Published in final edited form as:

J Pediatr Gastroenterol Nutr. 2012 January ; 54(1): 62–70. doi:10.1097/MPG.0b013e3182288766.

Impact of Personalized Feeding Program in 100 NICU Infants: Pathophysiology-based Approach for Better Outcomes

Sudarshan R. Jadcherla^{*}, Juan Peng[†], Rebecca Moore[‡], Jason Saavedra[§], Edward Shepherd^{||}, Soledad Fernandez[¶], Steven H. Erdman[#], and Carlo DiLorenzo^{**}

^{*}Neonatal and Infant Feeding Disorders Program, Center for Perinatal Research, Innovative Infant Feeding Disorders Research Program, the Research Institute at Nationwide Children's Hospital, Sections of Neonatology, Pediatric Gastroenterology, Hepatology and Nutrition, Ohio State University College of Medicine, Ohio State University College of Medicine, Columbus, OH.

[†]Neonatal and Infant Feeding Disorders Program, Center for Perinatal Research, the Research Institute at Nationwide Children's Hospital, Ohio State University College of Medicine, Columbus, OH.

[‡]Neonatal and Infant Feeding Disorders Program, Center for Perinatal Research, the Research Institute at Nationwide Children's Hospital, Ohio State University College of Medicine, Columbus, OH.

[§]Division of Neonatal Nurse Practitioners Program, Nationwide Children's Hospital, Ohio State University College of Medicine, Columbus, OH.

^{||}Section of Neonatology, Department of Pediatrics, Ohio State University College of Medicine, Ohio State University College of Medicine, Columbus, OH.

[¶]Department of Biostatistics, Ohio State University College of Medicine and Public Health, Ohio State University College of Medicine, Columbus, OH.

[#]Division of Pediatric Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Ohio State University College of Medicine, Ohio State University College of Medicine, Columbus, OH.

^{**}Division of Pediatric Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Ohio State University College of Medicine, Columbus, OH.

Abstract

Objectives—In neonatal intensive care unit infants referred for home-tube feeding methods, we evaluated the effect of an innovative diagnostic and management approach on feeding outcomes at discharge and 1 year, by comparing data from historical controls; we hypothesized that clinical and aerodigestive motility characteristics at evaluation were predictive of feeding outcomes at discharge; we assessed the economic impact of feeding outcomes.

Patients and Methods—Patients (N = 100) who were referred for development of long-term feeding management strategy at 46.4 ± 13.1 weeks' postmenstrual age were compared with 50 historical controls that received routine care. The focused approach included swallow-integrated pharyngoesophageal manometry, individualized feeding strategy, and prospective follow-up.

Copyright © 2012 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

Address correspondence and reprint requests to Sudarshan R. Jadcherla, MD, Section of Neonatology, 700 Children's Dr, Nationwide Children's Hospital, Columbus, OH 43205 (sudarshan.jadcherla@nationwidechildrens.org).

The authors report no conflicts of interest.

Feeding success was defined as ability to achieve oral feedings at discharge and 1 year. Motility characteristics were evaluated in relation to feeding success or failure at discharge.

Results—Higher feeding success was achieved in the innovative feeding program (vs historical controls) at discharge (51% vs 10%, $P < 0.0001$) and at 1 year (84.3% vs 42.9%, $P < 0.0001$), at a reduced economic burden ($P < 0.05$). Contributing factors to the innovative program's feeding success (vs feeding failure) were earlier evaluation and discharge (both $P < 0.05$), greater peristaltic reflex-frequency to provocation ($P < 0.05$), normal pharyngeal manometry ($P < 0.05$), oral feeding challenge success ($P < 0.05$), and suck-swallow-breath-esophageal swallow sequence ($P < 0.05$). Probability of feeding success demonstrated a prediction rate of 79.6%.

Conclusions—Short-term and long-term feeding outcomes in complex neonates can be significantly improved with innovative feeding strategies at a reduced cost. Clinical and aerodigestive motility characteristics were predictive of outcomes.

Keywords

dysphagia; feeding problems; feeding quality; infant; multidisciplinary approach

Healthy premature infants typically achieve full oral feeding skills by 36 to 38 weeks' postmenstrual age (PMA) (1). The prevalence of feeding problems in former premature infants is twice that of full-term born infants (2), and multiple etiological factors are involved in the pathogenesis of feeding problems (3,4). The American Academy of Pediatrics Guidelines for the discharge of the high-risk neonate requires that the essential physiological competencies including safe feeding methods must be established before consideration for discharge (5). However, persistence of dysphagia and delayed acquisition of self-sufficient feeding skills in convalescing neonatal intensive care unit (NICU) neonates often prolong hospitalization and increase health care costs (1,6,7). Long-term management of chronic feeding problems is possible using mechanical tube-feeding methods, such as gastrostomy and transpyloric feeding (8). Additionally, due to the potential concerns for complications of gastroesophageal reflux disease (GERD), empiric therapies with acid suppressive therapies and/or surgery are widely but variably used (9–11). Unfortunately, the need for, indication of, and benefits of such therapies remain poorly understood. The lack of accurate, pathophysiology-based definitions for neonatal feeding disorders has added to the confusion and fostered subjective symptom-based therapies.

Recently, we developed an innovative approach to the treatment of neonatal feeding problems using a combination of objective evaluation of pharyngoesophageal motility and aerodigestive protective mechanisms in human neonates (12–15), combined with multidisciplinary evaluation and therapy (7). Specifically, this strategy focuses on integrating parental and provider concerns, established feeding methods, extended periods of feeding observations under aerodigestive manometric surveillance, anatomical evaluation, and the pathophysiological status of the overall health of the infant. The present study pertains to NICU infants with severe feeding problems that were referred for gastrostomy placement. Feeding success is defined in 2 settings—as the ability to achieve oral feedings by the time of discharge and at 1 year of age. Feeding failure is defined as inability to achieve oral feedings resulting in gastrostomy placement as a long-term strategy to sustain adequate growth.

The purpose of the present study was to describe our innovative multidisciplinary approach to the diagnosis and modification of feeding outcomes in infants referred for gastrostomy tube placement as compared with historical controls that underwent conventional treatment, clarify the pathophysiology of neonatal pharyngoesophageal reflexes involved with feeding success or feeding failure, identify potential predictive factors that could allow for better

feeding outcomes, and evaluate the economic impact on quality of feeding milestones at discharge and at 1 year. In the present study we tested the hypothesis that clinical and neuromotor motility correlates differed between successful and unsuccessful oral feeders at discharge.

PATIENTS AND METHODS

Subjects

The subjects used in the present study were infants admitted to the NICU at Nationwide Children's hospital, an all-referral unit for specialty care of complex neonates. Patients demonstrated heterogeneous feeding problems including feeding-related bradycardia and desaturation, coughing, gagging, arching, refusal to feed, and/or poor nipping ability characterized by an inability to consume adequate feeding volume. These infants were at high risk and were referred to The Neonatal and Infant Feeding Disorders Program for the assessment and development of an evidence-based feeding strategy in an effort to avoid gastrostomy placement. We refer high risk in the context of ICU neonates that were at risk for gastrostomy feeding strategies. The multidisciplinary team consists of representatives of neonatology, gastroenterology, general pediatrics, behavioral and occupational feeding therapy, and dietitians. Referrals for evaluation were at the request of NICU nurses, neonatologists, pediatric surgeons, pediatric gastroenterologists, and parents who wished to avoid long-term tube feedings or surgery. ICU consecutive neonates ($N = 100$, 31.4 ± 4.9 weeks' gestational age (GA), mean $\pm$ standard deviation [SD]) underwent the evaluation at 46.4 ± 13.1 weeks' PMA (mean $\pm$ SD). Subjects with necrotizing enterocolitis, congenital anomalies, or birth defects were excluded in the present study. Feeding and outcomes data from these neonates were tracked through discharge and up to 1 year of age.

This is a report of the retrospectively collected data about feeding outcomes among those who were referred to the innovative feeding program for further management of feeding difficulties. Ethical approval to report our experience in the present study was obtained from the institutional research review board at the Nationwide Children's Hospital Research Institute. Informed consent was obtained from parent(s), and the study complied with the Health Insurance Portability and Accountability Act.

Conventional Approach to Infant Feeding Problems

For comparison, data from 50 consecutive historical controls were identified from chart reviews of NICU infants who were referred to the hospital for evaluation of long-term feeding strategies from December 2002 to August 2008, and information was obtained from chart reviews. These infants underwent conventional treatment as determined by their physicians of record. Most patients were evaluated by radiology, occupational and speech-language pathology, and diagnostic and therapeutic approaches were implemented at the discretion of the attending physician. These patients were cared for by 4 distinct physician groups using variable approaches to manage feeding and comorbidities. These infants did not have any manometry studies, and were not seen in our innovative feeding disorders program. When gastrostomy was prescribed, the procedure was performed by interventional radiologists or pediatric surgeons.

Innovative Approach to Infant Feeding Problems

The "innovative methods" to refer to the use of the process of esophageal provocative manometry methods in clarifying the physiology of aerodigestive reflexes in symptomatic infants with dysphagia, and applying such knowledge in an individualized setting to develop a multidisciplinary approach to feeding enhancement. This whole process is simply referred at Nationwide Children's Hospital as Dr Jadcherla's study. This approach was as follows:

we first evaluated demographic and clinical characteristics of the perinatal and neonatal course and aerodigestive symptoms related to feeding; videofluoroscopic swallow studies and or upper gastrointestinal fluoroscopy studies as indicated were evaluated for aerodigestive structure and function; to characterize the neuromotor mechanisms of symptoms related to feeding, swallow-integrated esophageal motility assessment with concurrent respiratory inductance plethysmography was performed at crib-side; multidisciplinary input of feeding-related symptoms and comprehensive evaluation findings were discussed with parents; an individualized feeding management strategy was formulated with special emphasis on feeding methods, nutrition and growth, the pathophysiological basis of symptoms, relevant pharmacological strategies, compliance to recommendations, and education of direct feeding providers (nursing, feeding therapists, parents).

Manometric Study Protocol

We have previously described the use of esophageal manometry methods in neonates during maturation (12–19). Briefly, the esophageal manometry catheter assembly with dual sleeves and 4 side-ports (pharynx, proximal, mid-, and distal esophagus) and stomach was used. Esophageal and pharyngeal infusion ports were used to test esophageal and pharyngeal reflexes, respectively. Subject safety was followed by concurrent monitoring of respiratory patterns with Resptrace (Viasys, Sensormedics, Palm Springs, CA), heart rate patterns, and pulse oximetry. All of the studies were performed by the same investigator (S.R.J.). Continuous data acquisition and analysis were performed per protocol during manometric study based on waveform characteristics (12–17). Specifically, basal and adaptive esophageal reflexes, sphincteric reflexes, pharyngeal reflexes, and oral feeding challenge tests were performed (7,12–17). Graded volumes of air and liquids were given at the mid-esophageal segment to test for peristaltic and upper esophageal sphincter (UES) reflex responses. Sterile water was infused via pharyngeal infusion port to test for pharyngeal swallowing reflexes. Oral feeding challenge tests were performed under manometric guidance to assess oromotor reflex synchrony with pharyngeal and esophageal phases of swallowing. Airway adaptation and respiratory patterns were observed in relation to swallowing, pharyngeal stimulation, esophageal stimulation, and oral feeding.

Multidisciplinary Management Strategy

A multidisciplinary feeding plan was established in collaboration with the dedicated neonatal nursing team and occupational therapists. The feeding management strategy complied with the following principles (7): Standard cue-based feeding approaches were used in all of the subjects. Additional oral feeding therapy methods included nonnutritive sucking, application of sucrose on a pacifier to stimulate taste sensation, and maintenance of optimal position and posture during feeding therapy sessions. Oral feeding attempts were begun cautiously in a stepwise manner (step-down or step-up), and were advanced based upon feeding performance and absence of symptoms. When a subject was noted to be tachypneic (respiratory rate >60/minute), no oral feedings were offered. A feeding session was attempted using 5 to 10mL of milk or formula, and the volume was increased at the next session in asymptomatic subjects as tolerated. In symptomatic subjects, approaches to relieve symptoms included pacing techniques and modification of milk flow rates using slow-flow nipples. Frequent pauses in feeding were made to allow adaptation, particularly when subjects began to feed higher volumes. When symptoms were noted during nipple feeding, the nipple was withdrawn to allow for clearance by swallowing and recovery. The goal was to improve the quality, rather than quantity, of each feeding session. Sessions lasted up to 20 to 30 minutes or as tolerated by the infant. Hunger manipulation methods were the preferred methods, using a bolus feeding regimen with 3-hour feeding cycles (20,21). Those infants who are fed continuously are rarely hungry; such infants are slowly weaned to 2 hours on feeds and 1 hour off feeds over a 3-hour feeding cycle. Next, they are

converted to 1 hour on feeds and 2 hour off feeds; this is followed by 30 minutes on feeds and 2½ off feeds. In our experience, these approaches improved their hunger cues and were able to accelerate with oromotor skills. In infants symptomatic during bolus feeds, alternative tube feeding (transpyloric or continuous) methods were used. Because gastrointestinal motility responses are cyclical, and involve fasting interdigestive phases and fed phases (18,22–24), we progressed gradually from continuous intragastric feeds to slow bolus feeds (infusing feed for 2 hours and pausing for 2 hours) to bolus feeds given for 30 minutes. This approach was based on our previous experience related to manometric responses during fasting, feeding, and swallowing reflexes (18,23–25). Objective evidence-based pharmacological management was applied based on the diagnosis, severity, or the presence of comorbidity factors including management of bronchopulmonary dysplasia (BPD), GERD, cardiac and neuropathology as clinically indicated. This part of the management was in collaboration with the primary care team.

Manometric Data Analysis

Manometric study findings were simplified based on our published studies (12–17) and described in brief as follows. Primary peristalsis was defined as swallows originating in the pharynx associated with UES relaxation, antegrade esophageal propagation, and lower esophageal sphincter relaxation. Such responses can happen during esophageal stimulation (deglutition response) or during pharyngeal stimulation (reflexive pharyngeal swallow) (12,15,16). Secondary peristalsis was defined as esophageal peristalsis during mid-esophageal infusion, and is not associated with pharyngeal swallowing; instead this mode of peristalsis may be associated with UES contractile reflex. Normal pharyngeal manometry is defined as >80% peristaltic responses to pharyngeal sterile water infusion of 0.1 to 0.5 mL. Suck-swallow-breathe-primary peristalsis sequences evoked with a pacifier that were associated with appropriate deglutition apneas were observed. During the oral feeding challenge test, about 10 to 15mL of milk was offered and swallow integrated-pharyngoesophageal manometry characteristics were observed. This test was considered successful when sequences of submental EMG activity, sucking, swallowing, primary peristalsis, and lower esophageal sphincter relaxation were associated with appropriate respiratory pauses (deglutition apneas) and absence of symptoms. Absence of such patterns and the presence of symptoms were considered failure.

Data Collection Methods and Outcome Measures

The data were collected at 4 time periods: at birth, at the time of feeding evaluation, at discharge, and at 1 year of chronological age. We recorded comorbidities including neuropathology (grade of intraventricular hemorrhage [IVH], periventricular leukomalacia, cerebral infarcts, cerebral hemorrhage), chronic lung disease (oxygen requirement beyond 36 weeks' PMA), and GERD (presence of abnormal pH or pH-impedance testing and or treatment with acid suppressive strategy). We recorded persistent symptom markers of feeding concern such as dysphagia, arching, emesis, irritability, bradycardia, straining, cough, stridor, feeding aversion, apnea, and bradycardiac events. Discharge outcomes including length of hospital stay and method of feeding at discharge were recorded. Infants were followed in the neonatal follow-up clinic and feeding outcomes at 1 year were documented. Economic outcomes were calculated based on estimated gastrostomy feeding costs as reported before (7,26). As majority of healthy neonates are discharged by 38 weeks' PMA, we estimated charges for the stay beyond 38 weeks' PMA by considering the average charge of each NICU day stay as \$2000 (\$14,000/week).

Statistical Analysis

Subjects with fully or primary oral feeding abilities at discharge were included in the oral feeding–success group, and those who did not achieve safe oral feeding and were dependent

on other methods of nutrition at discharge were included in the feeding failure group. All variables of interest (subject and disease characteristics, outcome characteristics, and manometric characteristics) were compared between the 2 groups. Discrete variables were compared between the groups using χ^2 tests or Fisher exact tests, whereas 2-sample t tests were used to analyze the intergroup differences for continuous variables. Logistic regression was used to examine the relation between the confounding variables versus feeding outcomes (success and failure). Variables that were highly intercorrelated ($r > 0.80$) were excluded because of multicollinearity. Data are presented as mean $\pm$ SD, median, and range, or as percentages. SAS version 9.1 (SAS Institute Inc, Cary, NC) was used to perform the analyses. $P < 0.05$ was considered significant.

RESULTS

Demographic and Feeding Outcome Characteristics: Comparison of Outcomes Within the Innovative Program Versus Historical Controls

Fifty-one (51%) patients fell into the feeding success group because they were oral-fed successfully; 6 (11.8%) were supplemented with nocturnal tube feeds to improve growth. Comparison of subjects in the innovative program versus 50 historical controls is described (Table 1). Subjects managed in the innovative program (vs historical controls) were more immature and smaller in size ($P < 0.05$), and yet achieved higher feeding success rate at discharge and 1 year ($P < 0.001$, Fig. 1). The demographics and discharge feeding outcomes (feeding success vs feeding failure) within the innovative program are described (Table 2).

Correlation Between Feeding Outcomes and Manometric Characteristics

Characteristics of esophageal infusion- and pharyngeal infusion-induced peristaltic reflexes are compared and are distinctly different (Table 3) between feeding success (Fig. 2) and failure (Fig. 3). The spontaneous swallow frequency (3.1 ± 1.5 vs 2.5 ± 1.9 swallow per minute, $P = 0.1$) and associated esophageal peristalsis velocity (centimeters per minute) were similar between success group and failures (0.5 ± 5.3 vs 2.2 ± 1.9 , $P = 0.07$).

Relationship Between Comorbidities and Feeding Outcomes

We tested the impact between comorbidities (Neuropathology, CLD, and GERD) and discharge feeding failure (logistic regression, Table 4). Additionally, a logistic regression model on the probability of feeding success (P_{FS}) was constructed (Table 5). Variables that were highly intercorrelated ($r > 0.80$) were excluded because of multicollinearity. Possible continuous confounders included GA and the proportion of primary peristalsis induced by esophageal infusions. Possible categorical confounders include CLD, neuropathology, feeding challenge success, and normal pharyngeal manometry. The predictive model for feeding success at discharge can be expressed as follows: $\log(P_{FS}/(1-P_{FS})) = 8.1643 - 0.2670*GA - 2.6153*CLD - 2.2108*neuropathology + 1.3222*feeding\ challenge\ test + 1.7282*normal\ pharyngeal\ manometry + 5.0555*primary\ peristalsis\ induced\ by\ esophageal\ infusions$. ($\chi^2 = 8.50$ and $P = 0.39$ for the Hosmer and Lemeshow goodness-of-fit test.) A good prediction rate of 79.6% was achieved based on posthoc modeling of 88 subjects from our data set (12 subjects were excluded for calculating prediction rates because feeding challenge test or pharyngeal manometry was not performed for clinical reasons).

In the prediction model, the adjusted odds ratio (95% confidence interval [CI]) for the effect of GA on the response (feeding success at discharge) is 0.77 (0.63–0.93), $P = 0.008$ (Table 5). This means that if subject's GA is increased by 1 unit (27), the odds ratio of achieving feeding success at discharge is 0.77 times (GA has a negative impact on the feeding success at discharge). This information implies that younger GA subjects with feeding problems have a better chance of feeding success than older GA subjects with feeding problems.

Impact of GA on Feeding Outcomes at 1 Year Old

If we look at 1-year outcome, the GA for the 14 subjects who did not achieve any oral feeding is 32.1 ± 1.4 (33.7, 23–38), whereas for the 75 subjects who achieved oral feeding is 31.0 ± 0.56 (30.3, 23–39, $P = \text{NS}$). Out of those 14 subjects who did not achieve oral feeding at 1 year, the combination of comorbidities was 11 had chronic lung disease, 12 had neuropathology, and 9 did not pass the feeding challenge test; however, the 1-year outcome has 84.3% in the success group and 15.7% in the failure group. Therefore, prediction model for the 1-year outcome was not possible because of limited data comparison variables.

Effect of Neuropathology on Feeding Outcomes

In the predicting model, neuropathology is a categorical variable that has 2 levels (yes or no) and is based on whether the patient has neuropathology problems or not. Out of the 100 subjects we studied, 43 subjects had neuropathology (28 IVH, 5 hypoxic ischemic encephalopathy, 10 with combination of other neurological problems). None of the 5 hypoxic ischemic encephalopathy subjects achieved oral feeding success at discharge. Three out of the 10 (30%) other neuropathology patients achieved oral feeding. Of the 28 IVH subjects, 3 of 15 with grade 1 (20%), 2 of 4 with grade 2 (50%), 2 of 7 with grade 3 (29%), and 1 of 2 with grade 4 (50%) achieved oral feeding success at discharge; however, the sample size is small to make powerful comparisons with each neuropathology.

Approaches Associated With Modification of Feeding Outcomes

Multidisciplinary personalized recommendations were based on diagnostic observations, and are summarized as follows: changes in the feeding strategy ($N = 88$, 56.8% achieved success), that is, changing gradually from continuous feeds to simulated bolus feeds to bolus feeds >30 minutes; postural adaption during feeding sessions and postprandial postural adaptation; modification of caloric density; changing the feeding volume and duration ($N = 30$, 66.7% achieved success); changing the nipple flow rates by using slower flow nipples ($N = 24$, 79.2% achieved success); application of occupational therapeutic maneuvers ($N = 72$, 45.8% achieved success), such as swaddling infant in blanket, practicing cue-based oral feeding approach, preparation for feeding session by stimulating with pacifier and activating oro-motor reflexes (rooting, sucking, tongue lateralization, and tongue-palate apposition), providing cheek and chin support, maintaining airway position during sucking pauses, recognizing dysfunctional sucking patterns, and allowing time for infant to swallow; and pharmacological management of comorbidities as managed by the primary team with specific attention to lung disease and oxygen needs ($N = 75$, 45.3% achieved success), neurological pathology and seizure control ($N = 44$, 27.2% achieved success), GERD and acid suppressive medications ($N = 52$, 51.9% achieved success), and the use of erythromycin to enhance gastric emptying ($N = 4$, 75% achieved success).

Effect of Feeding Outcomes on Feeding-related Economics

Given the fact that infants in the present study were referred to our program for long-term feeding management, the total charges of feeding-related problems is estimated to be \$23.3 million beyond 38 weeks' PMA for the 98 infants in the present study (2 subjects were discharged before 38 weeks). Furthermore, given the estimated cost of home gastrostomy feeding methods (7) of \$46,875 for the first year, prevention of gastrostomy in 45% of subjects in the innovative feeding program resulted in savings of \$2.1 million more than 1 year. In the historical control group, only 4 (8%) subjects were able to avoid gastrostomy placement at discharge. Cost savings for the 100 subjects referred to the innovative feeding group is estimated to be \$1.7 million more than 1 year without regard to feeding-related quality of life or parental satisfaction. At 1 year, 84.3% of our patients achieved feeding success (ie, accepted oral feeds).

DISCUSSION

Neonatal feeding disorders represent a heterogeneous and complex challenge for those caring for sick infants and are among the dominant reasons for prolonged length of hospital stay and the increased economic burden of chronic neonatal disease (5). This problem has often been underestimated due to the presence of more dominant overshadowing comorbidities. Furthermore, the indications and initiation of feeding strategies or gastrostomy placement in NICU infants remain unclear and controversial, as noted in the American Academy of Pediatrics' statement on neonatal discharge. In addition, individual health care providers are often highly variable in developing individualized feeding protocols; some "wait and see" or "wait for maturation" to change the feeding strategy whereas others rapidly implement pharmacological approaches with little objective evidence. Parental reluctance to implement chronic tube feeding strategies and/or a lack of resources to manage a technology-dependent infant at home may compound the situation. In the present study, the variability in overall length of stay may be attributed to the heterogeneity of the feeding problems and the comorbidity factors. Nevertheless, the pathophysiology-based individualized feeding strategy was successful in achieving feeding success in a significant group at discharge (51%) and at 1 year (84%).

We establish the proof of concept for an individualized pathophysiology evidence-based approach in modifying feeding outcomes among infants that were referred for gastrostomy evaluation. The infants seen in our program were those who have not responded to conventional approaches to modify feeding problems. We simply refer translational approach as to translating pathophysiology-based scientific approach to modify clinical care. The unique features of the present study are summarized as follows: This is the first study to describe an innovative, pathophysiology-based approach to the diagnosis of feeding problems and the implementation of evidence-based multidisciplinary, individualized management strategies to improve feeding outcomes among complex NICU infants referred for long-term feeding methods. We attempt to clarify the pathophysiology of neonatal pharyngoesophageal reflexes involved with feeding success or feeding failure. We develop the potential predictive ability of the innovative approach to modify feeding outcomes, which can be of use in future studies. We attempt to objectify the feeding-related economic burden by evaluating the economic impact of the innovative approach on feeding outcomes at discharge and at 1 year of age. We note the clinical and neuromotor motility correlates at evaluation, which differed between successful oral feeders versus feeding failures. Specifically, successful oral feeders had a greater frequency of peristaltic responses to esophageal and pharyngeal infusions, a greater tendency to pass the oral feeding challenge test and more suck-swallow-breath-esophageal swallow sequences were seen in success group compared to failures.

Many neonates recover from acute illness early in the neonatal course but go on to develop persistent feeding problems. In general, these feeding difficulties manifest as a failure to develop a safe rhythmic suck-swallow coordination with breathing sequence, frequent regurgitation or emesis, gastroesophageal reflux, delayed gastric emptying, gastrointestinal dysmotility, or airway aspiration. Some of these difficulties may further slow down recovery. Within our patients, significant morbidities associated with feeding failure at discharge were neuropathology, BPD, combined neuropathology and BPD, and all 3 morbidities together. Indeed, the subjects in the present study likely represented the sickest NICU survivors and had already failed conventional approaches to improve feeding performance and to prevent feeding failure. Despite the severity of their confounding comorbidity factors, we are extremely pleased that 84% achieved oral feeding success by 1 year of age.

In the present study, the personalized, pathophysiology-based approach resulted in feeding success in the majority of infants referred for long-term feeding strategy; this group previously would have uniformly undergone gastrostomy placement. The neuromotor markers of motility that participate in safe swallowing and airway protection were evaluated and included in the prediction model (28). A *P* value of 0.39 indicates that the numbers of success are not significantly different from those predicted by the model, and that the overall model fit is good. Notably, the presence of primary peristaltic reflexes evoked upon pharyngeal and mid-esophageal stimulation was highly suggestive of feeding success. This finding, in addition to the successful oral feeding challenge test under manometric guidance, offered confidence in the development of individualized approaches to oral feedings. In contrast, infrequent or absence of primary peristaltic reflexes, a failed oral feeding challenge test, or lack of suck-swallow-breathe coordination was found to be less amenable for oral feeding approaches. Nevertheless, even among the gastrostomy infants, the vast majority of patients went on to recover significant oromotor skills. Finally, the development of a pathophysiology-based approach before 43 weeks' PMA was associated with feeding success at discharge.

We believe that our approach is innovative in several ways. First, we combine objective data on the physiology of each infant's suck and swallow capabilities with subjective data obtained from all interested parties. This allows us to provide evidence-based treatment protocols that are specifically directed at the underlying pathology affecting each infant, and to provide reasonably certain diagnostic and prognostic information to parents. Second, we have significantly reduced the variability of treatment for these infants; previously such infants received care based almost entirely on each individual attending physician's interpretation of variables that are often highly subjective. Under the innovative program, care plans are carefully laid out and followed over extended periods, and sources of variability such as frequent nipple changes have been essentially eliminated. These results are consistent with the experiences of other groups in older children (29), but have not yet been reported in this particularly vulnerable patient population.

Feeding-related costs were calculated based on the notion that most healthy premature infants are discharged by 38 weeks' PMA (1) and on an estimated average charge of hospitalization of \$2000 per NICU day (\$14,000/week). These were at best estimates, as the exact charges are difficult to compute in a retrospective review, and may be a limitation of the present study. Previously published costs for gastrostomy feeding methods were also used in calculating savings resulting from prevention of gastrostomy using the innovative approach (7,26). These costs likely underestimate true expenditures because costs for inflation and benefits of superior quality of life from oral feeding methods have not been determined.

In summary, our experience with a large cohort of NICU infants with feeding problems suggests that a pathophysiology-based feeding management approach yields good outcomes. In the present study of neonatal feeding disorders we assessed neuromotor deficits in propulsion of feeding bolus from mouth to stomach, as well as lack of aerodigestive safety mechanisms that protect the esophagus and airway in relation to feeding. These observations led us to develop individualized feeding strategies. The present study provides a framework for future prospective, objective evidence-based studies, and offers guidance to pediatric gastroenterologists and neonatologists who are often confronted with the challenging dilemmas of long-term tube feeding strategies. The present study also offers hope and anticipatory guidance to parents of NICU infants when confronted with the decision of gastrostomy for feeding reasons.

Acknowledgments

This study was supported in part by Nationwide Children's Hospital and NIH grant R01 DK 068158 (Jadcherla).

REFERENCES

1. Jadcherla SR, Wang M, Vijayapal AS, et al. Impact of prematurity and co-morbidities on feeding milestones in neonates: a retrospective study. *J Perinatol*. 2010; 30:201–208. [PubMed: 19812589]
2. Mercado-Deane MG, Burton EM, Harlow SA, et al. Swallowing dysfunction in infants less than 1 year of age. *Pediatr Radiol*. 2001; 31:423–428. [PubMed: 11436889]
3. Burklow KA, Phelps AN, Schultz JR, et al. Classifying complex pediatric feeding disorders. *J Pediatr Gastroenterol Nutr*. 1998; 27:143–147. [PubMed: 9702643]
4. Rommel N, De Meyer AM, Feenstra L, et al. The complexity of feeding problems in 700 infants and young children presenting to a tertiary care institution. *J Pediatr Gastroenterol Nutr*. 2003; 37:75–84. [PubMed: 12827010]
5. American Academy of Pediatrics Committee on Fetus and Newborn. Hospital discharge of the high-risk neonate. *Pediatrics*. 2008; 122:1119–1126. [PubMed: 18977994]
6. Jadcherla SR, Vijayapal AS, Leuthner S. Feeding abilities in neonates with congenital heart disease: a retrospective study. *J Perinatol*. 2009; 29:112–118. [PubMed: 18818664]
7. Jadcherla SR, Stoner E, Gupta A, et al. Evaluation and management of neonatal dysphagia: impact of pharyngoesophageal motility studies and multidisciplinary feeding strategy. *J Pediatr Gastroenterol Nutr*. 2009; 48:186–192. [PubMed: 19179881]
8. Malcolm WF, Smith PB, Mears S, et al. Transpyloric tube feeding in very low birthweight infants with suspected gastroesophageal reflux: impact on apnea and bradycardia. *J Perinatol*. 2009; 29:372–375. [PubMed: 19242488]
9. Malcolm WF, Gantz M, Martin RJ, et al. Use of medications for gastroesophageal reflux at discharge among extremely low birth weight infants. *Pediatrics*. 2008; 121:22–27. [PubMed: 18166553]
10. Clark RH, Bloom BT, Spitzer AR, et al. Reported medication use in the neonatal intensive care unit: data from a large national data set. *Pediatrics*. 2006; 117:1979–1987. [PubMed: 16740839]
11. Orenstein SR, Di Lorenzo C. Postfundoplication complications in children. *Curr Treat Options Gastroenterol*. 2001; 4:441–449. [PubMed: 11560791]
12. Jadcherla SR, Duong HQ, Hofmann C, et al. Characteristics of upper oesophageal sphincter and oesophageal body during maturation in healthy human neonates compared with adults. *Neurogastroenterol Motil*. 2005; 17:663–670. [PubMed: 16185304]
13. Jadcherla SR, Hoffmann RG, Shaker R. Effect of maturation of the magnitude of mechanosensitive and chemosensitive reflexes in the premature human esophagus. *J Pediatr*. 2006; 149:77–82. [PubMed: 16860132]
14. Jadcherla SR, Duong HQ, Hoffmann RG, et al. Esophageal body and upper esophageal sphincter motor responses to esophageal provocation during maturation in preterm newborns. *J Pediatr*. 2003; 143:31–38. [PubMed: 12915821]
15. Gupta A, Gulati P, Kim W, et al. Effect of postnatal maturation on the mechanisms of esophageal propulsion in preterm human neonates: primary and secondary peristalsis. *Am J Gastroenterol*. 2009; 104:411–419. [PubMed: 19174814]
16. Jadcherla SR, Gupta A, Stoner E, et al. Pharyngeal swallowing: defining pharyngeal and upper esophageal sphincter relationships in human neonates. *J Pediatr*. 2007; 151:597–603. [PubMed: 18035137]
17. Pena EM, Parks VN, Peng J, et al. Lower esophageal sphincter relaxation reflex kinetics: effects of peristaltic reflexes and maturation in human premature neonates. *Am J Physiol Gastrointest Liver Physiol*. 2010; 299:G1386–G1395. [PubMed: 20864655]
18. Jadcherla SR, Sty JR, Rudolph CD. Mechanical small bowel obstruction in premature infants diagnosed by intestinal manometry. *J Pediatr Gastroenterol Nutr*. 2005; 41:247–250. [PubMed: 16056108]

19. Jadcherla SR. Manometric evaluation of esophageal-protective reflexes in infants and children. *Am J Med.* 2003; 115(suppl 3A):157S–160S. [PubMed: 12928093]
20. Byars KC, Burklow KA, Ferguson K, et al. A multicomponent behavioral program for oral aversion in children dependent on gastrostomy feedings. *J Pediatr Gastroenterol Nutr.* 2003; 37:473–480. [PubMed: 14508219]
21. Dollberg S, Kuint J, Mazkereth R, et al. Feeding tolerance in preterm infants: randomized trial of bolus and continuous feeding. *J Am Coll Nutr.* 2000; 19:797–800. [PubMed: 11194534]
22. Jadcherla SR, Berseth CL. Acute and chronic intestinal motor activity responses to two infant formulas. *Pediatrics.* 1995; 96:331–335. [PubMed: 7630694]
23. Jadcherla SR, Berseth CL. Antroduodenal motility and feeding outcome among neonatal extracorporeal membrane oxygenation survivors. *J Pediatr Gastroenterol Nutr.* 2005; 41:347–350. [PubMed: 16131992]
24. Jadcherla SR, Klee G, Berseth CL. Regulation of migrating motor complexes by motilin and pancreatic polypeptide in human infants. *Pediatr Res.* 1997; 42:365–369. [PubMed: 9284278]
25. Goyal RK, Padmanabhan R, Sang Q. Neural circuits in swallowing and abdominal vagal afferent-mediated lower esophageal sphincter relaxation. *Am J Med.* 2001; 111(suppl 8A):95S–105S. [PubMed: 11749933]
26. Linscheid, TR.; Budd, KS.; Rasnake, LK. *Pediatric Feeding Disorders.* New York: Guilford Press; 2003.
27. Anderson SW, Todd MM, Hindman BJ, et al. Effects of intraoperative hypothermia on neuropsychological outcomes after intracranial aneurysm surgery. *Ann Neurol.* 2006; 60:518–527. [PubMed: 17120252]
28. Hosmer, DW., editor. *Applied Logistic Regression.* New York: Wiley; 2000.
29. Silverman AH. Interdisciplinary care for feeding problems in children. *Nutr Clin Pract.* 2010; 25:160–165. [PubMed: 20413696]

Innovative feeding program **Historical controls** **FIGURE 1.**

Feeding success rate comparisons between innovative feeding program and historical controls.

FIGURE 2.

Pharyngoesophageal manometry recording in a subject with feeding success. LES = lower esophageal sphincter; UES = upper esophageal sphincter.

FIGURE 3.

Pharyngoesophageal manometry recording in a subject with feeding failure. LES = lower esophageal sphincter; UES = upper esophageal sphincter.

TABLE 1

Comparison of demographics and outcomes: innovative feeding program versus historical controls

	Innovative feeding program, N = 100	Historical control group, N = 50	P
Gestation age, wk	31.4 ± 4.9 (31.5, 23.0–41.0)	33.3 ± 5.1 (34.0, 23.0–41.0)	0.04
Sex, M:F	62:38	24:27	0.08
Birth weight, kg	1.8 ± 1.1 (1.5, 0.5–7.2)	2.3 ± 1.2 (2.4, 0.5–5.5)	0.007
Neuropathology, %	44	54	0.2
BPD, %	74	48	0.002
GER symptoms, %	66	54	0.2
Feeding success at discharge, %	51	10	<0.0001
Feeding success at 1st birthday, % *	84.3 (75/89)	42.9 (21/49)	<0.0001
Length of stay, wk	18.8 ± 20.3 (11.9, 0.3–110.7)	17.9 ± 16.6 (11.3, 2.7–79)	1.0

Data are represented as mean ± SD (median, range). BPD = bronchopulmonary dysplasia; GER = gastroesophageal reflux.

* In the innovative feeding program, 9 patients died after discharge and 2 patients were transferred to other hospitals; thus, data from the remaining 89 patients are shown. In the historical control group, 1 patient died after discharge; thus, data from 49 patients are shown.

TABLE 2

Comparison of demographics and discharge outcomes within the innovative feeding program: feeding success versus feeding failure

	Feeding success, N = 51	Feeding failure, N = 49
Gestation age, wk	31.2 ± 4.7 (30.3, 24.0–39.0)	31.6 ± 5.2 (32.9, 23.0–41.0)
Sex, M:F	29: 22	33: 16
Birth weight, kg	1.9 ± 1.3 (1.4, 0.5–7.2)	1.7 ± 1.0 (1.7, 0.5–4.7)
APGAR score at 1 min	5 (0–9)	5 (0–9)
APGAR score at 5 min	8 (1–9)	8 (0–10)
Postmenstrual age at evaluation, wk	42.9 ± 7.2 (41.4, 29.6–76.7) *	50.0 ± 16.6 (45.7, 37–124.7) *
Weight at evaluation, kg	3.5 ± 1.4 (3.2, 1.0–8.3)	4.1 ± 2.2 (3.4, 1.6–12.4)
Postmenstrual age at discharge, wk	47.0 ± 9.0 (45.6, 36.1–90.4) #	62.5 ± 25.5 (51.9, 40.0–135.1) #

Data are represented as mean ± SD (median, range).

* $P = 0.03$ for group comparison;

$P = 0.0002$ for group comparison.

TABLE 3

Comparison of pharyngoesophageal manometric characteristics: feeding success versus feeding failure

Characteristics	Feeding success, N = 51	Feeding failure, N = 49	P
Peristaltic responses to esophageal infusion, %	71.10 ± 14.1	65.3 ± 18.5	0.04
Primary peristalsis induced by esophageal infusion, %	49.8 ± 25.5	32.8 ± 22.9	0.0008
Secondary peristalsis induced by esophageal infusion, %	50.9 ± 25.5	64.4 ± 24.2	0.009
Normal pharyngeal manometry, %	59.6	22.2	0.0003
Oral feeding challenge success, %	60.9	29.8	0.003
Suck-swallow-breath-esophageal swallow sequence, %	63.8	31.9	0.002

Data are presented as mean ± SD or percentage. See manometric data analysis section for definition of characteristics.

TABLE 4

Relation between comorbidity and feeding outcomes

Comorbidity factors	OR (95% CI) for feeding failure	P
Neuropathology, N = 44	7.5 (3.1, 18.4)	0.0001
Chronic lung disease, N = 55	3.2 (1.4, 7.4)	0.005
Gastroesophageal reflux symptoms, N = 52	0.9 (0.4, 2.0)	0.9
Neuropathology and chronic lung disease, N = 32	13.5 (4.1, 44.5)	0.0001
Chronic lung disease and gastroesophageal reflux symptoms, N = 32	2.6 (0.9, 7.6)	0.08
Neuropathology and gastroesophageal reflux symptoms, N = 22	7.2 (2.0, 26.0)	0.002
All 3 morbidities, N = 16	11.3 (2.3, 54.6)	0.003

To characterize the relationship between the independent variables (disease comorbidity) and the dependent variable (binary feeding outcomes), simple and multiple logistic regressions were applied. Significant values denote a positive correlation between the comorbidity and the feeding failure as an outcome. For example, those patients with neuropathology has 7.5 times odds ratio to get feeding failure as an outcome compared to those without. CI = confidence interval; OR = odds ratio.

TABLE 5

Logistic regression of feeding success on possible confounders

Parameters	Estimate	Adjusted OR (95% CI)	P
Intercept	8.15	NA	0.02
Gestational age, wk	−0.27	0.77 (0.63–0.93)	0.008
Chronic lung disease	−2.62	0.08 (0.01–0.43)	0.004
Neuropathology	−2.21	0.11 (0.03–0.48)	0.003
Pass oral feeding challenge test	1.32	3.75 (1.10–12.84)	0.04
Normal pharyngeal manometry	1.73	5.63 (1.46–21.78)	0.01
Primary peristalsis induced by esophageal infusion, %	5.06	156.88 (2.52–>999.99)	0.02

CI = confidence interval; OR = odds ratio.