The following excerpts from the provided articles may help focus our thinking about guiding principles for RPC NICU policies on enteral feeding of VLBW infants.

**Berseth**
Gastric emptying is not altered by feeding temperature or non-nutritive sucking. However, it is delayed during extreme stress, such as the presence of systemic illness.

…infants who have feeding intolerance are more likely to have more immature patterns than those who are tolerant of feedings. However, giving small enteral feedings during the first 10 postnatal days causes more mature motor patterns to appear precociously, which is associated with better feeding tolerance.

Giving preterm infants small feedings (20 to 24 mL/kg per day) induces maturation of fasting motor patterns.

…there is no dose-response relationship for feeding volume and maturation of motor patterns; that is, infants fed 150 to 160 mL/kg per day exhibit similar motor patterns to those exhibited by infants fed 20 to 24 mL/kg per day. This observation has two elements of practical application for the clinician. First, if there are concerns that large feeding volumes precipitate necrotizing enterocolitis, small feedings can be employed as effectively as larger volumes to induce maturation of motor patterns. Second, when feeding volumes must be limited because of concerns for feeding intolerance or for other nongastrointestinal-related issues such as surgery or sepsis, such smaller feeding volumes are providing the same benefit with respect to maturation of motor patterns.

Approximately 50% of preterm infants fail to exhibit a mature fed response when fed by bolus over 1 to 2 minutes. When these same infants are provided the same feeding volume more slowly over 1 to 2 hours, they exhibit a mature fed response. An infant who has large gastric residuals may tolerate feedings better when longer intervals between feedings are provided.

**Adamkin**
The goal of nutrition management in VLBW infants, which is supported by the American Academy of Pediatrics Committee on Nutrition, is the achievement of postnatal growth at a rate that approximates the intrauterine growth of a normal fetus at the same postconceptional age.

Although non-nutritional factors (morbidities) are involved in the slow growth of VLBW infants, nutrient intakes are low and critical in explaining their poor growth. Considerable evidence suggests that early growth deficits have long-lasting effects, including short stature and poor neurodevelopmental outcomes.

***Nutrition management of VLBW infants is marked by a lack of uniformity from one neonatal intensive care unit to the next as well as within individual practices. Such heterogeneity of practice persists from the first hours after birth to hospital discharge and***
Diversity of practice thrives where there is uncertainty. Because undernutrition is, by definition, unphysiologic and undesirable, any measure that diminishes it is inherently good, as long as safety is not compromised.

An increase in blood urea nitrogen, which often is observed after the start of PN, is not an adverse effect or sign of toxicity; rather, it is a normal accompaniment of an increase in the intake of amino acids or protein.

The timing of initial feedings for the preterm infant has been debated for nearly a century and remains controversial. Total parenteral nutrition (TPN) was believed to be a logical continuation of the transplacental nutrition that infants would have received in utero. However, this view discounts any role that swallowed amniotic fluid may play in nutrition and in the development of the gastrointestinal tract. In fact, by the end of the third trimester, amniotic fluid provides the fetus with the same enteral volume intake and approximately 25% of the enteral protein intake as that of a term, breastfed infant. PN does little to support the function of the gastrointestinal tract.

Enteral feedings have both direct trophic effects and indirect effects due to the release of intestinal hormones. Lucas and associates demonstrated significant increases in plasma concentrations of enteroglucagon, gastrin, and gastric-inhibiting polypeptide in preterm infants after milk feedings of as little as 12 mL/kg per day. Similar surges in the trophic hormones were not seen in intravenously nourished infants.

Regardless of feeding strategy, the advancement of feedings is based on perceived evidence of intolerance because of increased pregavage residuals or greenish aspirates. Gastric residuals are very frequent in the early neonatal period and are virtually always benign (ie, not associated with NEC). A 2002 study by Mihatsch and associates demonstrated that in VVLBW infants, excessive gastric residual volume (GRV), either determined by percent of the previous feeding or an absolute volume (~2 mL or ~3 mL), did not necessarily affect feeding success, as determined by the volume of total feeding on day 14. Similarly, the color of the GRV (green, milky, clear) did not predict feeding intolerance. Nonetheless, the volume of feeding on day 14 correlated with a higher proportion of episodes of no GRVs and with predominantly milky gastric residuals. Thus, isolated findings related to gastric emptying alone should not be the sole criteria to initiate or advance feedings. Stooling pattern, abdominal distention, and the nature of the stools also should be considered.

A 2004 retrospective case-control study comparing gastric residuals among VLBW infants who had proven NEC and controls showed more gastric residuals in those who developed NEC. However, the clinical usefulness of these findings is limited by the overlap in the volumes of gastric residuals with the control infants. The maximum residual volume seems to be the best predictor for NEC. A GRV of less than 1.5 mL or less than 25% of a feeding (the 25th percentile for NEC group) is probably within the range of normal. However, a GRV of more than 3.5 mL or 33% of a feeding (75th percentile for control infants) may be associated with a higher risk for NEC.
Efforts aimed at minimizing the risk of NEC have focused on the time of introduction of feedings, feeding volumes, and the rate of feeding volume increments. Each strategy that had been developed with the aim of reducing the risk of NEC has been shown to be ineffective and unnecessary. These strategies linger today, however, distracting neonatologists from concentrating on the real challenge, which is faltering growth in VLBW infants.

…early introduction of feedings shortens the time to full feedings as well as the length of hospitalization and did not lead to an increase in the incidence of NEC. A controlled study involving 100 VLBW infants not only confirmed these findings, but also found a significant reduction of serious infections when feedings were introduced early. Thus, delayed introduction of feedings now is known to have no beneficial effects, such as reduction in incidence of NEC, and yet has substantial negative effects.

A recent study compared a gut stimulation protocol that involved holding feeding volumes constant for 10 days before advancement with a traditional enteral feeding protocol that used standard rates of volume advancement. The study was closed early because the incidence of NEC in the group randomized to immediate volume advancement was 10% versus 1.4% in those receiving the gut stimulation protocol. These studies raise several important questions: Is gut stimulation protective? Do early advancing protocols contribute to NEC? The answer to both questions may be “yes.” Regardless, the data reinforce previous conclusions that gut stimulation protocols are beneficial to VLBW infants and should be routine in all NICUs. There are few contraindications to using these protocols, even in infants weighing 500 to 600 g who have indwelling umbilical catheters and are receiving assisted ventilation.

Preoccupation with preventing necrotizing enterocolitis has contributed to the chronic undernourishment of stable, growing very low-birthweight (VLBW) infants. Inadequate nutrient intakes have the potential for adversely effecting neurocognitive development.

However, the protein content of human milk decreases with the duration of lactation, making fortified human milk likely to provide less protein than 3.1 to 3.25 g/100 kcal. Formulas provide between 2.7 and 3.0 g/100 kcal. Thus, feedings typically provide less protein (relative to energy) than is required, at least until the infant reaches a weight of 1,500 g. This suggests that inadequate protein intake is at least partially responsible for the poor growth of VLBW infants. Supplementation with additional protein and increasing the amount of commercial fortifier beyond the standard amount are options if growth is unsatisfactory or if low blood urea nitrogen concentrations (_4 mg/dL [1.43 mmol/L]) suggest that protein intake is low.

Feeding volumes must be adjusted daily to meet requirements that sustain growth of greater than 15 g/kg per day. This means providing nutrients to support not only the intrauterine rate of growth, but also “catch-up” growth (to correct deficits incurred prior to regaining birthweight) after birthweight is regained and the infant is more stable.

McGuire – Cochrane Review
Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants

There is insufficient evidence to determine whether delaying the introduction of enteral milk feeds given to very low birth weight infants reduces the incidence of necrotising enterocolitis. Very low birth weight infants (birth weight less than 1500 grams) are at risk of developing a severe bowel disorder called “necrotizing enterocolitis”. It is thought that one possible way to prevent this condition is to delay the introduction of milk feeds until several days (or longer) after birth. Only two small trials have assessed the effect of delayed rather than early introduction of milk feeds for very low birth weight infants. Data from these trials are insufficient to guide clinical practice. Further trials are needed to provide evidence to inform this key area of care.

M Chauhan, G Henderson and W McGuire

WHAT IS FEED INTOLERANCE (AND DOES IT PREDICT NEC)?

Feeding regimens for VLBW infants are often interrupted by the development of signs of “feed intolerance”, principally the detection of “gastric residuals,” the gastric content aspirated before a planned gastric tube feed, and abdominal distension. Few studies have examined the clinical importance of these findings. The available data suggest that gastric residual volumes of up to 2 ml in infants weighing less than 750 g, or up to 3 ml in heavier VLBW infants, are well tolerated and not associated with failure to establish full enteral feeding. Little evidence exists that the volume or colour (green, milky, clear) of gastric residuals is predictive of the risk of NEC for infants whose feed volumes are advanced conservatively. Similarly, the clinical importance of abdominal distension or bowel loops visible through the abdominal wall (without other features of intra-abdominal disease) is unclear, especially in the modern era when early and prolonged use of continuous positive airway pressure results in intestinal gaseous distension.

Umbilical arterial catheter

Evidence exists that enteral feeding while an umbilical arterial catheter (UAC) is in place does not affect superior mesenteric blood flow, the risk of feed intolerance or the incidence of NEC. Data from randomised trials are insufficient to exclude an important effect on the UAC tip position (“high” (descending aorta above the level of the diaphragm) vs “low” (above the aortic bifurcation and below the renal arteries)) on the risk of NEC. However, high UAC tip placement results in a lower incidence of aortic thrombosis, fewer ischaemic complications and a longer duration of catheter use.

Patent ductus arteriosus and non-steroidal anti-inflammatory agents

The presence of a patent ductus arteriosus (PDA) has been inconsistently reported as an independent risk factor for development of NEC. Currently, no evidence exists that a practice of withholding enteral feeds in infants with a PDA affects clinical outcomes. Similarly, meta-analyses of trials of non-steroidal anti-inflammatory agents for PDA closure have not demonstrated any significant effects on the incidence of NEC.

Red blood cell transfusion
Although several case reports have described infants developing NEC during red blood cell transfusion, a large randomized controlled trial of high versus low thresholds for red blood cell transfusion in extremely low birth weight infants did not find an effect on the incidence of NEC. The currently available evidence is insufficient to conclude that adopting a policy of enteral fasting during blood transfusion cause more benefit than harm.

**Hay**

...there are many adverse consequences of intravenous feeding without any enteral nutrition. The absence of food in the gastrointestinal tract produces mucosal and villous atrophy and reduction of enzymes necessary for digestion and substrate absorption. Trophic hormones normally produced in the mouth, stomach, and gut in response to enteral feeding are diminished. A variety of immune deficits also develop, including decreased mucosal IgA from Peyer’s patches and increased production of adhesion molecules and polymorphonuclear cell attraction, all with the potential to increase the incidence and severity of the systemic inflammatory response syndrome. Necrotizing enterocolitis (NEC) may be a direct result of such changes when enteral feeding is then introduced along with the pathogenic bacteria that by now are commonly part of the infant’s skin, pharyngeal, tracheal, and gastrointestinal flora.

The most common approach to successfully initiating and then advancing enteral feeding is to use the ‘minimal enteral feeding’ (MEF) strategy. MEF generally refers to small amounts of enteral feedings of formula and/or breast milk at intakes of 5–25 ml/kg/day. MEFs also are called ‘priming’ feedings because of their role in stimulating many aspects of gut function, ‘trophic’ feedings for their positive impact on gut growth, and ‘non-nutritive’ feedings to indicate that they are not intended to be a primary source of nutrition, at least initially, as they do increase the rate at which full enteral feedings can be developed.

Regarding the efficacy of MEF, studies universally have shown a shorter time to full enteral feeds, faster weight gain, less feeding intolerance, less need for phototherapy, enhanced serum gastrin concentrations, enhanced maturation of the small intestine function, lower bilirubin concentrations, and shorter duration of hospitalization. As for safety concerns, there appears to be no increased incidence of NEC in infants who receive MEF, particularly when the mother’s own milk is used; more recent studies, in fact, have shown reduced rates of NEC, although there has been little data collected to define associated risks, particularly those of prolonged intravenous feeding (risk of catheter sepsis, other catheter related complications, hepatic disorders, and so forth).

There also have been few studies that have specifically addressed the optimal time to start MEF in terms of safety and efficacy. In stable preterm infants, starting MEF on day 1–2 is reasonable and cautious advances of ~ 20 ml/kg/day do not necessarily increase the incidence of NEC, although other studies have shown that rapid advancement of enteral feedings tends to increase the risk of NEC. Most groups that have initiated rigorous feeding protocols that include strict attention to reducing the risks of prolonged intravenous feeding (and these vary considerably among the groups) have noted a reduction in rates of NEC. Breast milk is the optimal enteral feeding. There are relatively few contraindications to MEF. Generally, MEF should be used cautiously in any situation associated with either marked gut hypoxia or associated with decreased intestinal blood flow, such as cases of fetal/ neonatal ‘asphyxia’ (hypoxic-ischemic
injury to the gut), persistent severe hypoxemia, hypotension, marked diastolic intestinal blood flow ‘steal’ secondary to a patent ductus arteriosus, and transient decreased superior mesenteric artery blood flow caused by rapid, high-dose, intravenous bolus infusions of indomethacin. As for the mode of enteral feedings, bolus versus continuous drip, there appear to be almost as many different approaches as there have been different trials to determine the best mode. Generally, slow bolus feedings (those lasting at least 30 min to an hour or two) may be preferable to continuous feeds, but this is highly controversial and institution-dependent. Transpyloric feedings are used by some groups, particularly when gastroesophageal reflux is clinically serious, but no data exist to support their more routine use in preterm infants regarding efficacy and safety.

**McGuire, Bombell - Cochrane**

The currently available data do not provide evidence that slow advancement of enteral feed volumes reduces the risk of necrotizing enterocolitis in very low birth weight infants. Increasing the volume of enteral feeds at slow rather than faster rates results in several day delay in regaining birth weight and establishing full enteral feeds but the long-term clinical importance of these effects is unclear. Further randomised controlled trials are needed to determine how the rate of daily increment in enteral feed volumes affects important clinical outcomes in very low birth weight infants, and particularly in extremely low birth weight or growth restricted infants.

**AlFalch KM, Bassler D**

Enteral supplementation of probiotics reduced the risk of severe NEC and mortality in preterm infants. This analysis supports a change in practice in premature infants > 1000 g at birth. Data regarding outcome of ELBW infants could not be extracted from the available studies; therefore, a reliable estimate of the safety and efficacy of administration of probiotic supplements cannot be made in this high risk group. A large randomized controlled trial is required to investigate the potential benefits and safety profile of probiotics supplementation in ELBW infants.

**McGuire W, McEwan P**

Transpyloric versus gastric tube feeding for preterm infants

Preterm infants often have poor co-ordination of sucking and swallowing and this can delay the establishment of safe oral feeding. Enteral feeds may be delivered through a catheter passed via the nose or the mouth into the stomach or upper small bowel. The review of trials found that babies receiving transpyloric tube feeding had more adverse effects, without any evidence of any increased benefit over gastric tube feeding.

**S K Patole and N de Klerk**

A significant and prolonged decline in the incidence of necrotising enterocolitis (NEC),
nearing virtual elimination in some centres, has been observed consistently since implementation of a standardised feeding regimen...Standardised feeding regimens may provide the single most important global tool to prevent/minimise NEC in preterm neonates...

This article also provides a framework for feeding guidelines. Additionally, the findings suggest we re-consider including NEC rates as one of our outcome variables

G Henderson, S Craig, P Brocklehurst, et al.

Results: Significantly fewer cases than controls had received human breast milk (75% vs 91%; OR 0.32, 95% CI 0.11 to 0.98). The day on which enteral feeding was started did not differ significantly (mean (SD) days after birth: cases 2.9 (2.8) and controls 2.8 (1.8)). The mean (SD) duration of trophic feeding (.1 ml/kg/h) was significantly shorter in the cases (3.3 (3.1) days) than controls (6.2 (6.7) days) (mean difference (MD) 22.9, 95% CI 24.9 to 20.9) days. Cases were fully fed significantly earlier than controls (mean (SD) days after birth: cases 9.9 (4.2) and controls 14.3 (9.8); MD 24.4, 95% CI 27.3 to 21.5).

Conclusions: These data suggest that the duration of trophic feeding and rate of advancement of feed volumes may be modifiable risk factors for NEC in preterm infants. Further randomised controlled trials are warranted to assess the effect of different rates of feed advancement on the incidence of NEC, as well as other outcomes.

Pinelli J, Symington AJ

Non-nutritive sucking for promoting physiologic stability and nutrition in preterm infants

An infant born prematurely may be fed through a tube into the stomach, so is often given a pacifier to suck on to improve nutrition. An infant needs coordinated sucking, swallowing and breathing to feed. The ability to suck and to swallow is present by 28 weeks gestation, but infants are not fully coordinated until 32 to 34 weeks. This means that preterm infants less than 32 weeks gestation are usually not able to feed effectively from the breast or a bottle. They are fed by a small tube that is placed up the nose into the stomach (gavage feeding). Sucking on a pacifier (non-nutritive sucking) during gavage feeding may encourage the development of sucking behaviour and improve digestion of the feeding. Non-nutritive sucking may also have a calming effect on infants, although it does have the potential to interfere with breastfeeding. The authors searched the medical literature and found 21 studies, 15 were randomized controlled trials and six were non-randomized. The total number of infants in each study ranged from 10 to 59. Weight gain was similar with and without use of a pacifier. Preterm infants with pacifiers did not stay in hospital as long as those without and hospital costs were less (two studies). These infants showed less defensive behaviors during tube feedings, spent less time in fussy and active states during and after tube feedings, and settled more quickly into sleep. Their transition to full enteral (by tube or mouth) or bottle feeds (three studies) and bottle feeding performance, in general, (one study) were easier. No negative outcomes were reported.

Jadcherla and Kliegman

“…there is no uniform definition of “feeding intolerance.” the definition of feeding intolerance varies and is based on an assessment of pre-feed gastric residual volumes (GRVs), the color of
these GRVs, and associated clinical manifestation such as abdominal distention, emesis, the presence of blood in stool, and apnea with bradycardia. Even if properly defined, the clinical significance of each of these criteria for feeding intolerance has yet to be determined. Are they predictive of serious disease, such as NEC, a delayed time to achieve full enteric alimentation, or are they developmental physiologic expectations when feeding VLBW neonates?