Abstract

Background: Among infants born prematurely, competence at oral feeding is necessary for growth and a criterion for hospital discharge. Extremely preterm infants (EP, ≤ 28 weeks gestational age [GA]) are at risk for a variety of medical complication which can limit the infant’s capacity to develop oral feeding competence. Objective: This study examined feeding progression by assessing timing of acquisition of five early feeding milestones among EP infants, and the impact of illness characteristics on the progression. Study Design: A chart review was conducted for 94 EP infants who participated in a larger longitudinal randomized study. Feeding progression was defined as infant’s postmenstrual age (PMA) at five milestones: first enteral feeding, full enteral feeding, first oral feeding, half oral feeding, and full oral feeding. GA at birth and five medical complications (neurological risk, bronchopulmonary dysplasia [BPD], necrotizing enterocolitis [NEC], patent ductus arteriosus [PDA], gastroesophageal reflux disease [GERD]) were used as potential infant illness characteristics influencing the feeding progression. Linear mixed models examined the feeding progression across the milestones and contributions of infant illness characteristics on the progression. Result: EP infants gradually achieved feeding milestones; however, the attainment of the feeding milestones slowed significantly by weeks for infants with younger GA at birth and the presence of medical complications, including neurological risk, BPD, NEC, and PDA, but not GERD. Discussion: An improved understanding of the timing of essential feeding milestones among EP infants and the contribution of specific medical conditions to the acquisition of these milestones may allow for more targeted care to support feeding skill development.

Keywords: extremely preterm infant, feeding milestones, medical complications
Among infants born prematurely, competence at oral feeding is necessary for growth and a criterion for hospital discharge (American Academy of Pediatrics, 2008). Failure to develop oral feeding competence often leads to poor nutritional status, growth failure, longer hospital stays, and increased costs of care, (Jadcherla, Wang, Vijaypal, & Leuthner, 2010; Russell et al., 2007; St John, Nelson, Cliver, Bishnoi, & Goldenberg, 2000) and influences longer-term growth and neurodevelopmental outcomes (Thoyre, 2007). Preterm infants have difficulty establishing oral feeding skills because their neurologic, cardio-respiratory, gastrointestinal, and oral-motor systems are functionally immature. As a result, they require some degree of tube feeding in the weeks following birth, until they develop the necessary skills to feed by mouth. Preterm infants take 2 to 5 weeks to make this transition, which takes longer for preterm infants who are younger at birth and have medical complications (Dodrill, Donovan, Cleghorn, McMahon, & Davies, 2008; Hwang, Ma, Tseng, & Tsai, 2013; Jadcherla et al., 2010).

Extremely preterm (EP) infants who are born ≤ 28 weeks of gestational age (GA) are at risk for a variety of medical complications, including necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), patent ductus arteriosus (PDA), and intraventricular hemorrhage (IVH) (Costeloe et al., 2012), any of which may significantly limit the infant’s capacity to progress to oral feeding competence. Depending on types and degrees of medical complications as well as degrees of immaturity at birth, EP infants may exhibit different paths to competent oral feeding. The attainment of earlier feeding milestones can influence later milestones among EP infants, who are the most vulnerable group of preterm infants with respect to feeding. However, no research has described the attainment of their feeding milestones as a continuous process – from commencement of enteral feeding to attainment of full oral feeding –
or the contribution of medical complications to these milestones with sufficient number of EP
infants.

The purpose of this study was to describe feeding progression in EP infants by examining
the timing (postmenstrual age [PMA]) of the acquisition of five early feeding milestones that are
necessary for successful feeding skill development during hospitalization. This study also
examined how immaturity measured as gestational age at birth and the medical complications
(neurologic risk score, BPD, NEC, PDA, and gastroesophageal reflux disease [GERD]) were
associated with the PMA at which each feeding milestones was achieved. An improved
understanding of how EP infants progress to oral feeding competence and the impact of specific
medical complications on this progression may allow for more thorough clinical assessment and
development of targeted interventions to support feeding skill development.

Methods

Design

This descriptive exploratory study used data from a longitudinal two-group randomized
controlled trial of the effects of early and late cycled light on the health and developmental
outcomes of EP infants (R01 NR008044, PI: Debra Brandon). In the parent study, infants were
randomly assigned to one of two intervention groups: (1) early cycled light (28 weeks PMA; 0-5
weeks of near darkness, followed by 12-16 weeks of cycled light) or (2) late cycled light (36
weeks PMA; 8-13 weeks of near darkness, 4-8 weeks of cycled light). This study was approved
by the university Institutional Review Board.

Sample and Setting

The original sample included 118 infants who were born at ≤ 28 weeks of GA. Infants
were excluded from the parent study if they had a history of anomalies associated with
neurological or visual problems, such as congenital glaucoma or Down syndrome. In the current analysis, 24 infants were further excluded because they had structural anomalies that interfered with oral feeding (tracheoesophageal fistula, n=1; cleft palate, n=1), died before achieving all feeding milestones (n=5), or were transferred to a non-study nursery before discharge to home (n=17).

The current sample included 94 infants; 55.3% males (n=52) and 72.3% non-White infants (n=68). Infants’ mean GA at birth was 26.2 weeks (range = 22.4 - 28.6), mean birth weight was 868.1 g (range = 460-1450), APGAR score was 4 at 1 minutes (range = 0-9) and 6.5 at 5 minutes (range = 2-9), and mean length of hospitalization was 103 days (range = 36-268).

Forty-five infants were in the early cycled intervention, and 49 were in the late cycled intervention.

The infants received care in the level IV NICU and two transitional care nurseries in the Health Systems between 2003 and 2006. The neonatology team, consisting of neonatologists, nurses, neonatal nurse practitioners, speech and language pathologists, and occupational therapists, used a consistent approach to manage feeding difficulties across each of the nurseries, as follows. Enteral feedings were initiated by 48 hours of life and advanced if pre-feeding residuals were under 25% of the prior feeding volume with the presence of normal stooling patterns and the absence of abnormal abdominal/gastrointestinal signs and symptoms (progressive abdominal distention, absence of bowel sounds, and/or bilious aspirates). Oral feedings (breast and/or bottle) were initiated at 32-34 weeks PMA once infants demonstrated oral-motor cues, physiologic stability (no longer required positive airway pressure or manifested respiratory distress), and were able to receive enteral feedings of 100-130 kcal/kg/day. Oral feedings were advanced based on cardiorespiratory stability and gastrointestinal tolerance. When
feeding intolerance was present, standard evaluation and management were performed as deemed necessary.

**Measures**

**Feeding progression.** Feeding progression was defined as the infant’s PMA in weeks at each of five milestones: first enteral feeding (Step 1), first full (100cc/kg/day) enteral feeding (Step 2), first attempt at oral feeding at breast or bottle (Step 3), first half (50% of total nutritional intake) oral feeding (Step 4), and first full (100%) oral feeding followed by two consecutive days of full exclusively oral feeding (Step 5). Infant’s PMA was calculated as GA at birth plus postnatal age.

**Infant illness characteristics.** Infant illness characteristics included immaturity and five medical complications (neurological risk score, severity of lung disease, and the diagnoses of NEC, PDA, and GERD). *Immaturity* was measured as GA in weeks at birth. *Neurological risk score* was based on the presence of periventricular leukomalacia (PVL) and grade of intraventricular hemorrhage (IVH) (no risk = no PVL or IVH grade 1-2; risk = PVL or IVH grade 3-4) (Payne et al., 2013). *Severity of lung disease* was identified using diagnostic criteria for BPD (none, mild, moderate, or severe), depending on the duration and degree of supplemental oxygen required when the infant reached 36 weeks of PMA. (Jobe & Bancalari, 2001) *Diagnosis of NEC* was classified as no NEC, NEC with medical treatment, or NEC with surgical treatment; *PDA* was classified as no PDA, PDA with medical treatment, or PDA with surgical treatment. *GERD* was based on need for anti-reflux medications as determined by the physician.

**Procedures**
Data of the PMA for feeding progression and infant illness characteristics were determined from the parent study data as well as confirmatory retrospective chart reviews conducted by the first author. To assess reliability, n=9 charts were randomly selected and reviewed again separately 3 weeks later. There was 100% agreement between the first and second reviews of the 9 charts.

**Data Analysis**

Descriptive statistics were used to describe the sample. Linear mixed models were used to examine feeding progression in EP infants by assessing the timing (infant’s PMA) of the acquisition of five early feeding milestones and to examine if the progression is differed by intervention groups, immaturity at birth and each of five medical conditions. The covariance structure accounted for correlation and variance of PMAs at each feeding milestones within the same infant. First, a linear mixed model was conducted to examine patterns of infant’s PMA across the feeding milestones (fixed and random effects = infant’s PMA at feeding milestone). Then, a separate linear mixed model was conducted for each of seven infant characteristics. For each characteristic, a full factorial model was conducted with all possible fixed (infant’s PMA at feeding milestone, infant characteristic, and their interaction) and random effects (infant’s PMA at feeding milestone). Random effects were treated as random analysis of variance factors to account for different lengths of interval between the feeding milestones. Then, each full factorial fixed effects model was reduced by removing interaction terms, as long as Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) scores improved (two well-established model selection criteria).(Knafl, Beeber, & Schwartz, 2012)

**Results**

**Feeding Progression in EP Infants**
Overall, 90.4% of the infants (n=85) achieved full oral feeding by discharge; 9.6% (n=9) were discharged on gastrostomy feeding as the main feeding method. As expected, infants significantly progressed in oral feeding competence across the milestones ($F_{4,93} = 239.19; p < .001$). Infants’ predicted mean PMA was 27.8 weeks at first enteral feeding, 30.3 weeks at full enteral feeding, 35.5 weeks at first oral feeding, 38.2 weeks at half oral feeding, and 39.5 weeks at full oral feeding.

**Factors Associated with Feeding Progression**

**Intervention effect.** The sample included 45 infants (47.9%) from the early cycled intervention group and 49 (52.1%) from the late cycled intervention group. Patterns of feeding progression were not different by intervention group (early vs. late cycled light) ($F_{1,92} = 0.61, p = .437$).

**Gestational age.** Compared to those of older GA, infants of younger GA exhibited a significant delay in progress toward oral feedings across the milestones ($F_{1,92} = 5.31, p = .024$) with an interaction effect between GA and PMA at each feeding milestone ($F_{4,92} = 22.71, p < .001$). The significant interaction effect showed that infants of younger GA at birth commenced enteral feeding earlier because all infants initiated enteral feeding within 48 hours of life, but achieved subsequent oral feeding milestones at a later PMA (Steps 3-5). Figure 1 depicted how feeding progression is differed by GA using minimum, 25% quartile, median, 75% quartile, and maximum GA.

**Neurologic risk.** Of 94 infants, 14% (n=13) had a neurologic risk (PVL or IVH grade 3-4). Infants with neurologic risk were significantly delayed in achieving the five feeding milestones ($F_{1,91} = 22.17, p < .001$), compared to those without neurologic risk. There was also a significant interaction effect between neurologic risk and PMA at each feeding milestone ($F_{4,91}$...
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= 6.58, p < .001), suggesting the delays in progress towards full oral feedings were greater at later feeding milestones (Figure 2). More specifically, infants with neurologic risk had no delay in achieving first enteral feeding but delayed achievement of full enteral feeding by 1 week, first oral feeding by 2.4 weeks, half oral feeding by 4.9 weeks, and full oral feeding by 5.7 weeks, compared to those without neurological risk (based on differences in predicted mean PMA between the neurological risk groups).

Severity of lung disease. Out of 94 infants, 75.6% (n=71) had a diagnosis of BPD; 47.9% (n=45) met the definition of mild BPD, 14.9% (n=14) moderate, and 12.8% (n=12) severe. (Jobe & Bancalari, 2001) Infants with BPD showed a significant delay in progression to oral feedings across the milestones ($F_{3,90} = 23.24, p < .001$), compared to those without BPD. There was also a significant interaction effect between BPD severity and PMA at each feeding milestone ($F_{12,90} = 6.89, p < .001$), which suggested infants began enteral feedings and reached full enteral feeds around the same time regardless of the severity of BPD, however oral feeding milestones (Steps 3-5) were more delayed for those infants with more severe BPD (Figure 3). More specifically, compared to infants without BPD, infants with mild BPD delayed achievement of first oral feeding by 1.7 weeks, half oral feeding by 1.8 weeks, and full oral feeding by 2.4 weeks. Infants with moderate BPD delayed achievement of full enteral feeding by 1.4 weeks, first oral feeding by 3.8 weeks, half oral feeding by 5 weeks, and full oral feeding by 6.4 weeks. Infants with severe BPD delayed achievement of full enteral feeding by 1.1 weeks, first oral feeding by 5.1 weeks, half oral feeding by 6.3 weeks, and full oral feeding by 7.4 weeks (based on differences in predicted mean PMA between the no BPD and BPD group).

Necrotizing enterocolitis. Out of 94 infants, 28.7% (n=27) were diagnosed with NEC; 19.1% (n=18) were treated medically, and 9.6% (n=9) were treated surgically. Infants with NEC
were significantly delayed in progression to oral feedings across the milestones ($F_{2,91} = 5.38, p = 0.006$) with an interaction effect between NEC group and PMA at feeding milestone ($F_{8,91} = 3.42, p = 0.002$). The significant interaction effect suggested the delay was greater in those with surgically managed NEC, especially as they advanced to half and full oral feedings (Figure 4). More specifically, compared to infants without NEC, the infants with surgically managed NEC delayed achievement of first enteral feeding by 1.1 weeks, full enteral feeding by 1.3 weeks, first oral feeding by 1 week, half oral feeding by 3.1 weeks, and full oral feeding by 4.6 weeks. Infants with medically managed NEC delayed achievement of first oral feeding by 1.2 weeks but less than one week delay for other feeding milestones (based on differences in predicted mean PMA between the no NEC and NEC group).

**Patent ductus arteriosus.** Out of 94 infants, 64.5% (n=60) had the diagnosis of PDA; 47.3% (n=44) required medical treatment and 17.2% (n=16) surgical treatment. Infants with PDA exhibited a significant delay in progression to oral feedings across the milestones ($F_{2,90} = 6.83, p = 0.002$) with an interaction effect between PDA group and PMA at feeding milestone ($F_{8,90} = 5.66, p < 0.001$). The significant interaction effect suggested feeding delays were associated with surgical treatment as these infants initiated and advanced through oral feedings (Figure 5). More specifically, compared to infants without PDA, the infants with surgically treated PDA showed no delay in achieving first enteral feeding, but delayed achievement of full enteral feeding by 1 week, first oral feeding by 2.4 weeks, half oral feeding by 4.6 weeks, and full oral feeding by 5 weeks. Those with PDA treated medically were delayed by 1.2 weeks in achieving half oral feeding but were delayed less than one week for other feeding milestones (based on differences in predicted mean PMA between the no PDA and PDA group).
Gastroesophageal reflux disease. There were 57 infants (61.3%) diagnosed with GERD and receiving anti-reflux medications during hospitalization. Patterns of feeding progression did not differ by GERD status ($F_{1,91} = 0.10$, $p = .757$).

**Discussion**

This exploratory descriptive study examined feeding progression by assessing the timing of acquisition of five early feeding milestones among EP infants during their initial hospitalization, and the impact of immaturity at birth and five different medical complications on the feeding progression. EP infants gradually achieved feeding milestones; however, the attainment of the feeding milestones slowed significantly by weeks for infants with younger GA at birth and the presence of medical complications, including neurological risk, BPD, NEC, and PDA, but not GERD.

The current findings are consistent with other work that showed GA at birth affecting the transition time from initiation of oral feeding to full oral feeding in premature infants (Dodrill et al., 2008; Hwang et al., 2013; Jadcherla et al., 2010). As well, this study showed that infants of younger GA at birth had a significant delay in progress feedings across feeding milestones in general. However, this was the first study to show a more pronounced delay as EP infants moved from enteral to oral feeding milestones. The delay may be because of maturational delays in the neurologic, gastrointestinal, cardio-respiratory, and oral-motor control systems or the impact of various medical complications on the functionality of these systems. More importantly, although infants of younger GA at birth were likely to have more difficulty in initiating oral feeding, once they began oral feeding, they were able to transition to full oral feeding within about 3 to 5 weeks. Therefore, the timing when infants are able to initiate oral feeding may be a red flag for inadequate development of feeding skills, i.e., if infants are not able to initiate oral feeding by the
time skills necessary to oral feed are commonly present, i.e., 32-34 weeks PMA (Delaney, 2008), it may be considered delayed development of feeding skills.

This study also found that infants with neurologic risk, defined as having PVL or IVH grade 3-4, had a significant delay in the progression of feeding competence, especially once they began to attain oral feeding milestones. For safe oral feeding, appropriate neurodevelopmental maturation is necessary to coordinate sucking, swallowing, and breathing with well-timed reconfigurations of the airway for air and nutrient passage (Barlow, 2009; Goldfield, 2007). However, maturational neurodevelopment is constrained by neurologic morbidity, such as the presence of PVL or IVH grade 3-4 (O'Shea et al., 2012), and this may impede adequate development of oral feeding skills.

The adverse effects of BPD on the oral feeding capacity of preterm infants have been documented in several studies (Gewolb & Vice, 2006; Mizuno et al., 2007; Pridham et al., 1998). The current study further supported earlier findings that BPD is a significant medical complication that prolongs oral feeding progression in EP infants, such that infants with BPD have significant delays in initiating and advancing oral feedings, compared to those without BPD. The current study is the first to show that feeding progression is further slowed down as severity of BPD increases. These findings are consistent with previous findings that moderate to severe BPD is a significant factor associated with delay of attainment of full oral feeding (Hwang et al., 2013) and that duration of ventilation and continuous positive airway pressure are positively associated with delayed attainment of full oral feeding (Jadcherla et al., 2010). The current study extended those findings by examining feeding progression that includes a full range of the early feeding milestones that are necessary to achieve competent oral feeding skills.
In this study, infants with NEC delayed initiating oral feeding by about one week, compared to those without NEC, and infants with surgically treated NEC had a further delay in achieving half and full oral feedings, compared to those with medically treated NEC. These findings could be expected because, once NEC is suspected, infants are usually not allowed oral feedings until they have totally recovered. Moreover, surgical treatment usually is chosen when medical treatment has failed or infants have more severe NEC, and infants who underwent a surgical treatment for NEC often suffer from short gut syndrome (Cole et al., 2008), which may extend the length of time to feed by tube, thereby impeding development of oral feeding competence.

Infants with surgically treated PDA had a significant delay in the progression to oral feedings, compared to those with medically treated PDA or without PDA, which was more noticeable as they attained oral feeding milestones. Surgical treatment for PDA is usually elected when medical treatment has failed or is contraindicated; therefore, the timing of a closure of PDA is often delayed for infants with surgically treated PDA. The prolonged patency of ductus arteriosus is often related to cardiorespiratory failure, prolonged mechanical ventilation and subsequent BPD (Ehrenkranz et al., 2005; Lee, Tillett, Tulloh, Yates, & Kelsall, 2006; Vida et al., 2009). As a result, the complications of the prolonged closure of PDA may have resulted in delays in attaining oral feeding milestones for the group of infants with surgically treated PDA.

In the current study, oral feeding milestone progression was not affected by presence of GERD. GERD is not typically considered a pathological condition, and infants with GERD are usually allowed to proceed to oral feedings with supplements of anti-reflux medications and other non-pharmacological management, including body positioning, modification of feeding
methods, or milk thickening (Corvaglia et al., 2013), rather than being prohibited from feeding for a certain period as for other medical complications, such as NEC.

The strength of this study included the assessment of the full range of the early feeding milestones that are necessary to achieve competent feeding skills during the initial hospitalization with a relatively large number of EP infants. There are also some limitations to this study. First, all data were collected via chart review, so recording errors by nursing staff or physicians may have confounded the findings. Second, this study included information from one NICU and two transitional care nurseries in one large perinatal center and thus cannot be generalized to other centers with different nursery strategies to manage feeding. Finally, this study conducted a separate model for each medical condition, and either individual variability within the conditions or coexisting medical conditions may have affected the outcomes. Additional research with multiple sites and a larger sample would permit better understanding on the process of attaining feeding milestones in EP infants.

In summary, EP infants underwent the expected essential feeding milestones as they matured during the initial hospitalization; however, the timing of milestone achievements was delayed according to the types and degrees of medical complications and degree of prematurity at birth. This expanded evidence of the timing of essential feeding milestones among EP infants and the contribution of specific medical conditions to the acquisition of these feeding milestones may allow for a more thorough clinical assessment of these factors and development of individualized feeding plans to support their feeding skill development.
References


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Figure Legend

Figure 1. Feeding Progression according to Gestational Age at Birth.

Feeding milestones: (1) first enteral feeding, (2) full enteral feeding, (3) first oral feeding, (4) half oral feeding, and (5) full oral feeding. PMA = postmenstrual age, GA = gestational age, min = minimum, max = maximum.

Figure 2. Feeding Progression according to Neurologic Risk.

Feeding milestones: (1) first enteral feeding, (2) full enteral feeding, (3) first oral feeding, (4) half oral feeding, and (5) full oral feeding. PMA = postmenstrual age, PVL = periventricular leukomalacia, IVH = intraventricular hemorrhage.

Figure 3. Feeding Progression according to Severity of Lung disease.

Feeding milestones: (1) first enteral feeding, (2) full enteral feeding, (3) first oral feeding, (4) half oral feeding, and (5) full oral feeding. PMA = postmenstrual age, BPD = Bronchopulmonary Dysplasia

Figure 4. Feeding Progression according to Necrotizing Enterocolitis.

Feeding milestones: (1) first enteral feeding, (2) full enteral feeding, (3) first oral feeding, (4) half oral feeding, and (5) full oral feeding. PMA = postmenstrual age, NEC = Necrotizing Enterocolitis, tx = treatment.

Figure 5. Feeding Progression according to Patent Ductus Arteriosus.

Feeding milestones: (1) first enteral feeding, (2) full enteral feeding, (3) first oral feeding, (4) half oral feeding, and (5) full oral feeding. PMA = postmenstrual age, PDA = Patent Ductus Arteriosus, tx = treatment.