helps to explain the wide variations seen in assignment of Apgar scores after birth.

When the cyanosis is disappearing and the infant is pink to the umbilicus and blue below the umbilicus, what Apgar score do you give for color? If the infant's lips are pink, do you consider him pink? What does "centrally" pink really mean? What is acrocyanosis? More consistency in rating color is necessary.

According to Apgar, "a score of two was given only when the entire child was pink" and many infants remain blue at one minute of age.[1(p262)] Oxygen saturations slowly increase from 60 percent in utero to more than 90 percent by about five minutes of age in normal, healthy newborns after birth.[11] A score of 1 is given if the infant still has acrocyanosis, which is blue hands and feet. The entire extremity does not have to be blue. With cyanotic hands and feet, the infant would receive a score of 1. Acrocyanosis is common in newborns during the first 24 hours of life, but usually disappears after an infant is sufficiently warmed and perfusion to the hands and feet has improved. Therefore, the majority of infants will be scored a 1 at five minutes because of the presence of acrocyanosis. Infants with central or truncal cyanosis would score

a 0. A score of 1 is given when the entire body is pink even if extremities are still blue.

The new NRP manual states that "skin color can be a very poor indicator of oxygen saturation."[5(pIX)] Studies have shown inaccuracies with the clinical interpretation of color when compared with pulse oximetry readings.[12–14] The use of pulse oximetry in the delivery room is one way to make the color criterion more measurable and objective. A record of the infant's pulse oximeter reading at one and five minutes may facilitate the scoring of color. Of course, making the pulse oximeter work well on an infant who is still adjusting to extrauterine life will be a challenge to nursing staff in the delivery room. Then the questions we will be asking are "How high does the pulse oximeter reading have to be?" and "If the pulse oximeter reading is more than 90 percent on the foot, is that completely pink?" Work remains to be done in determining how pulse oximetry can be incorporated into Apgar scoring. It may eventually replace the color criterion on the Apgar score.

ACRONYM OF APGAR

In 1962, two pediatricians, Butterfield and Covey, developed and published an acronym of the Apgar score to make it easier for house officers to remember the five areas of assessment based on Apgar's name.[4] The five criteria are listed with their new titles subsequently:

A = Appearance (color)
P = Pulse (heart rate)
G = Grimace (reflex irritability)
A = Activity (muscle tone)
R = Respiration (respiratory effort)

This acronym can be used as a mnemonic device to facilitate our memory of the Apgar score but may also be more confusing to some individuals. The most important items (HR and respiratory effort) are no longer at the top of the list. The least important (color) is first. The appearance of the infant really includes more than just color, and the grimace is only one scored item under reflex irritability. Some published Apgar score charts use this nomenclature, and others use Apgar's original criteria. In the Apgar chart by Dr. Butterfield and Dr. Covey, the terminology used for respirations is again "irregular" or "slow" for a score of 1 and "good" or "strong cry" is listed for a score of 2.[4(p143)] Dr. Apgar had removed the term "irregular" in 1958 from her Apgar chart. Now it is back! Also, the terms "good" and "strong cry" could be interpreted as one term instead of the two possible terms. It should say "good" for respiratory effort meaning there is good respirations or a "strong cry." This is where many Apgar charts began writing that infants must have a "good, strong cry," instead of one or the other, to obtain a 2 on their respiratory criteria. There have been many various terms used in each category over the past 50 years (Table 1). This is one of the many reasons that there is so much variation in the assignment of Apgar scores to newborns.

VARIATIONS IN MEASUREMENT

Inflation of Scores

Some clinicians inadvertently inflate the Apgar score in the delivery room. The obstetrician would like the highest possible score. The nurse, pediatric resident, or NNP are the usual evaluator of the infant in the delivery room. Some of the causes of score inflation will be reviewed.

Case 1

A baby is born with spontaneous cry and respirations, HR of 146, and good tone. The baby is pink with blue hands and feet, although the upper arms and legs are pink.

One NNP interpreted "extremities blue" on the color criteria for score 1 to mean that the entire extremity must be totally blue, not just hands and feet. If this interpretation were true, then this NNP would give that baby an Apgar score of 2 for color and 10 for the overall score. Her interpretation was that acrocyanosis was normal in newborns; therefore, she would give a score of 10 to all infants who were normal with only acrocyanosis. If the body was pink, but upper arms and upper legs were still blue as the baby was "pinking up," then she would give the infant a 1 for color. This resulted in infants with much higher scores than normal when she was the NNP in attendance. The obstetricians loved her scoring—they love it when their infants receive a score of 10.

Case 2

A baby is born with spontaneous cry and respirations, HR of 156, and good tone. The baby is pinking up slowly and the lips are now pink as well as the upper chest, but there is a distinct line of blue color at the midabdomen.

One NNP gave an infant an Apgar score of 9 because the baby's lips were pink, even though the rest of the body was still blue. The head and lips were pinking, but the rest of the infant was still blue or cyanotic. Does the infant score a 0 or 1 for color? Is he completely pink? Is his body completely pink?

No, the trunk or body is still blue, although he is in the process of "pinking up." Dr. Apgar had stated that the entire body must be pink with only acrocyanosis to receive a score of "1." This is another incidence of elevation of scores.

Case 3

A preterm infant is born by cesarean section and had a HR of 90. He is intubated and ventilated in the delivery room. His HR increases readily to 166. He remains floppy without movement at one minute of age. The pediatric resident is bagging the infant on 100 percent oxygen, and he is very pink.

This infant was given an Apgar score of 7, with a score of 2 for color and 2 for respiratory effort because of the ventilation efforts of the pediatric resident. The infant has 2 for HR and 0 for tone. The resident gave him 1 for reflex irritability because the infant may have gagged during the intubation. These elevations of the Apgar scores may be unintentional. Many of us in the delivery rooms like to have the parents

happy with us. A higher score makes them happy. The issue is that it must be a true score. It is important to recognize your own bias as it pertains to the Apgar score.

Deflation of Scores

The same variations in measurement or measurement errors occur in the deflation of Apgar scores. Many score sheets list the terminology for a full score on the respiratory criterion as "good cry" (see Table 1). Therefore, many infants cannot achieve the full score without crying.

Case 4

An infant was born with a good HR and a respiratory rate of 60 and but was grunting, flaring, and retracting. The infant was active, moving all extremities, and crying between periods of grunting respirations. The infant's color was pink with oxygen blow at 40 percent.

A nurse evaluated this newborn term infant in the delivery room. She gave the infant a score of 1 for respiratory effort. According to this nurse, the infant was making a lot of effort to breathe, and therefore, she lowered the respiratory effort criterion of the Apgar score for that infant.

The amount or type of respiratory distress does not apply to the Apgar score. Its main criterion is whether the infant is breathing, not breathing, irregularly or intermittently breathing, or not breathing deep enough to maintain a HR more than 100 beats per minute. This seems to be a difficult concept for some evaluators who look at respiratory distress on a daily basis in the neonatal intensive care unit. This criterion deals with breathing (present = 2 points or absent = 0 points), and then all others in between receive a score of 1. This criteria has had the most controversy in my discussions with evaluators. There is more than one way to interpret the information. One must examine the original meaning of the Apgar score and its purpose for these infants.

Case 5

An infant who was breathing well is born with a HR of 140, respirations of 56, good tone, very active, but wouldn't withdraw his foot upon stimulation and is pink with acrocyanosis.

The nurse at the delivery stated that the infant didn't cry. She would not give the infant a score of 2 for respiratory effort or for reflex irritability because the sheet she used said "good cry" for both those criteria. The infant did not cry, so the infant lost two points on his total score, and received an Apgar score of 7. His score should have been 9 because he was breathing well, had a good HR, responded to stimulation, and had good muscle tone. He should have received only 1 point off for acrocyanosis. The score sheet should have stated "good" or "crying," not "good cry."

Most evaluators do not purposefully deflate the infant's Apgar score. But a lack of knowledge about the criteria, how to test it, and what the words really mean can influence the credibility of the evaluators.

Intubated and Ventilated Infants

A 26-week gestation infant is intubated at delivery and is pink on manual ventilation and supplemental FiO_2. The clinician assigns a score of 10, even though the infant was not breathing on his own. Another clinician may give this same infant a score of 5 because there was no respiratory effort on his own (0 for respirations), he was therefore blue without the oxygen (0 for color), and demonstrated minimal reaction to stimuli (1 for reflex grimace). The difference in these two assessments of the premature infant's Apgar scores presents a significant variation in scoring methods. Which method is correct? How should the premature on the ventilator be scored? Is it what the infant can do or what the evaluator is doing to the infant to accomplish the response?

So what should be done to evaluate the intubated and ventilated infants? Most of these infants are premature. Premature infants usually have decreased tone and decreased reflexes. Therefore, because of their immaturity, their overall Apgar scores will be lower.[15] There is controversy on this topic.[10,16] One suggestion in the literature is to stop the resuscitation momentarily at the one-minute or five-minute time period to quickly assess the extent of the infant's spontaneous respirations.[16] The rest of the evaluation can occur during the resuscitative efforts; this way, the evaluator is assessing the infant's abilities independent of the efforts of the resuscitation team, which has now led this infant to an improved chance of life. This approach accepts that premature infants may have lowered scores because of their immaturity. Other factors can also influence the Apgar score: drugs, congenital anomalies, neurologic defects, hypoxia, and infection. These factors can lower the Apgar score if they cause apnea, hypotonia, or bradycardia. Premature infants will have lower tone than the term infant, and this will also affect the Apgar score.

A newer, expanded variation of the Apgar score sheet was developed and published in 2006 (Figure 2).[15] This form was adopted for use by the NRP and is also used in many delivery rooms in the United States (AAP/AHA, 2011). Along with the numerical score, it allows the evaluator to document interventions on the Apgar score sheet along with the numbers scored. This way the clinician can identify that the baby is completely pink but receiving 100 percent oxygen. Justification of scores with the necessary interventions can provide a clearer picture of the infant at each time period. There is a place to continue to document the assessments every five minutes until the infant is 20 minutes of age; it also provides a comment section if needed. Providing a clear picture of the newborn, especially of those requiring intervention, is necessary to document the infant's assessment and the evaluator's responses. Clarity of scoring should be a goal for all evaluators while providing immediate and continuing assessment of the newborn.

Implications for Practice

There continues to be wide variations in scoring by health care providers in the delivery room.[6,10,16] The most senior neonatal health care provider in the delivery room should be the

FIGURE 2 ■ Twenty-minute Apgar scoring chart with resuscitation efforts.

Criteria 1 minute	0	1	2		**Total =**
Heart rate	Absent	<100	≥100		_____ O_2 (Amt) ❑ Oximeter ❑ CPAP ❑ PPV ❑ ETT ❑ Compressions _____ Other
Respirations	Absent	Weak/gasping	Breathing		
Muscle tone	Limp	Some flexion	Active motion		
Reflex irritability	No response	Facial grimace	Cry or withdrawal		
Color	Blue/pale	Acrocyanosis	Pink (≥90% sats)		
Criteria 5 minutes	**0**	**1**	**2**		**Total =**
Heart rate	Absent	<100	≥100		_____ O_2 (Amt) ❑ Oximeter ❑ CPAP ❑ PPV ❑ ETT ❑ Compressions _____ Other
Respirations	Absent	Weak/gasping	Breathing		
Muscle tone	Limp	Some flexion	Active motion		
Reflex irritability	No response	Facial grimace	Cry or withdrawal		
Color	Blue/pale	Acrocyanosis	Pink (≥90% sats)		
Criteria 10 minutes	**0**	**1**	**2**		**Total =**
Heart rate	Absent	<100	≥100		_____ O_2 (Amt) ❑ Oximeter ❑ CPAP ❑ PPV ❑ ETT ❑ Compressions _____ Other
Respirations	Absent	Weak/gasping	Breathing		
Muscle tone	Limp	Some flexion	Active motion		
Reflex irritability	No response	Facial grimace	Cry or withdrawal		
Color	Blue/pale	Acrocyanosis	Pink (≥90% sats)		
Criteria 15 minutes	**0**	**1**	**2**		**Total =**
Heart rate	Absent	<100	≥100		_____ O_2 (Amt) ❑ Oximeter ❑ CPAP ❑ PPV ❑ ETT ❑ Compressions _____ Other
Respirations	Absent	Weak/gasping	Breathing		
Muscle tone	Limp	Some flexion	Active motion		
Reflex irritability	No response	Facial grimace	Cry or withdrawal		
Color	Blue/pale	Acrocyanosis	Pink (≥90% sats)		
Criteria 20 minutes	**0**	**1**	**2**		**Total =**
Heart rate	Absent	<100	≥100		_____ O_2 (Amt) ❑ Oximeter ❑ CPAP ❑ PPV ❑ ETT ❑ Compressions _____ Other
Respirations	Absent	Weak/gasping	Breathing		
Muscle tone	Limp	Some flexion	Active motion		
Reflex irritability	No response	Facial grimace	Cry or withdrawal		
Color	Blue/pale	Acrocyanosis	Pink (≥90% sats)		

Note: sats = saturations; O_2 = oxygen; Amt = amount; CPAP = continuous positive airway pressure; PPV = positive pressure ventilation; ETT= endotracheal tube.

Source: Adapted from: AAP/ACOG. The Apgar Score [policy statement]. *Pediatrics*. 2006;117:1446, and Apgar, Holaday, James, Weisbrot, & Berrien. Evaluation of the newborn infant—Second report. *JAMA*. 1958:168(15),1985–1988.

one to assign the Apgar score. In O'Donnell and colleague's study, there was no difference in assignment of Apgar scores between the types of providers, whether nurse, obstetrical physician, obstetrical resident, pediatric resident, pediatric fellow, or neonatologist.[10] All providers who evaluate newborns for the Apgar score must have extensive training in assessing the infant quickly at the appropriate time. Timing is important, and evaluators need to know and understand the rationale for scoring that Dr. Apgar implemented. A timer in the delivery room or on the infant warmer should be used. All evaluators need to know what is meant by the scoring of each criterion to maintain the reliability and credibility of Apgar scores. The

interpretation of the score must be unbiased and discussed with colleagues and coworkers. Does everyone in your unit measure the five criteria in the same way? Are there differences between evaluators? O'Donnell and colleagues speculated that many Apgar scores are assigned retrospectively, as is the case from my experience.[10] When the timer alarm sounds, the infant should be evaluated at that point in time; even if it is by taking a mental picture of the infant into your mind. For experienced evaluators, a number often comes to your mind for that baby when the alarm sounds. The years of experience can help an evaluator "see" the infant and do the scoring almost instantaneously. Often the difficulty is hearing the alarms at one and five minutes. It is important to hear those alarms and respond accordingly.

After seeing the wide variations in the Apgar scoring of a number of case scenarios, Lopriore and associates asked that we "follow Apgar's original definitions more strictly."[16(p144)] A 20-minute Apgar scoring chart was developed with resuscitation efforts (Figure 2). The criteria are listed in order of importance instead of starting with color. This chart states the original intentions of Dr. Apgar with respirations listed, instead of respiratory effort, to clarify for the evaluator. Breathing is the goal of the respiration criteria. Heart rate ≥100 is the goal of the HR criteria. Other Apgar forms list <100 or >100, but what if it was 100? For color, the eventual change to oximeter scoring is in the future. The goal of color is saturation >90 percent. Future charts will have "oxygen saturation <70 percent or pale" being a score of "0," "oxygen saturations between 70 and 90 percent" gives a score of "1," and "oxygen saturations >90 percent" would give the infant a score of "2." These scores will eventually replace the blue, acrocyanosis, and pink color terminology.

Another future consideration would be for the neonatal team members to discuss the score together in the delivery room and decide the Apgar score. This may improve the interrater reliability and our credibility as evaluators. As Jobe and Papile both stated in their previous editorials on the subject, the Apgar score forces the caregivers to look at the infants, and that is good![17,18]

SUMMARY

The purpose and use of the Apgar score in clinical care has been questioned in the past and continues to be questioned today. The Apgar score, when done correctly, gives the clinician a picture of the infant at two different periods of time, four minutes apart. After a baby is born, the physician asks, "What is the Apgar?" The Apgar score has been used by lawyers to sue obstetricians. The parents often ask also, "What is the Apgar?" The Apgar score has been used by physicians to predict survival or possible handicap. The Apgar score is used around the world. So what is the purpose of the Apgar score? It provides the clinician with information. An initial low Apgar can tell the clinician that the infant was stressed *in utero* or endured a hypoxic or ischemic episode. The second Apgar score can provide information on how the infant responded to a skilled resuscitation. This provides additional information on the infant's present condition and will help the clinician manage the care of every newborn. Infants with lower Apgar scores require closer observation and may be at risk for ischemic injury. Infants with high Apgar scores are at less risk of death or morbidity.

There are many individual factors that affect the Apgar score, including the skill of the evaluator, the maturity of the infant, maternal medications, and the need for resuscitation. The imprecision of the Apgar scoring is a limitation of any predictive abilities of the tool. The scoring criteria are based on absent to present. The low score is absent, and the high score is present. The score of 1 is when the evaluator scores the criteria as somewhere in the middle. If the evaluators consider this when performing the scoring assessment, it may improve the reliability of the scoring system.

Some of the confusion about Apgar scores is over the many terms that have been used over the years to describe the different criteria. The various terms used to describe infants are listed in the Apgar score chart (see Table 1). Most score sheets list only one or two of the terms, and it varies with facility and country. The expanded Apgar scoring has some advantages in that the clinician can document the reasoning behind the scores. It includes the resuscitation efforts with the score and trends it over time (20 minutes). The 20-minute Apgar scoring chart (see Figure 2) has a quick check-box for each Apgar criteria, oximeter reading, and treatments given. The sheet would be a record of the infant's condition over time, and the resuscitation efforts given for the initial 20 minutes of life. This checklist could be used for preterm infants or those requiring resuscitation. Consistency in scoring can make the Apgar score a useful tool for assessing an infant's condition at birth. Research should be done on ways to improve the scoring inconsistencies to improve our risk assessments at birth.

Apgar Scoring Scenarios

A. A baby is born limp, pale with a HR of 40 beats per minute and no respiratory effort. What is the one-minute Apgar score?
ANSWER _____

B. At five minutes of age, the baby has a HR of 110, is tachypneic with significant grunting and retractions, coughs with bulb suctioning, has some flexion of the extremities, and is acrocyanotic. What is the five-minute Apgar score?
ANSWER _____

C. A preterm infant at 26 weeks gestation is born with no respiratory effort, blue color, and HR of 80. He is intubated and ventilated at about one minute of age. By five minutes of age, he has blue hands and feet, but is otherwise completely pink with a HR of 148, actively moving all extremities, responds well to stimulation of bulb syringe into the mouth (by grimacing his face and appearing to cry). He withdraws his foot when flicked. He appears to be "fighting" the ventilator. What is the five-minute Apgar score now?
ANSWER _____

A. Apgar = 1 B. Apgar = 8 C. Apgar = 9

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Buprenorphine: A Newer Drug for Treating Neonatal Abstinence Syndrome

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Neonates may be exposed to various legal and illicit substances during gestation, including cigarettes, alcohol, narcotics, benzodiazepines, antidepressants, and stimulants. Many of these substances can result in varying degrees of drug withdrawal after delivery. Polysubstance use can complicate the clinical evaluation of a newborn both in terms of assessment of withdrawal and treatment of symptoms. For the purpose of this column, the focus is on those infants with in utero narcotic exposure. The primary circumstances under which pregnant women use narcotics are illicit drug abuse, prescribed narcotic maintenance as treatment for abuse, and treatment of chronic pain conditions.

Fifty-five percent to 94 percent of neonates with in utero narcotic exposure will develop neonatal abstinence syndrome (NAS).[1] Neonatal abstinence syndrome is characterized by respiratory, gastrointestinal, central nervous system, and autonomic symptoms.[2] In a national survey in the United Kingdom and Ireland, researchers found that the majority of clinicians in neonatal units prescribed morphine sulfate as the first-line agent for both opiate (92 percent) and polysubstance (69 percent) withdrawal in neonates.[3] Similar results were found in an earlier survey of chiefs of neonatology in the United States; tincture of opium or morphine sulfate were most commonly used for management of both opioid (63 percent) and polysubstance (52 percent) use withdrawal in neonates.[4] Recently, there has been interest in buprenorphine as an alternative to morphine sulfate or other drugs to manage NAS. This column will describe buprenorphine and explore the research literature on the use of buprenorphine for NAS.

BUPRENORPHINE

Buprenorphine is a narcotic analgesic and opioid partial agonist (see sidebar, "Opioid Pharmacology Basics"). The U.S. Food and Drug Administration (FDA) has approved two sublingual formulations for treatment of opioid addiction in adults: Subutex buprenorphine monotherapy and Suboxone buprenorphine/naloxone combination therapy.[5,6] As an opioid partial agonist, buprenorphine produces the typical narcotic effects, such as euphoria and respiratory depression, but the maximal effects are less than those of heroin or methadone. At low doses, buprenorphine facilitates cessation of opioid misuse without causing withdrawal symptoms.[6] Buprenorphine is metabolized in the liver into norbuprenorphine and other metabolites. The half-life of buprenorphine in adults is 24 to 60 hours.[6]

The safety and efficacy of injectable buprenorphine (Buprenex) has been established for the management of pain in children aged 2 to 12 years.[5] There is a single report of pharmacokinetic parameters for buprenorphine in premature infants requiring opioid analgesia.[8]

Review of the Literature

Because of the relative novelty of buprenorphine as a treatment for NAS, there currently are a limited number of studies of this drug in neonates. Searching both Ovid MEDLINE and PubMed from 2000 to 2011 using keywords *buprenorphine* and *NAS* and limiting the search to English language resulted in only two studies.[9,10] These studies are described later.

Opioid Pharmacology Basics[13]

Opioid receptors—molecules on the surface of cells to which opioid compounds attach and exert their effects. Although there are several opioid receptors in the brain, the mu (μ) receptor is the receptor most relevant to opioid abuse and its treatment.

Full opioid agonists—an opiate that binds to the opioid receptor in the brain and turns it on to produce an effect in the organism. Increasing the dose of a full agonist increases the effects until a maximum effect is reached, or the receptor is fully activated. Morphine, methadone, heroin, oxycodone, and hydrocodone are examples of full opioid agonist.

Opioid antagonist—a substance that binds to opioid receptors to block activation by preventing the attachment of an agonist to the receptor. Naloxone (Narcan, Endo Pharmaceutical, Newark, NJ) is the opioid antagonist with which NICU nurses are most familiar.

Partial opioid agonist—an opioid with some of the properties of both agonist and antagonists. Partial agonists bind to the receptors and activate them but not the same degree as a full agonist. At lower doses, agonists and partial agonist produce the same effects. With increasing doses of a partial agonist, there is an increasing effect but only up to a point. At this point, increased doses do not produce increased effects. This is known as the *ceiling effect*. Additionally, partial opioid agonist displace or block full agonist from the receptors. Buprenorphine is an example of a partial opioid agonist.

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Kraft and colleagues sought to demonstrate feasibility and safety of sublingual buprenorphine for the treatment of NAS.[9] Additionally, the researchers sought to evaluate the efficacy of buprenorphine relative to standard therapy of neonatal opium solution (NOS) for the endpoints of length of treatment and length of stay. Because of the preliminary nature of the study, the study was not adequately powered to detect a difference in these efficacy endpoints. The researchers also explored buprenorphine pharmacokinetics "within the limits of what [could] be accomplished in this sized otherwise healthy neonatal study population." [9(pe602)]

Twenty-six infants, ≥37 weeks gestation with in utero exposure to opioids and demonstrating signs and symptoms of NAS, were randomly assigned in a 1:1 ratio to receive either buprenorphine or NOS. Exclusion criteria were major congenital malformation or intrauterine growth retardation; medical illness that required escalation of medical therapy, concomitant maternal benzodiazepine, or severe alcohol abuse; maternal benzodiazepine or alcohol use in the 30 days prior to enrollment; or concomitant neonatal use of cytochrome P450 inducers or inhibitors before the initiation of NAS treatment, seizures, or other neurologic abnormality. Neonatal abstinence syndrome was scored using the modified Finnegan scale,* which is standard of care at the study facility. (Treatment was initiated based on any three consecutive modified Finnegan scores ≥24.)[9]

Infants in the buprenorphine group received an initial dose of 13.2 mcg/kg/day sublingual in three divided doses. This dose was selected for this clinical trial using a pharmacokinetic model that determined a target steady-state buprenorphine concentration of 2 ng/mL.[9] The dose was increased by 20 percent for a combined Finnegan score of >24 on two or three measures or a score of 12 on a single measure of the Finnegan score. Infants in whom inadequate control had been achieved could receive a rescue dose of 50 percent of the previous dose; the subsequent dose was increased by 20 percent of the previous maintenance dose. Adjuvant therapy with phenobarbital was added if an infant reached a maximum buprenorphine dose of 39 mcg/kg/day. After three days at a stable dose, weaning was begun for modified Finnegan scores <8. The dose was weaned by 10 percent, and dosing was stopped when the dose was near or at the original starting dose. The researchers did not describe the frequency of weaning.[9]

Infants in the standard treatment group received a starting NOS dose of 0.4 mg/kg divided in six doses. The dose was escalated by 10 percent for a Finnegan score of >24 on two or three measures or a single score of 12. If a rescue dose was needed, the dose was the equivalent of one extra NOS dose. If an infant reached a dose of NOS of 1 mg/kg/day, phenobarbital was added as an adjuvant. Weaning from NOS began when infants demonstrated control of their NAS for 48 hours. Control of NAS was measured by the modified Finnegan scale; however, the researchers did not mention a specific score as a criterion for weaning. All infants, regardless of treatment allocation were observed for at least two days following the cessation of medication. The addition of phenobarbital in either group was considered a treatment failure but not an adverse event.[9]

Thirteen infants were assigned to each group. All of the mothers had been maintained on methadone. One infant in the buprenorphine group did not complete the treatment caused by onset of seizures. This infant was withdrawn from the study and treated with phenobarbital and NOS. The researchers reported that the cause of the seizures did not appear to be related to either undertreatment of withdrawal or a dose-dependent effect of the buprenorphine. The researchers reported no drug-related adverse events.[9]

The lengths of treatment and stay trended lower in the buprenorphine group than in the NOS group, but the differences between the two groups were not statistically significant. The mean length of treatment in the buprenorphine group (n = 12) was 22 days (r = 11–47 days). The mean length of treatment in the NOS group (n = 13) was 32 (r = 14–60 days). The mean length of stay in the buprenorphine group (n = 12) was 27 days (r = 17–51 days). The mean length of treatment in the NOS group (n = 13) was 38 (r = 19–66 days). Three infants in the buprenorphine group required adjuvant treatment with phenobarbital compared to one in the NOS group.

The study target steady-state concentration for buprenorphine was 2 ng/mL. Nine of the 12 infants in buprenorphine group had concentrations of <0.6 ng/mL. There were three outliers with steady-state concentrations ranging of 0.85, 1.80, and 3.69 ng/mL. Interestingly, these concentrations were not dose-dependent. The highest steady-state concentration (3.69 ng/mL) was in an infant at the initial 13.2 mcg/kg dose. The other outlying concentrations were in infants who received the protocol-specified maximum dose of 39 mcg/kg. Despite the lower steady-state concentration in the majority of the infants, the researchers reported good control of withdrawal symptoms. The researchers also noted significant dose-to-dose intrasubject variability in buprenorphine and norbuprenorphine concentrations. They suggested that the variability could not be explained only by developmental ontogeny of metabolic enzymes, but that it was likely a reflection of the extent of sublingual dosing. That is, variable amounts of each dose may have been swallowed and metabolized presystemically. The researchers further noted that morphine pharmacokinetics is also variable in neonates, and therefore clinical efficacy, rather than pharmacokinetics, will ultimately determine dose selection.[9]

In a subsequent study to build upon the study described earlier, Kraft and associates randomized 24 term infants,

*For more information on the modified Finnegan scale, see Zimmermann-Baer U, Nötzli U, Rentsch K, Bucher, HU. Finnegan neonatal abstinence scoring system: normal values for first 3 days and weeks 5–6 in non-addicted infants. *Addiction*. 2010;105(3):524–528. http://dx.doi.org/10.1111/j.1360-0443.2009.02802.x

≥37 weeks gestation with in utero exposure to opioids and a need for pharmacologic management of NAS, in a 1:1 ratio to receive either sublingual buprenorphine or oral morphine.[10] The goal of this study was to optimize the dose of sublingual buprenorphine for the treatment of NAS. Exclusion criteria were major congenital malformation or intrauterine growth retardation, medical illness that required escalation of medical therapy, concomitant maternal benzodiazepine or severe alcohol abuse, maternal benzodiazepine or alcohol use in the 30 days prior to enrollment or concomitant neonatal use of cytochrome P450 inducers or inhibitors before the initiation of NAS treatment, seizures or other neurologic abnormality. Neonatal abstinence syndrome was monitored using a modified Finnegan scale which is standard of care at the study facility. Treatment was initiated based on any three consecutive scores ≥24 or a single score ≥12 on the modified Finnegan scale.[10]

Infants randomized to the buprenorphine group received an initial dose of 15.9 mcg/kg/day sublingual divided in three doses. Several factors lead the researchers to the dosing regimen used in this study. In their previous study, the researchers observed that infants in the buprenorphine group required an initial rapid up-titration of dosing and that the infants frequently attained maximum dosage.[9] Additionally, pharmacokinetic studies revealed lower than anticipated plasma buprenorphine levels. Finally, opioid toxicity related to buprenorphine was not observed.[10] The researchers' goal was to optimize dosing by increasing the initial dose, increasing rate of dose up-titration, and increasing the maximum daily dose.[10] The dose was increased by 25 percent for combined NAS score of ≥24 total on three measures or a score of ≥12 on a single measure. Infants who demonstrated inadequate control between scheduled doses could receive a rescue dose equal to 50 percent of the previous dose; subsequent doses were increased by 25 percent of the previous maintenance dose. When the dose was stable for at least three days, buprenorphine weaning could begin for scores <8. The weaning interval was 10 percent daily. Buprenorphine was discontinued when the dose was within 10 percent of the initial dose. All dose calculations were based on birth weight. If NAS was not controlled on a maximum buprenorphine dose of 60 mcg/kg/day, the infant received a 20 mg/kg loading dose of phenobarbital followed by 2.5 mg/kg doses every 12 hours for at least two days. Phenobarbital was discontinued prior to weaning buprenorphine. Once scores were <8, the phenobarbital dose was reduced by 50 percent, and then discontinued as tolerated based on scores. The researchers reported that phenobarbital was generally discontinued two days following the initial 50 percent reduction.[10]

Standard treatment consistent of morphine 0.4 mg/kg divided in 6 doses. The dose was escalated by 10 percent for a Finnegan score of ≥24 on three measures or a single score ≥12. All dose calculations were based on daily weights. If a rescue dose was needed, the dose was the equivalent to one extra morphine dose. If an infant reached a dose of morphine 1 mg/kg/day, phenobarbital was added as an adjuvant. Phenobarbital was also discontinued as described earlier prior to weaning morphine. Morphine was weaned by 10 percent per day and discontinued when a dose of 0.15 mg/kg/day was reached. Infants in both groups were observed for a minimum of two days following discontinuation of the drugs.[10]

The infants in both groups were similar in relation to gestational age, race, gender, birth weight, and Apgar scores. All mothers had been treated with methadone. None of the adverse events reported in the study were felt likely to be related to either drug. One infant in the buprenorphine group had cytomegalovirus infection, prolonged reflux and poor feeding, elevated liver function tests (LFTs), aminoaciduria, and paronychia of a finger. The study's data safety monitor board (DSMB) reviewed the case and determined that buprenorphine was not responsible for this infant's clinical course. The DSMB did agree with the researchers' suggestion to monitor LFTs in future study participants. Predose, 7 day, and 21-day postrandomization LFTs were normal in six subsequent patients; three in buprenorphine group and three in the morphine group.[10]

The length of treatment in the buprenorphine group was 23 ± 12 days versus 38 ± 14 days in the morphine group (p=.01) representing a 40 percent reduction in length of treatment. The length of stay for the buprenorphine group was 32 ± 24 days versus 42 ± 13 days in the morphine group (p=.05). This represents a 24 percent reduction in length of stay. Three infants in the buprenorphine group and one infant in the morphine group required phenobarbital. None of the infants was readmitted for withdrawal after initial discharged.[10]

PHENOBARBITAL AS AN ADJUVANT

In the study by Kraft and colleagues published in 2008, the researchers asserted that need for phenobarbital in 3 of the 12 neonates in buprenorphine group suggested that the maximal dose of 39 mg/kg/day used in this study may not have been high enough to control symptoms of NAS. The researchers also judged the need for phenobarbital as a treatment failure.[9] However, in the subsequent study, Kraft and associates argued that the need for adjuvant phenobarbital might not be an indication of treatment failure in infants with more severe withdrawal.[10] It is still not clear where the maximum buprenorphine dose lies on the dose-response curve in this population. More infants in the buprenorphine group required phenobarbital than in the morphine group (three vs one). Because buprenorphine is a partial agonist, it is possible that it "may not be able to induce the dense signal generation at the mu opioid receptor obtained with morphine."[10(p578)] Alternatively, as asserted by the researchers, a higher maximum dose of buprenorphine may eliminate the need for phenobarbital. Kraft and associates concluded their discussion related to phenobarbital by noting that short-

term use of phenobarbital has few adverse effects and that a short course may be a useful adjunct for neonates who experience more severe withdrawal.[10]

POSSIBLE ADVANTAGES OF BUPRENORPHINE

The advantages of buprenorphine over morphine for treatment of NAS still need to be determined. Because buprenorphine has a longer duration of action and resides on the mu opioid receptor for a longer period of time, buprenorphine use may decrease sudden shifts in receptor antagonism and thus, reduce withdrawal symptoms. Additionally, a prolonged persistence of drug effect following discontinuation may also reduce symptoms. The higher up-titration of buprenorphine versus morphine (25 percent vs 10 percent) may result in more rapid attainment of symptom control in infants receiving buprenorphine. A 10 percent per day weaning schedule is used for both drugs, however, buprenorphine is discontinued sooner, within 10 percent of the starting dose, whereas morphine is weaning to 0.15 mg/kg/day before discontinuing; this is significantly lower than the initial starting dose of 0.4 mg/kg/day. Finally, because buprenorphine dosing is based on birth weight, not daily weight as morphine dosing is, there is a relative decrease in the buprenorphine dose per kilogram of current weight as the infant grows.

The results of the initial trail by Kraft colleagues suggested improved efficacy of buprenorphine over morphine in terms of length of stay and length of treatment.[9] In the second study with the revised dosing schema, the researchers reported a statistically significant difference between the buprenorphine and morphine groups in both length of stay and length of treatment, thus, demonstrating an advantage of buprenorphine over morphine in this sample of infants with NAS.[10]

Adverse Events

In the study published in 2008, Kraft and colleagues reported adverse events in two infants.[9] One infant in the buprenorphine group had generalized seizures 78 hours after the initial dose resulting in discontinuation of the buprenorphine. The trial was also placed on hold at that point. This infant had normal serum hematology, chemistries, C-reactive protein, and cerebrospinal fluid laboratory values and negative cultures. The electroencephalogram was normal. Magnetic resonance imaging revealed a small subdural hemorrhage in the posterior fossa felt to be related to the birthing process; there was no parenchymal abnormality. The researchers did not feel that there was a causal link between undertreatment of withdrawal or a dose-dependent effect of the drug. An independent review determined that the trial could resume using the established protocol.[9] A second infant in the buprenorphine group experienced a mild fungal paronychia that was deemed unrelated to the drug.[9]

In the subsequent study, the researchers reported two cases of oral thrush, one case of conjunctivitis, and one case of reflux among the infants in the morphine group. None of these adverse events were related to the drug. One infant in the buprenorphine group had a fractured clavicle at birth, which was clearly unrelated to the study drug. Another infant in buprenorphine group experienced several adverse events. Paronychia of the finger, cytomegalovirus infection, and aminoaciduria were judged to be unrelated to the drug; reflux and poor feeding and elevation of liver transaminases were deemed probably not related to the drug.[10]

CONCLUSIONS

The published studies at the time of this printing were both open label studies of buprenorphine and morphine in small samples at one center. Blinded randomized clinical trials comparing morphine to buprenorphine are needed. Several questions need to be answered before buprenorphine becomes standard therapy for NAS, including:

- Is buprenorphine safe and efficacious for treating NAS in the presence of maternal polysubstance use?
- Is buprenorphine safe in preterm infants?
- How is dosing adjusted when scores begin to rise during weaning?
- Is buprenorphine useful in preventing and treating withdrawal associated with iatrogenic physiologic opioid tolerance in infants receiving narcotics for pain management?

Jones asserted the importance of reexamining our methods for measuring neonatal abstinence.[11] Is it possible for one tool to assess withdrawal from opioids alone and in combination with other substances? The items used for measures should be clearly defined and quantifiable. Tools should be easy to use and place limited burden on the neonate, the family, and the staff.

Neonatal abstinence syndrome is a serious health issue. A recent report from SAMHSA noted that 4.4 percent of pregnant women between the ages of 15 and 44 years used illicit drugs.[7] The rate is highest among the youngest group (15.8 percent or 14,000 15- to 17-year-olds; the rate for 18- to 25-year-olds is 7.4 percent and 1.9 percent for 26- to 44-year-olds.[7,12] Assessing and managing NAS is labor intensive and fiscally costly. It is essential that research continues to focus on effective means of assessing and managing NAS with the goal of safely decreasing both the lengths of treatment and the lengths of hospitalization for these infants.

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